Clinical trial results:
Phase 3, Prospective, Multi-center, Open Label Study to Investigate Safety, Immunogenicity, and Hemostatic Efficacy of PEGylated Factor VIII (BAX 855) in Previously Untreated Patients (PUPs) <6 years With Severe Hemophilia A (FVIII <1%)

Summary

EudraCT number	2015-002136-40
Trial protocol	GB BG ES CZ AT HU DE NL BE NO DK FI IT Outside EU/EEA
Global end of trial date	29 October 2024

Results information

Result version number	v1 (current)
This version publication date	15 May 2025
First version publication date	15 May 2025

Trial information

Trial identification

Sponsor protocol code	261203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02615691
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	500 Kendall Street, Cambridge, Massachusetts, United States, 02142
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 October 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trail was to determine safety including immunogenicity of BAX 855 based on the incidence of inhibitor development to FVIII (≥ 0.6 Bethesda unit (BU)/mL using the Nijmegen modification of the Bethesda assay).

Protection of trial subjects:

Each participant signed an informed consent form (ICF) before participating in the study.

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	12 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Thailand: 12
Country: Number of subjects enrolled	Malaysia: 24
Country: Number of subjects enrolled	India: 3
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Türkiye: 16
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Ukraine: 5
Country: Number of subjects enrolled	Ireland: 9
Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	Hong Kong: 1
Worldwide total number of subjects	120
EEA total number of subjects	20

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)	109
Children (2-11 years)	11
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at various investigative sites globally from 12 November 2015 to 29 October 2024.

Pre-assignment

Screening details:

Previously untreated patients(PUPs)<6 years with severe hemophilia A(Factor VIII[FVIII]<1%)were treated with BAX 855 in Part A for >=100 exposure days(EDs) or until development of FVIII inhibitor.Then,participants who developed high or low titer FVIII inhibitors entered Part B.In Part B they underwent immune tolerance induction(ITI) with BAX 855.

Period 1

Period 1 title	Part A: Main Study (5 years)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	All Participants

Arm description:

PUPs < 6 years of age with severe hemophilia A (FVIII < 1%) and < 3 EDs to ADVATE, BAX 855 or plasma transfusion were enrolled in a single arm group.
Part A (Main Study): Participants age <3 years - who had not experienced two joint bleeds received on-demand treatment of 10-80 international units per kilogram (IU/kg) intravenously (IV) depending on the severity of the bleeding episode; and - who experienced maximum of two joint bleeds received prophylaxis treatment with dose of 25-80 IU/kg of BAX 855 IV (based on investigator discretion) once weekly for up to 100 EDs.
Part B (ITI Portion): Participants who met the pre-defined Part B treatment criteria entered Part B of the study for ITI. Participants either received prophylaxis treatment of BAX 855 low dose 50 IU/kg IV, three times a week (Q3W) or high dose 100-200 IU/kg IV, daily at the discretion of the investigator according to the institution’s standard of care.

Arm type	Experimental
Investigational medicinal product name	PEGylated rFVIII
Investigational medicinal product code	BAX855
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

For Part A: 10-50 IU/kg, up to 80 IU/kg, depending on the severity of the bleeding episode and for Part B: 25-50 IU/kg, up to 80 IU/kg at investigator discretion, at least once weekly.

Number of subjects in period 1	All Participants
Started	120
Part A: On-demand Treatment	80
Part A: Prophylaxis Treatment	112
Completed	106
Not completed	14
Physician decision	2

Consent withdrawn by subject	7
Adverse event, non-fatal	3
Reason Not Specified	2

Period 2

Period 2 title	Part B: ITI Portion (3.5 years)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	All Participants

Arm description:

PUPs < 6 years of age with severe hemophilia A (FVIII < 1%) and < 3 EDs to ADVATE, BAX 855 or plasma transfusion were enrolled in a single arm group.
Part A (Main Study): Participants age <3 years - who had not experienced two joint bleeds received on-demand treatment of 10-80 international units per kilogram (IU/kg) intravenously (IV) depending on the severity of the bleeding episode; and - who experienced maximum of two joint bleeds received prophylaxis treatment with dose of 25-80 IU/kg of BAX 855 IV (based on investigator discretion) once weekly for up to 100 EDs.
Part B (ITI Portion): Participants who met the pre-defined Part B treatment criteria entered Part B of the study for ITI. Participants either received prophylaxis treatment of BAX 855 low dose 50 IU/kg IV, three times a week (Q3W) or high dose 100-200 IU/kg IV, daily at the discretion of the investigator according to the institution’s standard of care.

Arm type	Experimental
Investigational medicinal product name	PEGylated rFVIII
Investigational medicinal product code	BAX855
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

For Part A: 10-50 IU/kg, up to 80 IU/kg, depending on the severity of the bleeding episode and for Part B: 25-50 IU/kg, up to 80 IU/kg at investigator discretion, at least once weekly.

Number of subjects in period 2	All Participants
Started	7
Part B:FVII Inhibitor Dose(50 IU/kg Q3W)	4 [1]
Part B:FVII Inhibitor100-200IU/kg Daily	3 [2]
Completed	7

Notes:

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

Justification: A participant that received on-demand treatment first and then moved to prophylaxis treatment was counted for both on-demand and prophylaxis regimens. A participant that started with prophylaxis treatment was counted only for the prophylaxis regimen even if the participant received on-demand treatment while on the prophylaxis regimen.

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

Justification: A participant that received on-demand treatment first and then moved to prophylaxis treatment was counted for both on-demand and prophylaxis regimens. A participant that started with prophylaxis treatment was counted only for the prophylaxis regimen even if the participant received on-demand treatment while on the prophylaxis regimen.

Baseline characteristics

Reporting groups	
Reporting group title	All Participants

Reporting group description:

PUPs < 6 years of age with severe hemophilia A (FVIII < 1%) and < 3 EDs to ADVATE, BAX 855 or plasma transfusion were enrolled in a single arm group.
Part A (Main Study): Participants age <3 years - who had not experienced two joint bleeds received on-demand treatment of 10-80 international units per kilogram (IU/kg) intravenously (IV) depending on the severity of the bleeding episode; and - who experienced maximum of two joint bleeds received prophylaxis treatment with dose of 25-80 IU/kg of BAX 855 IV (based on investigator discretion) once weekly for up to 100 EDs.
Part B (ITI Portion): Participants who met the pre-defined Part B treatment criteria entered Part B of the study for ITI. Participants either received prophylaxis treatment of BAX 855 low dose 50 IU/kg IV, three times a week (Q3W) or high dose 100-200 IU/kg IV, daily at the discretion of the investigator according to the institution's standard of care.

Reporting group values	All Participants	Total	
Number of subjects	120	120	
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	0.90		
standard deviation	± 0.717	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	120	120	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	45	45	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	7	7	
White	61	61	
More than one race	4	4	
Unknown or Not Reported	3	3	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	6	
Not Hispanic or Latino	114	114	
Unknown or Not Reported	0	0	

End points reporting groups

Reporting group title	All Participants

Reporting group description:

PUPs < 6 years of age with severe hemophilia A (FVIII < 1%) and < 3 EDs to ADVATE, BAX 855 or plasma transfusion were enrolled in a single arm group.
Part A (Main Study): Participants age <3 years - who had not experienced two joint bleeds received on-demand treatment of 10-80 international units per kilogram (IU/kg) intravenously (IV) depending on the severity of the bleeding episode; and - who experienced maximum of two joint bleeds received prophylaxis treatment with dose of 25-80 IU/kg of BAX 855 IV (based on investigator discretion) once weekly for up to 100 EDs.
Part B (ITI Portion): Participants who met the pre-defined Part B treatment criteria entered Part B of the study for ITI. Participants either received prophylaxis treatment of BAX 855 low dose 50 IU/kg IV, three times a week (Q3W) or high dose 100-200 IU/kg IV, daily at the discretion of the investigator according to the institution’s standard of care.

Reporting group title	All Participants

Reporting group description:

PUPs < 6 years of age with severe hemophilia A (FVIII < 1%) and < 3 EDs to ADVATE, BAX 855 or plasma transfusion were enrolled in a single arm group.
Part A (Main Study): Participants age <3 years - who had not experienced two joint bleeds received on-demand treatment of 10-80 international units per kilogram (IU/kg) intravenously (IV) depending on the severity of the bleeding episode; and - who experienced maximum of two joint bleeds received prophylaxis treatment with dose of 25-80 IU/kg of BAX 855 IV (based on investigator discretion) once weekly for up to 100 EDs.
Part B (ITI Portion): Participants who met the pre-defined Part B treatment criteria entered Part B of the study for ITI. Participants either received prophylaxis treatment of BAX 855 low dose 50 IU/kg IV, three times a week (Q3W) or high dose 100-200 IU/kg IV, daily at the discretion of the investigator according to the institution’s standard of care.

Subject analysis set title	Part A: Main Study
Subject analysis set type	Per protocol

Subject analysis set description:

Participants age <3 years - who had not experienced two joint bleeds received on-demand treatment of 10-80 IU/kg IV depending on the severity of the bleeding episode; and - who experienced maximum of two joint bleeds received prophylaxis treatment with dose of 25-80 IU/kg of BAX 855 IV (based on investigator discretion) once weekly for up to 100 EDs.

Subject analysis set title	Part B: ITI Portion
Subject analysis set type	Per protocol

Subject analysis set description:

Participants who met the pre-defined Part B treatment criteria entered in the Part B of the study for ITI. Participants either received prophylaxis treatment of low dose BAX 855 50 IU/kg IV, three times a week or high dose 100-200 IU/kg IV, daily at the discretion of the investigator according to the institution’s standard of care.

Subject analysis set title	Part A: Main Study: On-demand
Subject analysis set type	Per protocol

Subject analysis set description:

Participants age <3 years and who had not experienced two joint bleeds received on-demand treatment of 10-80IU/kg of BAX 855 IV depending on the severity of the bleeding episode.

Subject analysis set title	Part A: Main Study: Prophylaxis
Subject analysis set type	Per protocol

Subject analysis set description:

Participants age <3 years or after a maximum of two joint bleeds received prophylaxis treatment with dose of 25-80 IU/kg of BAX 855 IV (based on investigator discretion) once weekly for up to 100 EDs.

Subject analysis set title	Part B: ITI Portion (50 IU/kg Three Times Weekly Regimen)
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received prophylaxis treatment of 50 IU/kg BAX 855 IV three times in a week.

Subject analysis set title	Part B: ITI Portion (100-200 IU/kg Daily Regimen)

Subject analysis set type	Per protocol

Subject analysis set description:

Participants received prophylaxis treatment of 100-200 IU/kg BAX 855 IV daily.

Primary: Number of Participants With FVIII Inhibitor Development

End point title	Number of Participants With FVIII Inhibitor Development[1]

End point description:

Number of participants who developed an inhibitor (at any time) confirmed by a central laboratory based on a second repeat blood sample draw within 2 weeks of site notification of an inhibitor and all participants who had not developed an inhibitor and had greater than or equal to (>=) 100 EDs when the sample for the last valid inhibitor test was drawn. The SAS included all participants in the enrolled population with at least one BAX 855 infusion. Included in the analysis were participants who had equal or greater than 100 EDs or developed a confirmed FVIII inhibitor.

End point type	Primary

End point timeframe:

Throughout Part A of the study, approximately 5 years

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: Only descriptive analyses were planned for this endpoint.

End point values	Part A: Main Study			
Subject group type	Subject analysis set			
Number of subjects analysed	100			
Units: participants	11			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Success of Immune Tolerance Induction (ITI)

End point title	Number of Participants With Success of Immune Tolerance Induction (ITI)[2]

End point description:

Success is defined as 1) a persistently negative inhibitor titer less than (<) 0.6 Bethesda unit (BU), 2) FVIII IR >=66% of the baseline value following a wash-out period of 84-96 hours, and 3) a FVIII half-life of >=6 hours. The FVIII Inhibitor Treatment Analysis Set (IAS) included all participants who received at least one FVIII inhibitor treatment with BAX 855 during the study after the date that participant moved to FVIII inhibitor treatment.

End point type	Primary

End point timeframe:

Up to 33 months in Part B of the study

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: Only descriptive analyses were planned for this endpoint.

End point values	Part B: ITI Portion			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: participants	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Binding Immunoglobulin G (IgG) and Immunoglobulin M (IgM) Antibodies

End point title	Number of Participants With Binding Immunoglobulin G (IgG) and Immunoglobulin M (IgM) Antibodies

End point description:

Binding IgG and IgM antibodies (Ab) to FVIII , Factor VIII-Polyethylene glycol (PEG-FVIII) and Polyethylene glycol (PEG) was assessed. A participant that received on-demand treatment first and then moved to prophylaxis treatment was counted for both on-demand and prophylaxis regimens. A participant that started with prophylaxis treatment was counted only for the prophylaxis regimen even if the participant received on-demand treatment while on the prophylaxis regimen. Visits and their approximate time in weeks after baseline visit for individual participants: Visit 1(Week 5), Visit 2 (Week 10), Visit 3 (Week 15), Visit 4 (Week 20), Visit 5 (Week 30), Visit 6 (Week 40), Visit 7 (Week 55), Visit 8 (Week 75) and Study Completion Visit (Weeks 100-110). The SAS included all participants in the enrolled population with at least one BAX 855 infusion. 'n' indicates the number of participants with data available for analyses for each category. Study Completion is denoted as SC.

End point type	Secondary

End point timeframe:

Throughout Part A of the study, approximately 5 years

End point values	Part A: Main Study: On-demand	Part A: Main Study: Prophylaxis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80	112		
Units: participants				
Screening- Binding IgG Ab to FVIII (n=75,40)	1	0		
Screening- Binding IgM Ab to FVIII (n=75,40)	0	0		
Screening- Binding IgG Ab to PEG-FVIII (n=75,40)	3	2		
Screening- Binding IgM Ab to PEG-FVIII (n=75,40)	4	1		
Screening- Binding IgG Ab to PEG (n=75,40)	0	0		
Screening- Binding IgM Ab to PEG (n=75,40)	6	4		
Baseline- Binding IgG Ab to FVIII (n=79,38)	2	1		
Baseline- Binding IgM Ab to FVIII (n=79,38)	0	0		
Baseline- Binding IgG Ab to PEG-FVIII (n=79,38)	7	3		

Baseline- Binding IgM Ab to PEG-FVIII (n=79,38)	4	2		
Baseline- Binding IgG Ab to PEG (n=79,38)	0	0		
Baseline- Binding IgM Ab to PEG (n=79,38)	8	2		
Visit 1- Binding IgG Ab to FVIII (n=47,62)	0	4		
Visit 1- Binding IgM Ab to FVIII (n=47,62)	0	0		
Visit 1- Binding IgG Ab to PEG-FVIII (n=47,62)	14	36		
Visit 1- Binding IgM Ab to PEG-FVIII (n=47,62)	0	2		
Visit 1- Binding IgG Ab to PEG (n=47,62)	4	8		
Visit 1- Binding IgM Ab to PEG (n=47,62)	0	3		
Visit 2- Binding IgG Ab to FVIII (n=20,76)	1	1		
Visit 2- Binding IgM Ab to FVIII (n=20,76)	0	0		
Visit 2- Binding IgG Ab to PEG-FVIII (n=20,76)	6	27		
Visit 2- Binding IgM Ab to PEG-FVIII (n=20,76)	0	0		
Visit 2- Binding IgG Ab to PEG (n=20,76)	2	3		
Visit 2- Binding IgM Ab to PEG (n=20,76)	0	0		
Visit 3- Binding IgG Ab to FVIII (n=11,86)	0	2		
Visit 3- Binding IgM Ab to FVIII (n=11,86)	0	0		
Visit 3- Binding IgG Ab to PEG-FVIII (n=11,86)	4	25		
Visit 3- Binding IgM Ab to PEG-FVIII (n=11,86)	0	0		
Visit 3- Binding IgG Ab to PEG (n=11,86)	1	4		
Visit 3- Binding IgM Ab to PEG (n=11,86)	0	0		
Visit 4- Binding IgG Ab to FVIII (n=5,87)	0	0		
Visit 4- Binding IgM Ab to FVIII (n=5,87)	0	0		
Visit 4- Binding IgG Ab to PEG-FVIII (n=5,87)	1	18		
Visit 4- Binding IgM Ab to PEG-FVIII (n=5,87)	0	0		
Visit 4- Binding IgG Ab to PEG (n=5,87)	0	1		
Visit 4- Binding IgM Ab to PEG (n=5,87)	0	0		
Visit 5- Binding IgG Ab to FVIII (n=3,94)	0	0		
Visit 5- Binding IgM Ab to FVIII (n=3,94)	0	0		
Visit 5- Binding IgG Ab to PEG-FVIII (n=3,94)	1	13		
Visit 5- Binding IgM Ab to PEG-FVIII (n=3,94)	0	0		
Visit 5- Binding IgG Ab to PEG (n=3,94)	0	1		

Visit 5- Binding IgM Ab to PEG (n=3,94)	0	0		
Visit 6- Binding IgG Ab to FVIII (n=1,94)	0	0		
Visit 6- Binding IgM Ab to FVIII (n=1,94)	0	0		
Visit 6- Binding IgG Ab to PEG-FVIII (n=3,94)	1	5		
Visit 6- Binding IgM Ab to PEG-FVIII (n=3,94)	0	0		
Visit 6- Binding IgG Ab to PEG (n=1,94)	0	0		
Visit 6- Binding IgM Ab to PEG (n=1,94)	0	0		
Visit 7- Binding IgG Ab to FVIII (n=1,93)	0	0		
Visit 7- Binding IgM Ab to FVIII (n=1,93)	0	0		
Visit 7- Binding IgG Ab to PEG-FVIII (n=1,93)	1	4		
Visit 7- Binding IgM Ab to PEG-FVIII (n=1,93)	0	0		
Visit 7- Binding IgG Ab to PEG (n=1,93)	0	0		
Visit 7- Binding IgM Ab to PEG (n=1,93)	0	0		
Visit 8- Binding IgG Ab to FVIII (n=1,90)	0	0		
Visit 8- Binding IgM Ab to FVIII (n=1,90)	0	0		
Visit 8- Binding IgG Ab to PEG-FVIII (n=1,90)	0	1		
Visit 8- Binding IgM Ab to PEG-FVIII (n=1,90)	0	0		
Visit 8- Binding IgG Ab to PEG (n=1,90)	0	0		
Visit 8- Binding IgM Ab to PEG (n=1,90)	0	0		
SC- Binding IgG Ab to FVIII (n=4,96)	0	1		
SC- Binding IgM Ab to FVIII (n=4,96)	0	0		
SC- Binding IgG Ab to PEG-FVIII(n=4,96)	1	2		
SC- Binding IgM Ab to PEG-FVIII (n=4,96)	1	0		
SC- Binding IgG Ab to PEG (n=4,96)	1	1		
SC- Binding IgM Ab to PEG (n=4,96)	1	0		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

AE:any untoward medical occurrence in participant administered investigational product(IP) that does not necessarily have causal relationship with treatment.SAE:any untoward clinical manifestation of signs,symptoms or outcomes(whether considered related to IP or not & at any dose)which results in death,is lifethreatening,requires inpatient hospitalization,prolongation of hospitalization,is important medical event.A participant that received on-demand treatment 1st & then moved to prophylaxis treatment was counted for both on-demand & prophylaxis regimens.A participant that started with prophylaxis treatment was counted only for that regimen even if the participant received on-demand

treatment while on prophylaxis regimen.SAS:all participants in enrolled population with at least 1 BAX855 infusion for Part A of study & IAS:all participants who received at least 1 FVIII inhibitor treatment with BAX855 during study after date that participant moved to FVIII inhibitor treatment for Part B.

End point type	Secondary

End point timeframe:

Throughout Part A and Part B of the study, approximately 9 years

End point values	Part A: Main Study: On-demand	Part A: Main Study: Prophylaxis	Part B: ITI Portion (50 IU/kg Three Times Weekly Regimen)	Part B: ITI Portion (100-200 IU/kg Daily Regimen)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	80	112	4	3
Units: participants				
AEs	57	94	4	3
SAEs	18	35	1	3

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With At Least One Clinically Significant Changes in Clinical Laboratory Parameters

End point title	Number of Participants With At Least One Clinically Significant Changes in Clinical Laboratory Parameters

End point description:

Clinical laboratory parameters included hematology and clinical chemistry. Changes in laboratory values could be considered as AE if they were judged to be clinically significant. The SAS included all participants in the enrolled population with at least one BAX 855 infusion for Part A of the study and the IAS included all participants who received at least one FVIII inhibitor treatment with BAX 855 during the study after the date that participant moved to FVIII inhibitor treatment for Part B of the study.

End point type	Secondary

End point timeframe:

Throughout Part A and Part B of the study, approximately 9 years

End point values	Part A: Main Study	Part B: ITI Portion		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	120	7		
Units: participants	53	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With At Least One Clinically Significant Changes in Vital Signs

End point title	Number of Participants With At Least One Clinically Significant Changes in Vital Signs

End point description:

Vital signs were assessed based on body temperature, respiratory rate, blood pressure, and heart rate. The SAS included all participants in the enrolled population with at least one BAX 855 infusion for Part A of the study and the IAS included all participants who received at least one FVIII inhibitor treatment with BAX 855 during the study after the date that participant moved to FVIII inhibitor treatment for Part B of the study.

End point type	Secondary

End point timeframe:

Throughout Part A and Part B of the study, approximately 9 years

End point values	Part A: Main Study	Part B: ITI Portion		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	120	7		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rate (ABR) for Prophylactic and On-demand Treatment and Immune Tolerance Induction (ITI)

End point title	Annualized Bleeding Rate (ABR) for Prophylactic and On-demand Treatment and Immune Tolerance Induction (ITI)

End point description:

ABR was assessed based upon each individual bleeding episode.Bleeding episode:subjective (pain consistent with a joint bleed) or objective evidence of bleeding which may or may not require treatment with FVIII.Bleeding occurring at multiple locations related to same injury(example,knee & ankle bleed following a fall) was counted as single bleeding episode.Mean total annualized bleed rate is reported.A participant that received on-demand treatment first & then moved to prophylaxis treatment was counted for both on-demand & prophylaxis regimens.A participant that started with prophylaxis treatment was counted only for that regimen even if participant received on-demand treatment while on the prophylaxis regimen.SAS:all participants in the enrolled population with at least 1 BAX855 infusion for Part A of study & IAS:all participants who received at least 1 FVIII inhibitor treatment with BAX855 during study after the date that participant moved to FVIII inhibitor treatment for Part B.

End point type	Secondary

End point timeframe:

Throughout Part A and Part B of the study, approximately 9 years

End point values	Part A: Main Study: On-demand	Part A: Main Study: Prophylaxis	Part B: ITI Portion (50 IU/kg Three Times Weekly Regimen)	Part B: ITI Portion (100-200 IU/kg Daily Regimen)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	80	112	4	3
Units: unique bleeds per year				
arithmetic mean (standard deviation)	10.004 (± 15.533)	4.536 (± 8.657)	7.673 (± 8.965)	6.432 (± 14.518)

Statistical analyses

No statistical analyses for this end point

Secondary: Bleeding Episodes Categorized by Number of BAX 855 Infusions Required for Treatment

End point title	Bleeding Episodes Categorized by Number of BAX 855 Infusions Required for Treatment

End point description:

A bleeding episode is defined as subjective (pain consistent with a joint bleed) or objective evidence of bleeding which may or may not require treatment with FVIII. The number of BAX 855 infusions needed for each bleeding episode was determined by the participant, caregiver, clinician treating the participant, and is based upon the participant's response to treatment, using the Efficacy Rating Scale for Treatment of Bleeding Episodes. Number of bleeding episodes are categorized by number of infusions required to treat the bleeding episodes. A participant that received on-demand treatment first and then moved to prophylaxis treatment was counted for both on-demand and prophylaxis regimens. A participant that started with prophylaxis treatment was counted only for the prophylaxis regimen even if the participant received on-demand treatment while on the prophylaxis regimen. The SAS included all participants in the enrolled population with at least one BAX 855 infusion.

End point type	Secondary

End point timeframe:

Throughout Part A of the study, approximately 5 years

End point values	Part A: Main Study: On-demand	Part A: Main Study: Prophylaxis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80[3]	112[4]		
Units: bleeding episodes				
number (not applicable)				
Number of infusions per bleed: 0	7	14		
Number of infusions per bleed: 1	302	312		
Number of infusions per bleed: 2	43	44		
Number of infusions per bleed: 3	18	19		
Number of infusions per bleed: 4	4	1		
Number of infusions per bleed: >4	5	6		

Notes:

[3] - Number of treated bleeds=379

[4] - Number of treated bleeds=396

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bleeds by Overall Hemostatic Efficacy Rating at 24 Hours After Initiation of Treatment

End point title	Number of Bleeds by Overall Hemostatic Efficacy Rating at 24 Hours After Initiation of Treatment

End point description:

Participant or caregiver rated overall treatment response using 4-point efficacy rating scale as Excellent:Full relief of pain & cessation of objective signs of bleeding after single infusion & no additional infusion is required for control of bleeding;Good:Definite pain relief &/or improvement in signs of bleeding after single infusion & possibly requires more than 1 infusion for complete resolution;Fair:Probable &/or slight relief of pain & slight improvement in signs of bleeding after single infusion & required more than 1 infusion for complete resolution & None:No improvement or condition worsens.Number of bleeds with each efficacy rating are reported.Participant that received on-demand treatment 1st & then moved to prophylaxis treatment was counted for both on-demand & prophylaxis regimens.Participant that started with prophylaxis treatment was counted only for that regimen even if the participant received on-demand treatment while on prophylaxis regimen.

End point type	Secondary

End point timeframe:

At 24 hours after study drug administration during Part A of the study

End point values	Part A: Main Study: On-demand	Part A: Main Study: Prophylaxis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80[5]	112[6]		
Units: bleeds				
number (not applicable)				
Excellent	76	102		
Good	67	71		
Fair	13	10		
None	2	1		

Notes:

[5] - Number of treated bleeds=158

[6] - Number of treated bleeds=184

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bleeds by Overall Hemostatic Efficacy Rating at Bleed Resolution

End point title	Number of Bleeds by Overall Hemostatic Efficacy Rating at Bleed Resolution

End point description:

The participant or caregiver rated overall treatment response using a 4-point efficacy rating scale as Excellent:Full relief of pain & cessation of objective signs of bleeding after single infusion & no additional infusion is required for the control of bleeding; Good:Definite pain relief &/or improvement in signs of bleeding after a single infusion & possibly requires more than 1 infusion for complete resolution; Fair:Probable &/or slight relief of pain & slight improvement in signs of bleeding after single infusion & required more than 1 infusion for complete resolution & None:No improvement or condition worse.Number of bleeds with each efficacy rating are reported.Participant that received on-demand treatment first & then moved to prophylaxis treatment was counted for both on-demand & prophylaxis regimens.

Participant that started with prophylaxis treatment was counted only for prophylaxis regimen even if the participant received on-demand treatment while on prophylaxis regimen.

End point type	Secondary

End point timeframe:

From start of study treatment up to bleed resolution throughout Part A of the study (up to approximately 5 years)

End point values	Part A: Main Study: On-demand	Part A: Main Study: Prophylaxis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	80[7]	112[8]		
Units: bleeds				
number (not applicable)				
Excellent	166	166		
Good	83	77		
Fair	12	9		
None	3	1		

Notes:

[7] - Number of treated bleeds=264

[8] - Number of treated bleeds=253

Statistical analyses

No statistical analyses for this end point

Secondary: Weight-adjusted Consumption of BAX 855: Average Number of Prophylactic Infusions

End point title	Weight-adjusted Consumption of BAX 855: Average Number of Prophylactic Infusions

End point description:

Weight-adjusted consumption of BAX 855 was determined based upon the record in participants diaries of the actual number of BAX 855 infusions as measured in the clinic. Average (Avg.) number (no.) of infusions per month and year are reported as categories. The SAS included all participants in the enrolled population with at least one BAX 855 infusion. Number analyzed (n) for each category is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Throughout Part A and Part B of the study, approximately 9 years

End point values	Part A: Main Study: Prophylaxis			
Subject group type	Subject analysis set			
Number of subjects analysed	112			
Units: infusions				
arithmetic mean (standard deviation)				
Avg. No. of Prophylactic Infusions/Month (n=111)	4.900 (± 1.877)			

Avg. No. of Prophylactic Infusions per Year (n=83)	57.067 (± 16.361)			

Statistical analyses

No statistical analyses for this end point

Secondary: Weight-adjusted Consumption of BAX 855: Average Prophylactic Dose

End point title	Weight-adjusted Consumption of BAX 855: Average Prophylactic Dose

End point description:

Weight-adjusted consumption of BAX 855 was determined based upon the record in participants diaries of the actual amount of BAX 855 infused as measured in the clinic. Average dose per prophylactic infusion, per month and per year are reported as categories. The SAS included all participants in the enrolled population with at least one BAX 855 infusion. Number analyzed (n) for each category is the number of participants with data available for analyses. n=112 for Average Dose [IU/kg] per Prophylactic Infusion; n=111 for Average Prophylactic Dose [IU/kg] per Month and n=83 for Average Prophylactic Dose [IU/kg] per Year.

End point type	Secondary

End point timeframe:

Throughout Part A of the study, approximately 5 years

End point values	Part A: Main Study: Prophylaxis			
Subject group type	Subject analysis set			
Number of subjects analysed	112			
Units: IU/kg				
arithmetic mean (standard deviation)				
Average Dose [IU/kg] per Prophylactic Infusion	45.514 (± 7.831)			
Average Prophylactic Dose [IU/kg] per Month	221.568 (± 85.925)			
Average Prophylactic Dose [IU/kg] per Year	2597.079 (± 783.089)			

Statistical analyses

No statistical analyses for this end point

Secondary: Weight-adjusted Consumption of BAX 855: Average Dose

End point title	Weight-adjusted Consumption of BAX 855: Average Dose

End point description:

Weight-adjusted consumption of BAX 855 was determined based upon the record in participants diaries of the actual amount of BAX 855 infused as measured in the clinic. Average dose to treat bleeding episode and average FVIII inhibitor treatment Dose [IU/kg] per Week, Month and per Year are reported as categories. A participant that received on-demand treatment first and then moved to prophylaxis

treatment was counted for both on-demand and prophylaxis regimens. A participant that started with prophylaxis treatment was counted only for the prophylaxis regimen even if the participant received on-demand treatment while on the prophylaxis regimen. SAS was used. Number analyzed (n) for each category is the number of participants with data available for analyses. n for the categories: per bleeding episode (n=80,112,0,0), per Week(n=0,0,2,3), per Month(n=0,0,2,3), per Year(n=0,0,2,3).

End point type	Secondary

End point timeframe:

Throughout Part A of the study, approximately 5 years

End point values	Part A: Main Study: On-demand	Part A: Main Study: Prophylaxis	Part B: ITI Portion (50 IU/kg Three Times Weekly Regimen)	Part B: ITI Portion (100-200 IU/kg Daily Regimen)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	80	112	4	3
Units: IU/kg				
arithmetic mean (standard deviation)				
Average Dose [IU/kg] to Treat Bleeding Episode	55.445 (± 32.826)	63.864 (± 44.818)	99999 (± 99999)	99999 (± 99999)
Average FVIII Inhibitor Dose[IU/kg]/Week	99999 (± 99999)	99999 (± 99999)	123.510 (± 65.563)	417.750 (± 319.694)
Average FVIII Inhibitor Dose[IU/kg]/Month	99999 (± 99999)	99999 (± 99999)	537.038 (± 285.076)	1816.427 (± 1390.068)
Average FVIII Inhibitor Dose[IU/kg]/Year	99999 (± 99999)	99999 (± 99999)	6444.460 (± 3420.911)	21797.128 (± 16680.821)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants by Hemostatic Efficacy Rating in Case of Surgery

End point title	Number of Participants by Hemostatic Efficacy Rating in Case of Surgery

End point description:

Hemostatic efficacy assessed during & after any surgical/invasive procedures,& overall perioperatively.Operating surgeon assessed it compared to that expected for type of procedure performed in non-hemophilic population,prior to discharge from recovery room(intraoperative),on postoperative Day1&at discharge/14 days post-surgery(perioperative).Participants rated efficacy:1.Excellent:Postoperative blood loss≤100%than expected;2.Good:Postoperative blood loss up to50%more(101-150%)than expected;3.Fair:Postoperative blood loss50%(>150%)more than expected;4.None:Significant postoperative bleeding that due to inadequate therapeutic response despite proper dosing,necessitating rescue therapy.Perioperative ratings:based on amount of blood components required for transfusions versus expected.Categories=Participant-provided ratings.Invasive Procedure Analysis Set(IPRAS):participants receiving BAX 855 for≤1surgeries/invasive procedures in study.n=participants with data available for analyses.

End point type	Secondary

End point timeframe:

Surgery Day 0 up to postoperative Day 14 or discharge (whichever occurs first)

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: participants				
Intraoperative - Excellent (n=11)	10			
Intraoperative - Good (n=11)	0			
Intraoperative - Fair (n=11)	0			
Intraoperative - None (n=11)	1			
Postoperative - Excellent (n=11)	11			
Postoperative - Good (n=11)	0			
Postoperative - Fair (n=11)	0			
Postoperative - None (n=11)	0			
Perioperative - Excellent (n=11)	10			
Perioperative - Good (n=11)	0			
Perioperative - Fair (n=11)	0			
Perioperative - None (n=11)	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental Recovery (IR) of BAX 855

End point title	Incremental Recovery (IR) of BAX 855

End point description:

BAX 855 was administered in participants for the determination of FVIII IR at the study site at baseline and every study visit other than study visits at 5 EDs, 15 EDs and 30 EDs. The FVIII assays were done using following methods: 1-stage clotting FVIII activity and FVIII chromogenic activity. Data is reported for each of these methods as categories per visit. The Pharmacokinetic (PK) analysis set (PKAS) included all participants in the SAS who had at least one post-dose measurement of FVIII activity without protocol deviations and/or events with potential to affect concentration (FVIII activity levels). Number analyzed (n) is the number of participants with data available for analyses for each category. n=4 for the Preoperative Assessments Surgery timepoint.

End point type	Secondary

End point timeframe:

Pre-infusion within 30 minutes; and post-infusion at 15-30 minutes and 24-48 hours (Up to 9 years)

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: (IU/dL)/(IU/kg)				
geometric mean (geometric coefficient of variation)				
Baseline-1-Stage Clotting (n=99)	1.546 (± 46.991)			
Baseline-Chromogenic (n=100)	1.594 (± 55.555)			
Visit 1-1-Stage Clotting (n=45)	1.452 (± 49.680)			

Visit 1-Chromogenic (n=45)	1.651 (± 43.755)			
Visit 2-1-Stage Clotting (n=88)	1.345 (± 72.207)			
Visit 2-Chromogenic (n=88)	1.451 (± 57.891)			
Visit 3-1-Stage Clotting (n=47)	1.439 (± 61.369)			
Visit 3-Chromogenic (n=47)	1.586 (± 54.653)			
Visit 4-1-Stage Clotting (n=79)	1.558 (± 33.938)			
Visit 4-Chromogenic (n=79)	1.802 (± 31.897)			
Visit 5-1-Stage Clotting (n=56)	1.588 (± 51.122)			
Visit 5-Chromogenic (n=54)	1.916 (± 28.373)			
Visit 6-1-Stage Clotting (n=87)	1.714 (± 34.037)			
Visit 6-Chromogenic (n=87)	1.809 (± 46.022)			
Visit 7-1-Stage Clotting (n=89)	1.742 (± 46.707)			
Visit 7-Chromogenic (n=88)	1.965 (± 20.272)			
Visit 8-1-Stage Clotting (n=83)	1.634 (± 43.470)			
Visit 8-Chromogenic (n=82)	1.893 (± 36.334)			
Study Completion-1-Stage Clotting (n=89)	1.819 (± 25.513)			
Study Completion-Chromogenic (n=90)	1.979 (± 23.846)			
Preoperative Assessments Surgery-1-Stage Clotting	1.481 (± 42.457)			
Preoperative Assessments Surgery-Chromogenic	1.716 (± 45.340)			

Statistical analyses

No statistical analyses for this end point

Secondary: Blood Loss Per Participant in Case of Surgery

End point title	Blood Loss Per Participant in Case of Surgery

End point description:

The intraoperative blood loss was measured by determining the volume of blood and fluid removal through suction into the collection container (waste box and/or cell saver) and the estimated blood loss into swabs and towels during the procedure, per the anesthesiologist's record. Post-operatively, blood loss was determined by the drainage volume collected, which mainly consisted of drainage fluid via vacuum or gravity drain, as applicable. The assessment was done for the intra-operative time period (prior to discharge from recovery room) and for the post-operative time period (from completion of the procedure until approximately 24 hours post-surgery). The IPRAS included all participants who were treated with BAX 855 for one or more surgeries or invasive procedures in the context of the study. Number analyzed are the participants who experienced blood loss.

End point type	Secondary

End point timeframe:

Surgery Day 0 up to postoperative Day 14 or discharge (whichever occurs first)

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: milliliters (mL)				
arithmetic mean (standard deviation)				
Observed Intra-Operative Blood Loss (n=17)	4.8 (± 5.43)			
Observed Post-Operative Blood Loss (n=0)	99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The Half-life to determine FVIII half-life was an optional assessment that was planned to be performed at baseline, Visit 1, or Visit 2. As pre-specified in the protocol, the determination of FVIII half-life by abbreviated PK at baseline was optional and was not performed.

End point type	Secondary

End point timeframe:

Pre-infusion, Post-infusion: 15-30 minutes and 24-48 hours at Baseline

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	0[9]			
Units: hours				
median (full range (min-max))	(to)			

Notes:

[9] - Determination of FVIII half-life by abbreviated PK at baseline was optional and was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Immune Tolerance Induction (ITI) – Number of Participants With Partial Success and Failure of ITI

End point title	Immune Tolerance Induction (ITI) – Number of Participants With Partial Success and Failure of ITI

End point description:

Partial success defined as which meet two of following criteria, 1) inhibitor titer <0.6 BU (confirmed by a central laboratory with a second blood specimen obtained within 2 months), 2) FVIII in vivo recovery >=66% of baseline value (confirmed within a two month period), and 3) FVIII half-life >=6 hours.

Failure defined as the failure to meet the criteria for partial success. FVIII inhibitor treatment analysis set (IAS) included all participants who received at least one FVIII inhibitor treatment with BAX 855 during the study after the date that participant moved to FVIII inhibitor treatment.

End point type	Secondary

End point timeframe:

Up to 33 months in Part B of the study

End point values	Part B: ITI Portion			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: participants				
Partial Success	1			
Failure	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Immune Tolerance Induction (ITI) - Number of Participants With At Least One Catheter-related Complication

End point title	Immune Tolerance Induction (ITI) - Number of Participants With At Least One Catheter-related Complication

End point description:

Number of participants with catheter-related complications are reported. IAS included all participants who received at least one FVIII inhibitor treatment with BAX 855 during the study after the date that participant moved to FVIII inhibitor treatment for Part B of the study.

End point type	Secondary

End point timeframe:

Up to 33 months in Part B of the study

End point values	Part B: ITI Portion (50 IU/kg Three Times Weekly Regimen)	Part B: ITI Portion (100-200 IU/kg Daily Regimen)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	3		
Units: participants	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Immune Tolerance Induction (ITI) – Number of Participants With Binding Immunoglobulin G (IgG) and Immunoglobulin M (IgM) Antibodies

End point title	Immune Tolerance Induction (ITI) – Number of Participants With Binding Immunoglobulin G (IgG) and Immunoglobulin M (IgM) Antibodies

End point description:

Binding IgG and IgM antibodies to Factor VIII (FVIII), Factor VIII-Polyethylene glycol (PEG-FVIII) and Polyethylene glycol (PEG) are reported as categories per visit. The IAS included all participants who received at least one FVIII inhibitor treatment with BAX 855 during the study after the date that participant moved to FVIII inhibitor treatment. Follow-Up Visit is denoted as FU and Treatment Completion is denoted as TC.

End point type	Secondary

End point timeframe:

Up to 33 months in Part B of the study

End point values	Part B: ITI Portion (50 IU/kg Three Times Weekly Regimen)	Part B: ITI Portion (100-200 IU/kg Daily Regimen)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	3		
Units: participants				
Screening- Binding IgG Ab to FVIII (n=2,1)	0	1		
Screening- Binding IgM Ab to FVIII (n=2,1)	0	0		
Screening- Binding IgG Ab to PEG-FVIII (n=2,1)	0	1		
Screening- Binding IgM Ab to PEG-FVIII (n=2,1)	0	0		
Screening- Binding IgG Ab to PEG (n=2,1)	0	1		
Screening- Binding IgM Ab to PEG (n=2,1)	0	0		
First Infusion- Binding IgG Ab to FVIII (n=2,2)	2	0		
First Infusion- Binding IgM Ab to FVIII (n=2,2)	0	0		
First Infusion- Binding IgG Ab to PEG-FVIII(n=2,2)	2	1		
First Infusion- Binding IgM Ab to PEG-FVIII(n=2,2)	0	0		
First Infusion- Binding IgG Ab to PEG (n=2,2)	0	0		
First Infusion- Binding IgM Ab to PEG (n=2,2)	0	0		
Visit 1(Week 2) - Binding IgG Ab to FVIII (n=4,3)	2	1		
Visit 1(Week 2) - Binding IgM Ab to FVIII (n=4,3)	0	0		
Visit 1 (Week 2)-Binding IgGAb to PEG-FVIII(n=4,3)	0	2		
Visit 1 (Week 2)-Binding IgMAb to PEG-FVIII(n=4,3)	0	0		
Visit 1 (Week 2) - Binding IgG Ab to PEG (n=4,3)	0	2		

Visit 1 (Week 2) - Binding IgM Ab to PEG (n=4,3)	0	0		
Visit 2 (Week 4) - Binding IgG Ab to FVIII (n=4,3)	1	1		
Visit 2 (Week 4) - Binding IgM Ab to FVIII (n=4,3)	0	0		
Visit 2 (Week 4)-Binding IgGAb to PEG-FVIII(n=4,3)	1	1		
Visit 2 (Week 4)-Binding IgMAb to PEG-FVIII(n=4,3)	0	0		
Visit 2 (Week 4) - Binding IgG Ab to PEG (n=4,3)	0	0		
Visit 2 (Week 4) - Binding IgM Ab to PEG (n=4,3)	0	0		
FU Month 1- Binding IgG Ab to FVIII (n=2,2)	1	0		
FU Month 1- Binding IgM Ab to FVIII (n=2,2)	0	0		
FU Month 1- Binding IgG Ab to PEG-FVIII (n=2,2)	0	0		
FU Month 1- Binding IgM Ab to PEG-FVIII (n=2,2)	0	0		
FU Month 1- Binding IgG Ab to PEG (n=2,2)	0	0		
FU Month 1- Binding IgM Ab to PEG (n=2,2)	0	0		
FU Month 2- Binding IgG Ab to FVIII (n=4,2)	1	0		
FU Month 2- Binding IgM Ab to FVIII (n=4,2)	0	0		
FU Month 2- Binding IgG Ab to PEG-FVIII (n=4,2)	0	0		
FU Month 2- Binding IgM Ab to PEG-FVIII (n=4,2)	0	0		
FU Month 2- Binding IgG Ab to PEG (n=4,2)	0	0		
FU Month 2- Binding IgM Ab to PEG (n=4,2)	0	0		
FU Month 3- Binding IgG Ab to FVIII (n=4,2)	0	0		
FU Month 3- Binding IgM Ab to FVIII (n=4,2)	0	0		
FU Month 3- Binding IgG Ab to PEG-FVIII (n=4,2)	1	0		
FU Month 3- Binding IgM Ab to PEG-FVIII (n=4,2)	0	0		
FU Month 3- Binding IgG Ab to PEG (n=4,2)	0	0		
FU Month 3- Binding IgM Ab to PEG (n=4,2)	0	0		
FU Month 4- Binding IgG Ab to FVIII (n=3,2)	0	0		
FU Month 4-Binding IgM Ab to FVIII (n=3,2)	0	0		
FU Month 4- Binding IgG Ab to PEG-FVIII (n=3,2)	0	0		
FU Month 4- Binding IgM Ab to PEG-FVIII (n=3,2)	0	0		
FU Month 5- Binding IgG Ab to FVIII (n=3,2)	1	0		
FU Month 5- Binding IgM Ab to FVIII (n=3,2)	0	0		

FU Month 5- Binding IgG Ab to PEG-FVIII (n=3,2)	0	0		
FU Month 5- Binding IgM Ab to PEG-FVIII (n=3,2)	0	0		
FU Month 5- Binding IgG Ab to PEG (n=3,2)	0	0		
FU Month 5- Binding IgM Ab to PEG (n=3,2)	0	0		
FU Month 6- Binding IgG Ab to FVIII (n=4,2)	0	0		
FU Month 6- Binding IgM Ab to FVIII (n=4,2)	0	0		
FU Month 6- Binding IgG Ab to PEG-FVIII (n=4,2)	0	0		
FU Month 6- Binding IgM Ab to PEG-FVIII (n=4,2)	0	0		
FU Month 6- Binding IgG Ab to PEG (n=4,2)	0	0		
FU Month 6- Binding IgM Ab to PEG (n=4,2)	0	0		
FU Month 7-Binding IgG Ab to FVIII (n=3,2)	0	0		
FU Month 7-Binding IgM Ab to FVIII (n=3,2)	0	0		
FU Month 7-Binding IgG Ab to PEG-FVIII (n=3,2)	0	0		
FU Month 7-Binding IgM Ab to PEG-FVIII (n=3,2)	0	0		
FU Month 7-Binding IgG Ab to PEG (n=3,2)	0	0		
FU Month 7-Binding IgM Ab to PEG (n=3,2)	0	0		
FU Month 8-Binding IgG Ab to FVIII (n=3,1)	0	0		
FU Month 8-Binding IgM Ab to FVIII (n=3,1)	0	0		
FU Month 8-Binding IgG Ab to PEG-FVIII (n=3,1)	0	0		
FU Month 8-Binding IgM Ab to PEG-FVIII (n=3,1)	0	0		
FU Month 8-Binding IgG Ab to PEG (n=3,1)	0	0		
FU Month 8-Binding IgM Ab to PEG (n=3,1)	0	0		
FU Month 9-Binding IgG Ab to FVIII (n=2,1)	0	0		
FU Month 9-Binding IgM Ab to FVIII (n=2,1)	0	0		
FU Month 9-Binding IgG Ab to PEG-FVIII (n=2,1)	0	0		
FU Month 9-Binding IgM Ab to PEG-FVIII (n=2,1)	0	0		
FU Month 9-Binding IgG Ab to PEG (n=2,1)	0	0		
FU Month 9-Binding IgM Ab to PEG (n=2,1)	0	0		
FU Month 10- Binding IgG Ab to FVIII (n=1,1)	0	0		
FU Month 10- Binding IgM Ab to FVIII (n=1,1)	0	0		
FU Month 10- Binding IgG Ab to PEG-FVIII (n=1,1)	0	0		

FU Month 10- Binding IgM Ab to PEG-FVIII (n=1,1)	0	0		
FU Month 10- Binding IgG Ab to PEG (n=1,1)	0	0		
FU Month 10- Binding IgM Ab to PEG (n=1,1)	0	0		
FU Month 11- Binding IgG Ab to FVIII (n=4,1)	0	0		
FU Month 11- Binding IgM Ab to FVIII (n=4,1)	0	0		
FU Month 11- Binding IgG Ab to PEG-FVIII (n=4,1)	0	0		
FU Month 11- Binding IgM Ab to PEG-FVIII (n=4,1)	0	0		
FU Month 11- Binding IgG Ab to PEG (n=4,1)	0	0		
FU Month 11- Binding IgM Ab to PEG (n=4,1)	0	0		
FU Month 12- Binding IgG Ab to FVIII (n=4,1)	0	0		
FU Month 12- Binding IgM Ab to FVIII (n=4,1)	0	0		
FU Month 12- Binding IgG Ab to PEG-FVIII (n=4,1)	0	0		
FU Month 12- Binding IgM Ab to PEG-FVIII (n=4,1)	0	0		
FU Month 12- Binding IgG Ab to PEG (n=4,1)	0	0		
FU Month 12- Binding IgM Ab to PEG (n=4,1)	0	0		
FU Month 13- Binding IgG Ab to FVIII (n=2,1)	0	0		
FU Month 13- Binding IgM Ab to FVIII (n=2,1)	0	0		
FU Month 13- Binding IgG Ab to PEG-FVIII (n=2,1)	0	0		
FU Month 13- Binding IgM Ab to PEG-FVIII (n=2,1)	0	0		
FU Month 13- Binding IgG Ab to PEG (n=2,1)	0	0		
FU Month 13- Binding IgM Ab to PEG (n=2,1)	0	0		
FU Month 14- Binding IgG Ab to FVIII (n=1,1)	0	0		
FU Month 14- Binding IgM Ab to FVIII (n=1,1)	0	0		
FU Month 14- Binding IgG Ab to PEG-FVIII (n=1,1)	0	0		
FU Month 14- Binding IgM Ab to PEG-FVIII (n=1,1)	0	0		
FU Month 14- Binding IgG Ab to PEG (n=1,1)	0	0		
FU Month 14- Binding IgM Ab to PEG (n=1,1)	0	0		
FU Month 15- Binding IgG Ab to FVIII (n=1,1)	0	0		
FU Month 15- Binding IgM Ab to FVIII (n=1,1)	0	0		
FU Month 15- Binding IgG Ab to PEG-FVIII (n=1,1)	0	0		
FU Month 15- Binding IgM Ab to PEG-FVIII (n=1,1)	0	0		

FU Month 15- Binding IgG Ab to PEG (n=1,1)	0	0		
FU Month 15- Binding IgM Ab to PEG (n=1,1)	0	0		
FU Month 16- Binding IgG Ab to FVIII (n=1,1)	0	0		
FU Month 16- Binding IgM Ab to FVIII (n=1,1)	0	0		
FU Month 16- Binding IgG Ab to PEG-FVIII (n=1,1)	0	0		
FU Month 16- Binding IgM Ab to PEG-FVIII (n=1,1)	0	0		
FU Month 16- Binding IgG Ab to PEG (n=1,1)	0	0		
FU Month 16- Binding IgM Ab to PEG (n=1,1)	0	0		
FU Month 17- Binding IgG Ab to FVIII (n=1,1)	0	0		
FU Month 17- Binding IgM Ab to FVIII (n=1,1)	0	0		
FU Month 17- Binding IgG Ab to PEG-FVIII (n=1,1)	0	0		
FU Month 17- Binding IgM Ab to PEG-FVIII (n=1,1)	0	0		
FU Month 17- Binding IgG Ab to PEG (n=1,1)	0	0		
FU Month 17- Binding IgM Ab to PEG (n=1,1)	0	0		
FU Month 18- Binding IgG Ab to FVIII (n=1,1)	0	0		
FU Month 18- Binding IgM Ab to FVIII (n=1,1)	0	0		
FU Month 18- Binding IgG Ab to PEG-FVIII (n=1,1)	0	0		
FU Month 18- Binding IgM Ab to PEG-FVIII (n=1,1)	0	0		
FU Month 18- Binding IgG Ab to PEG (n=1,1)	0	0		
FU Month 18- Binding IgM Ab to PEG (n=1,1)	0	0		
FU Month 19- Binding IgG Ab to FVIII (n=1,0)	0	0		
FU Month 19- Binding IgM Ab to FVIII (n=1,0)	0	0		
FU Month 19- Binding IgG Ab to PEG-FVIII (n=1,0)	0	0		
FU Month 19- Binding IgM Ab to PEG-FVIII (n=1,0)	0	0		
FU Month 19- Binding IgG Ab to PEG (n=1,0)	0	0		
FU Month 19- Binding IgM Ab to PEG (n=1,0)	0	0		
FVIII Inhibitor TC- Binding IgG Ab to FVIII(n=0,0)	0	0		
FVIII Inhibitor TC- Binding IgM Ab to FVIII(n=0,0)	0	0		
FVIII InhibitorTC-Binding IgGAb toPEG-FVIII(n=0,0)	0	0		
FVIII InhibitorTC-Binding IgMAb toPEG-FVIII(n=0,0)	0	0		
FVIII Inhibitor TC- Binding IgG Ab to PEG (n=0,0)	0	0		

FVIII Inhibitor TC- Binding IgM Ab to PEG (n=0,0)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 9 years

Adverse event reporting additional description:

SAS and IAS is used. Participant that received on-demand treatment 1st and then moved to prophylaxis treatment was counted for both on-demand and prophylaxis regimens. Participant that started with prophylaxis treatment was counted only for the prophylaxis regimen even if participant received on-demand treatment while on the prophylaxis regimen.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Part A: Main Study: On-demand

Reporting group description:

Participants age <3 years and who had not experienced two joint bleeds received on-demand treatment of 10-80IU/kg of BAX 855 IV depending on the severity of the bleeding episode.

Reporting group title	Part B: ITI Portion (100-200 IU/kg Daily Regimen)

Reporting group description:

Participants received prophylaxis treatment of 100-200 IU/kg BAX 855 IV daily.

Reporting group title	Part B: ITI Portion (50 IU/kg Three Times Weekly Regimen)

Reporting group description:

Participants received prophylaxis treatment of 50 IU/kg BAX 855 IV three times in a week.

Reporting group title	Part A: Main Study: Prophylaxis

Reporting group description:

Participants age <3 years or after a maximum of two joint bleeds received prophylaxis treatment with dose of 25-80 IU/kg of BAX 855 IV (based on investigator discretion) once weekly for up to 100 EDs.

Serious adverse events	Part A: Main Study: On-demand	Part B: ITI Portion (100-200 IU/kg Daily Regimen)	Part B: ITI Portion (50 IU/kg Three Times Weekly Regimen)
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 80 (22.50%)	3 / 3 (100.00%)	1 / 4 (25.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 80 (1.25%)	0 / 3 (0.00%)	0 / 4 (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
Haemorrhage			

subjects affected / exposed	1 / 80 (1.25%)	0 / 3 (0.00%)	0 / 4 (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
General disorders and administration site conditions			
Vascular device occlusion			
subjects affected / exposed	0 / 80 (0.00%)	1 / 3 (33.33%)	0 / 4 (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
Pyrexia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 3 (33.33%)	0 / 4 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Pharyngeal haemorrhage			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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			
Accidental exposure to product			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Extradural haematoma			

subjects affected / exposed	1 / 80 (1.25%)	0 / 3 (0.00%)	0 / 4 (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
Head injury			
subjects affected / exposed	1 / 80 (1.25%)	0 / 3 (0.00%)	0 / 4 (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
Lip injury			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Mouth injury			
subjects affected / exposed	1 / 80 (1.25%)	0 / 3 (0.00%)	0 / 4 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Road traffic accident			
subjects affected / exposed	1 / 80 (1.25%)	0 / 3 (0.00%)	0 / 4 (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
Skin laceration			
subjects affected / exposed	1 / 80 (1.25%)	0 / 3 (0.00%)	0 / 4 (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
Subcutaneous haematoma			
subjects affected / exposed	1 / 80 (1.25%)	0 / 3 (0.00%)	0 / 4 (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
Tongue injury			

subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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			
Febrile convulsion			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Blood and lymphatic system disorders			
Immune thrombocytopenia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Factor VIII inhibition			
subjects affected / exposed	5 / 80 (6.25%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	4 / 5	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Strabismus			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Gastrointestinal disorders			
Intussusception			

subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Tongue haemorrhage			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Mouth haemorrhage			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingival bleeding			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 80 (1.25%)	0 / 3 (0.00%)	0 / 4 (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
Gastritis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Tongue ulceration			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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			
Nail bed bleeding			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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			

Arthralgia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Haemarthrosis			
subjects affected / exposed	5 / 80 (6.25%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle haemorrhage			
subjects affected / exposed	2 / 80 (2.50%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma muscle			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 80 (0.00%)	1 / 3 (33.33%)	0 / 4 (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
Bronchitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Cellulitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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 influenzal			
subjects affected / exposed	1 / 80 (1.25%)	0 / 3 (0.00%)	0 / 4 (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
Device related sepsis			

subjects affected / exposed	0 / 80 (0.00%)	1 / 3 (33.33%)	0 / 4 (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
Croup infectious			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Gastroenteritis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Pharyngitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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
Systemic viral infection			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	0 / 4 (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 / 80 (0.00%)	1 / 3 (33.33%)	0 / 4 (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
Vascular device infection			
subjects affected / exposed	0 / 80 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part A: Main Study: Prophylaxis		
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 112 (31.25%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Vascular device occlusion			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	4 / 112 (3.57%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngeal haemorrhage				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Irritability				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Accidental exposure to product				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Extradural haematoma				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lip injury				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mouth injury				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Post procedural haemorrhage				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin laceration				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subcutaneous haematoma				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tongue injury				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Tachycardia				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Febrile convulsion				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Blood and lymphatic system disorders			
Immune thrombocytopenia			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Factor VIII inhibition			
subjects affected / exposed	6 / 112 (5.36%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Strabismus			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intussusception			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tongue haemorrhage			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mouth haemorrhage			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gingival bleeding			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tongue ulceration				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Nail bed bleeding				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemarthrosis				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscle haemorrhage				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematoma muscle				
subjects affected / exposed	3 / 112 (2.68%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia influenzal			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Croup infectious			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			

subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Systemic viral infection				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular device infection				
subjects affected / exposed	0 / 112 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Part A: Main Study: On-demand	Part B: ITI Portion (100-200 IU/kg Daily Regimen)	Part B: ITI Portion (50 IU/kg Three Times Weekly Regimen)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 80 (58.75%)	2 / 3 (66.67%)	4 / 4 (100.00%)
Investigations			
Bacillus test positive			
subjects affected / exposed	0 / 80 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Injury, poisoning and procedural complications			
Skin wound			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Head injury			
subjects affected / exposed	1 / 80 (1.25%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	5 / 80 (6.25%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	5	0	0
Anaemia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	17 / 80 (21.25%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	36	2	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 80 (6.25%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	6	0	1
Constipation			
subjects affected / exposed	3 / 80 (3.75%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	3	1	1
Oral discomfort			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	5 / 80 (6.25%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	6	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 80 (8.75%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	7	1	0
Rhinorrhoea			

subjects affected / exposed	4 / 80 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	6	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	3 / 80 (3.75%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	3	1	0
Dermatitis allergic			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 80 (7.50%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	10	0	2
Otitis media			
subjects affected / exposed	5 / 80 (6.25%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	8	0	0
Gastroenteritis			
subjects affected / exposed	3 / 80 (3.75%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Influenza			
subjects affected / exposed	3 / 80 (3.75%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Ear infection			
subjects affected / exposed	4 / 80 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	8	0	0
COVID-19			
subjects affected / exposed	1 / 80 (1.25%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Pharyngitis			

subjects affected / exposed	1 / 80 (1.25%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	5 / 80 (6.25%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	5	0	0
Viral infection			
subjects affected / exposed	3 / 80 (3.75%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	4	0	1
Scarlet fever			
subjects affected / exposed	0 / 80 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Vessel puncture site cellulitis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vascular device infection			
subjects affected / exposed	0 / 80 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	12 / 80 (15.00%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	15	0	3

Non-serious adverse events	Part A: Main Study: Prophylaxis		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 112 (68.75%)		
Investigations			
Bacillus test positive			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Skin wound			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences (all)	0		
Head injury			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences (all)	3		
Blood and lymphatic system disorders			

Iron deficiency anaemia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	6 / 112 (5.36%) 6 2 / 112 (1.79%) 2		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	31 / 112 (27.68%) 54		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Oral discomfort subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	9 / 112 (8.04%) 9 2 / 112 (1.79%) 2 0 / 112 (0.00%) 0 6 / 112 (5.36%) 7		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	16 / 112 (14.29%) 28 7 / 112 (6.25%) 11		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash	0 / 112 (0.00%) 0		

subjects affected / exposed	3 / 112 (2.68%)		
occurrences (all)	4		
Dermatitis allergic			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 112 (16.07%)		
occurrences (all)	27		
Otitis media			
subjects affected / exposed	7 / 112 (6.25%)		
occurrences (all)	8		
Gastroenteritis			
subjects affected / exposed	7 / 112 (6.25%)		
occurrences (all)	7		
Influenza			
subjects affected / exposed	8 / 112 (7.14%)		
occurrences (all)	8		
Ear infection			
subjects affected / exposed	7 / 112 (6.25%)		
occurrences (all)	13		
COVID-19			
subjects affected / exposed	5 / 112 (4.46%)		
occurrences (all)	5		
Pharyngitis			
subjects affected / exposed	6 / 112 (5.36%)		
occurrences (all)	9		
Rhinitis			
subjects affected / exposed	7 / 112 (6.25%)		
occurrences (all)	12		
Viral infection			

subjects affected / exposed	12 / 112 (10.71%)		
occurrences (all)	16		
Scarlet fever			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences (all)	0		
Vessel puncture site cellulitis			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences (all)	0		
Vascular device infection			
subjects affected / exposed	0 / 112 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	27 / 112 (24.11%)		
occurrences (all)	54		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2015	The following changes were made as per Amendment 3: 1. The definition of high-titer inhibitor was changed from ≥5 BU to 5 BU, to comply with standard definition of high-titer FVIII inhibitor. 2. The use of anti-cluster of differentiation 20 (CD20) chimeric monoclonal antibody rituximab with BAX 855 during ITI/inhibitor treatment was allowed. 3. The definitions of ITI/inhibitor treatment success, partial success, and failure were revised. 4. The inclusion criteria for Part B (ITI/inhibitor treatment) were revised. 5. The duration of Part B was revised. 6. Section on BAX 855 dosing for PK assessment was newly added to provide guidance on half-life determination in Part A but also Part B as half-life constitutes a criterion for ITI/inhibitor treatment success.
08 February 2018	The following changes were made as per Amendment 4: 1. The total number of Advate exposures was limited to 2 EDs total, including prior to enrollment and during the screening period. 2. The ITI/inhibitor treatment failure definition was updated to be conditional on the absence of an infection that could explain a failure of inhibitory titers to decrease, in the opinion of the investigator. 3. Wording was added that unless consent is withdrawn, participants may be contacted by the investigator after the trial completion visit for up to 3 months for supplemental clinical information related to the trial, if needed. 4. Wording was added that any site changes/corrections to participant diary data need to be supported by source documentation.
21 June 2021	The following changes were made as per Amendment 8: 1. The definition of target joint was amended to be consistent with International Society on Thrombosis and Haemostasis (ISTH) 2014 criteria. 2. A new section was added due to the coronavirus disease 2019 (COVID-19) pandemic that added the provision to include remote source document verification (rSDV), if needed, at sites where it was allowed. 3. Optional extension of access sections was added to describe the terms and conditions under which participants who completed the protocol may have continued access to BAX 855.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported