Clinical trial results:
A Phase 3, Multicenter, Single-arm, Open-label Study of the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (BAX 802) in Subjects with Congenital Hemophilia A with Factor VIII Inhibitors Undergoing Surgical or Other Invasive Procedures

Summary

EudraCT number	2015-005521-39
Trial protocol	GB ES NL PL DE NO BG IT
Global end of trial date	22 January 2021

Results information

Result version number	v1 (current)
This version publication date	28 August 2021
First version publication date	28 August 2021

Trial information

Trial identification

Sponsor protocol code	241502

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02895945
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
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)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 January 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 January 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the perioperative hemostatic efficacy of BAX 802 in male subjects with congenital hemophilia A (CHA) with inhibitors to human factor VIII (hFVIII) undergoing major or minor elective surgical, dental, or other invasive procedures as determined by the Global Hemostatic Efficacy Assessment (GHEA) score.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in compliance with all applicable industry regulations, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 (1996), European Union (EU) Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 2016
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	Italy: 2
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Turkey: 3
Worldwide total number of subjects	8
EEA total number of subjects	5

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 5 sites in Italy, Netherlands, Poland, Germany and Turkey. Study was initiated on 22 December 2016 and terminated on 22 January 2021.

Pre-assignment

Screening details:

A total of 14 subjects were screened, 5 subjects were screen failures, and 2 subjects did not receive treatment. 1 subject was re-screened and enrolled in the study. 8 subjects were grouped into 2 cohorts (Major Surgeries and Minor Surgeries), and received recombinant porcine factor VIII (rpFVIII) (BAX 802).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Major Surgeries

Arm description:

Male subjects with congenital hemophilia A (CHA) with inhibitors to human factor VIII (hFVIII) undergone major surgical invasive procedures initially received loading dose BAX 802 infusion, intravenously to maintain a minimum target factor VIII (FVIII) level of greater than or equal to (>=) 80 percent (%) approximately 1 to 2 hours prior to the surgery. Subsequent dosing was based on subject's FVIII activity levels, body weight and investigator's clinical judgement.

Arm type	Experimental
Investigational medicinal product name	Recombinant Porcine Factor VIII (rpFVIII)
Investigational medicinal product code	BAX 802
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subject received loading dose BAX 802 infusion, intravenously to maintain a minimum target FVIII level of >=80% approximately 1 hour prior to the surgery, and subsequent dosing was based on subject's FVIII activity levels, body weight and investigator's clinical judgement.

Arm title	Minor Surgeries

Arm description:

Male subjects with CHA with inhibitors to hFVIII undergone minor surgical invasive procedures initially received loading dose BAX 802 infusion, intravenously to maintain a minimum target FVIII level of >=50% approximately 1 to 2 hours prior to the surgery. Subsequent dosing was based on subject's FVIII activity levels, body weight and investigator's clinical judgement.

Arm type	Experimental
Investigational medicinal product name	rpFVIII
Investigational medicinal product code	BAX 802
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subject received loading dose BAX 802 infusion, intravenously to maintain a minimum target FVIII level of >=50% approximately 1 hour prior to the surgery. Subsequent dosing was based on subject's FVIII activity levels, body weight and investigator's clinical judgement.

Number of subjects in period 1	Major Surgeries	Minor Surgeries
Started	7	1
SAS	7	1
FAS	7	0
Completed	5	0
Not completed	2	1
Physician decision	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Major Surgeries
Reporting group description:	
Male subjects with congenital hemophilia A (CHA) with inhibitors to human factor VIII (hFVIII) undergone major surgical invasive procedures initially received loading dose BAX 802 infusion, intravenously to maintain a minimum target factor VIII (FVIII) level of greater than or equal to (>=) 80 percent (%) approximately 1 to 2 hours prior to the surgery. Subsequent dosing was based on subject's FVIII activity levels, body weight and investigator's clinical judgement.	
Reporting group title	Minor Surgeries
Reporting group description:	
Male subjects with CHA with inhibitors to hFVIII undergone minor surgical invasive procedures initially received loading dose BAX 802 infusion, intravenously to maintain a minimum target FVIII level of >=50% approximately 1 to 2 hours prior to the surgery. Subsequent dosing was based on subject's FVIII activity levels, body weight and investigator's clinical judgement.	

Reporting group values	Major Surgeries	Minor Surgeries	Total
Number of subjects	7	1	8
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	1	8
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Here "99999" refers to data not available and we have added it as space-fillers.			
Units: years			
arithmetic mean	35.9	58.0	
standard deviation	± 14.39	± 99999	-
Sex: Female, Male Units: Subjects			
Female	0	0	0
Male	7	1	8
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	7	1	8
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	0	0	0
White	6	1	7
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Major Surgeries

Reporting group description:

Male subjects with congenital hemophilia A (CHA) with inhibitors to human factor VIII (hFVIII) undergone major surgical invasive procedures initially received loading dose BAX 802 infusion, intravenously to maintain a minimum target factor VIII (FVIII) level of greater than or equal to (>=) 80 percent (%) approximately 1 to 2 hours prior to the surgery. Subsequent dosing was based on subject's FVIII activity levels, body weight and investigator's clinical judgement.

Reporting group title	Minor Surgeries

Reporting group description:

Male subjects with CHA with inhibitors to hFVIII undergone minor surgical invasive procedures initially received loading dose BAX 802 infusion, intravenously to maintain a minimum target FVIII level of >=50% approximately 1 to 2 hours prior to the surgery. Subsequent dosing was based on subject's FVIII activity levels, body weight and investigator's clinical judgement.

Primary: Percentage of Surgeries With a "Good" or "Excellent" Response as Measured by the Global Hemostatic Efficacy Assessment (GHEA) Score

End point title	Percentage of Surgeries With a "Good" or "Excellent" Response as Measured by the Global Hemostatic Efficacy Assessment (GHEA) Score[1]

End point description:

GHEA score consisted of 3 individual rating scales: (1) Intra-operative Efficacy Assessment Scale, (2) Post-operative Efficacy Assessment Scale, and (3) Overall Peri-operative Efficacy Assessment Scale. Scales 1 and 2 was performed by the operating surgeon on Day 1, and Scale 3 was performed by the investigator on Day 14. Each rating scale was based on 4 points scale ranging from: 3 (Excellent), 2 (Good), 1 (Fair), and 0 (None). Total score ranged from 0 to 9, where scores evaluated as: excellent (7 to 9), good (5 to 7), fair (3 to 4), and none (0 to 2). The scores of 3 individual ratings scales were added together to form a GHEA score. For a GHEA score of 7 to be rated "excellent" with no individual assessment scores less than (<) 2 and at least 1 assessment score equal to (=) 3; otherwise a score of 7 was rated "good". Full analysis set (FAS) comprised of all subjects with at least one available hemostatic assessment.

End point type	Primary

End point timeframe:

Day 1 up to discharge or Day 14 (whichever was earlier)

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 data was planned to be analyzed for this endpoint.

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	0[2]		
Units: percentage of surgeries				
number (not applicable)				
GHEA rating: Good	14.3			
GHEA rating: Excellent	71.4			

Notes:

[2] - "Subjects analysed" were subjects who were evaluable for the end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Blood Loss, Estimated Volume of Expected Average Blood Loss and Expected Maximum Blood Loss During Intra-operative, Post-operative and Peri-operative Period

End point title	Actual Blood Loss, Estimated Volume of Expected Average Blood Loss and Expected Maximum Blood Loss During Intra-operative, Post-operative and Peri-operative Period

End point description:

The surgeon/investigator predicted and compared the estimated volume (in millilitre [mL]) of the expected average blood loss and expected maximum blood loss for the planned surgical intervention in a comparable healthy individual with similar demographic characteristics; for intraoperative, postoperative, and overall perioperative time periods. Intra-operative defined as period from start of surgery to completion of surgical procedure. Post-operative defined as period from completion of surgical procedure till 24 hours post-surgery. Peri-operative defined as period from start of surgical procedure till discharge or 14 days post surgery (whichever was earlier). Actual blood loss, estimated volume of expected average blood loss and expected maximum blood loss during each operative period was reported. FAS comprised of all subjects with at least one available hemostatic assessment. Here subjects analysed "n" were subjects who were evaluable for the end point at given categories.

End point type	Secondary

End point timeframe:

Intra-operative: up to completion of surgery (Day 1), Post-operative: at 24 hours post-surgery, and Peri-operative: at discharge or Day 14 (whichever was earlier)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	0[3]		
Units: milliliter (mL)				
arithmetic mean (standard deviation)				
Intra-operative:Actual Blood Loss(n = 7, 0)	141.1 (± 188.69)	()		
Intra-operative:Expected Average Blood Loss(n=7,0)	221.7 (± 286.76)	()		
Intra-operative:Expected Maximum Blood Loss(n=7,0)	414.7 (± 546.37)	()		
Post-operative:Actual Blood Loss(n=5,0)	31.0 (± 66.56)	()		
Post-operative:Expected Average Blood Loss(n=7,0)	171.4 (± 276.17)	()		
Post-operative:Expected Maximum Blood Loss(n=7,0)	378.0 (± 570.94)	()		
Peri-operative:Actual Blood Loss(n=7,0)	164.1 (± 215.15)	()		
Peri-operative:Expected Average Blood Loss(n=7,0)	465.0 (± 744.85)	()		
Peri-operative:Expected Maximum Blood Loss(n=7,0)	842.9 (± 1310.01)	()		

Notes:

[3] - "Subjects analysed" were subjects who were evaluable for the end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio of Actual Blood Loss and Estimated Volume of Expected Average Blood Loss During Intra-operative, Post-operative and Peri-operative Period

End point title	Ratio of Actual Blood Loss and Estimated Volume of Expected Average Blood Loss During Intra-operative, Post-operative and Peri-operative Period

End point description:

Prior to the surgery, the surgeon/investigator predicted and compared the estimated volume (mL) of the expected average blood loss and expected maximum blood loss for the planned surgical intervention in a comparable healthy individual with similar demographic characteristics; for intraoperative, postoperative, and overall perioperative time periods. Intra-operative defined as period from start of surgery to completion of surgical procedure. Post-operative defined as period from completion of surgical procedure till 24 hours post-surgery. Peri-operative defined as period from start of surgical procedure till discharge or 14 days post surgery (whichever was earlier). Ratio of actual blood loss and estimated volume of expected average blood loss during each operative period was reported. FAS comprised of all subjects with at least one available hemostatic assessment. Here subjects analysed "n" were subjects who were evaluable for the end point at given categories.

End point type	Secondary

End point timeframe:

Intra-operative: up to completion of surgery (Day 1), Post-operative: at 24 hours post-surgery, and Peri-operative: at discharge or Day 14 (whichever was earlier)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	0[4]		
Units: ratio				
arithmetic mean (standard deviation)				
Intra-operative Period (n = 7, 0)	0.970 (± 0.9486)	()		
Post-operative Period (n = 5, 0)	0.150 (± 0.2236)	()		
Peri-operative Period (n = 7, 0)	0.545 (± 0.3448)	()		

Notes:

[4] - “Subjects analysed” were subjects who were evaluable for the end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio of Actual Blood Loss and Expected Maximum Blood Loss During Intra-operative, Post-operative and Peri-operative Period

End point title	Ratio of Actual Blood Loss and Expected Maximum Blood Loss During Intra-operative, Post-operative and Peri-operative Period

End point description:

The surgeon/investigator predicted and compared the estimated volume (mL) of the expected average blood loss and expected maximum blood loss for the planned surgical intervention in a comparable healthy individual with similar demographic characteristics; for intraoperative, postoperative, and overall perioperative time periods. Intra-operative defined as period from start of surgery to completion of surgical procedure. Post-operative defined as period from completion of surgical procedure till 24 hours post-surgery. Peri-operative defined as period from start of surgical procedure till discharge or 14 days post surgery (whichever was earlier). Ratio of actual blood loss and expected maximum blood loss during each operative period was reported. FAS comprised of all subjects with at least one available hemostatic assessment. Here subjects analysed "n" were subjects who were evaluable for the end point at given categories.

End point type	Secondary

End point timeframe:

Intra-operative: up to completion of surgery (Day 1), Post-operative: at 24 hours post-surgery, and Peri-operative: at discharge or Day 14 (whichever was earlier)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	0[5]		
Units: ratio				
arithmetic mean (standard deviation)				
Intra-operative Period (n = 7, 0)	0.555 (± 0.6517)	()		
Post-operative Period (n = 5, 0)	0.058 (± 0.0846)	()		
Peri-operative Period (n = 7, 0)	0.306 (± 0.1962)	()		

Notes:

[5] - "Subjects analysed" were subjects who were evaluable for the end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Average Daily Weight-adjusted Dose of BAX 802 per Subject During Pre-operative, Intra-operative and Post-operative Period

End point title	Average Daily Weight-adjusted Dose of BAX 802 per Subject During Pre-operative, Intra-operative and Post-operative Period

End point description:

Body-weight adjusted dose equals to amount infused/body-weight (kilogram [kg]), where amount infused as amount of drug infused (International Units [IU]) and body-weight as the last available body-weight (kg) prior to the infusion. Pre-operative defined as period prior to surgery. Intra-operative defined as period from start of surgery to completion of surgical procedure. Post-operative defined as period from completion of surgical procedure till discharge or 14 days post surgery (whichever was earlier). Average daily weight-adjusted dose of BAX 802 per subject during each operative period was reported. SAS comprised of all subjects who received any amount of BAX 802. Here subjects analysed "n" were subjects who were evaluable for the end point at given categories. Here "99999" refers to data not available and we have added it as space-fillers.

End point type	Secondary

End point timeframe:

Pre-operative: before surgery, Intra-operative: up to completion of surgery (Day 1), Post-operative: from completion of surgical procedure till discharge or 14 days post surgery (whichever was earlier)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: International Units per kilogram (IU/kg)				
arithmetic mean (standard deviation)				

Pre-operative (n = 7, 1)	162.471 (± 125.7051)	208.779 (± 99999)		
Intra-operative (n = 6, 0)	76.083 (± 35.1339)	99999 (± 99999)		
Post-operative (n = 7, 0)	43.549 (± 56.0039)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Major Surgeries With Good or Excellent Hemostatic Score

End point title	Percentage of Major Surgeries With Good or Excellent Hemostatic Score[6]

End point description:

Percentage of major surgeries with good or excellent hemostatic score was analyzed by GHEA score. It consisted of 3 individual ratings: (1) Intra-operative Efficacy Assessment Scale, (2) Post-operative Efficacy Assessment Scale, (3) Overall Peri-operative Efficacy Assessment Scale. Ratings 1 and 2 was performed by the operating surgeon on Day 1, and Rating 3 was performed by the investigator on Day 14. Each rating scale was based on 4 point scale ranging from: 3 (Excellent), 2 (Good), 1 (Fair), and 0 (None). The scores of each of the 3 individual ratings scales, was added together to form a GHEA score. Total score ranged from 0 to 9. Hemostatic efficacy success was defined as "excellent" or "good "outcome for >=70% of hemostatic efficacy assessments. Percentage of major surgeries with good or excellent hemostatic score were reported. FAS comprised of all subjects with at least one available hemostatic assessment. As planned, this end point was only analysed for major surgeries.

End point type	Secondary

End point timeframe:

Day 1 up to discharge or Day 14 (whichever was earlier)

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: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Major Surgeries			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percentage of surgeries				
number (confidence interval 95%)	85.7 (42.1 to 99.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Weight-adjusted Dose of BAX 802 per Subject During Pre-operative, Intra-operative and Post-operative Period

End point title	Total Weight-adjusted Dose of BAX 802 per Subject During Pre-operative, Intra-operative and Post-operative Period

End point description:

Body-weight adjusted dose equals to amount infused/body-weight (kg), where amount infused as amount of drug infused (IU) and body-weight as the last available body-weight (kg) prior to the

infusion. Pre-operative defined as period prior to surgery. Intra-operative defined as period from start of surgery to completion of surgical procedure. Post-operative defined as period from completion of surgical procedure till discharge or 14 days post surgery (whichever was earlier). Total weight-adjusted dose of BAX 802 per subject during each operative period was reported. SAS comprised of all subjects who received any amount of BAX 802. Here subjects analysed "n" were subjects who were evaluable for the end point at given categories. Here "99999" refers to data not available and we have added it as space-fillers.

End point type	Secondary

End point timeframe:

Pre-operative: before surgery, Intra-operative: up to completion of surgery (Day 1), Post-operative: from completion of surgical procedure till discharge or 14 days post surgery (whichever was earlier)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: IU/kg				
arithmetic mean (standard deviation)				
Pre-operative (n = 7, 1)	162.471 (± 125.7051)	208.779 (± 99999)		
Intra-operative (n = 6, 0)	76.083 (± 35.1339)	99999 (± 99999)		
Post-operative (n = 7, 0)	625.520 (± 399.4913)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Blood Products Transfused

End point title	Volume of Blood Products Transfused

End point description:

The volume (in mL) of blood products transfused from initiation of the intervention to discharge or Day 14 (whichever came earlier) was reported. FAS comprised of all subjects with at least one available hemostatic assessment. Here “subjects analysed” were subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

From initiation of the surgery up to discharge or Day 14 (whichever came earlier)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	0[7]		
Units: mL				
arithmetic mean (standard deviation)	950.0 (± 70.71)	()		

Notes:

[7] - "Subjects analysed" were subjects who were evaluable for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With De Novo Inhibitors

End point title	Number of Subjects With De Novo Inhibitors

End point description:

De novo inhibitor was defined as a post-baseline inhibitor titer to FVIII (hFVIII or porcine factor VIII [pFVIII])of >=0.6 Bethesda units per milliliter (BU/mL) given a baseline of <0.6 BU/mL. Number of subjects with de novo inhibitors were reported. SAS comprised of all subjects who received any amount of BAX 802.

End point type	Secondary

End point timeframe:

Baseline up to end of study (EOS) (up to 44 months)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: Subjects				
hFVIII	0	0		
pFVIII	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Anamnestic Reactions

End point title	Number of Subjects With Anamnestic Reactions

End point description:

An anamnestic reaction was defined as an increase from a measurable baseline (>0.6 BU/mL) in the inhibitor titer to FVIII (human or porcine) of >=10 BU/mL. Number of subjects with anamnestic reactions were reported. SAS comprised of all subjects who received any amount of BAX 802.

End point type	Secondary

End point timeframe:

Baseline up to EOS (up to 44 months)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: Subjects				
hFVIII	5	0		
pFVIII	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline up to EOS in Inhibitory and Binding Antibodies to pFVIII

End point title	Mean Change From Baseline up to EOS in Inhibitory and Binding Antibodies to pFVIII

End point description:

The assessment of inhibitory antibodies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) to pFVIII was determined using Bethesda assay, and assessment of binding antibodies (IgG and IgM) to pFVIII was determined using validated enzyme-linked immunosorbent assays (ELISAs). Mean change from baseline in inhibitory and binding antibodies to pFVIII was reported. SAS comprised of all subjects who received any amount of BAX 802. Here "subjects analysed" were subjects who were evaluable for the end point. Here "99999" refers to data not available and we have added it as space-fillers.

End point type	Secondary

End point timeframe:

Baseline up to EOS (up to 44 months)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	1		
Units: BU/mL				
arithmetic mean (standard deviation)	111.15 (± 149.072)	-0.20 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline up to EOS in Inhibitory and Binding Antibodies to hFVIII

End point title	Mean Change From Baseline up to EOS in Inhibitory and Binding Antibodies to hFVIII

End point description:

The assessment of inhibitory antibodies (IgG and IgM) to hFVIII was determined using Bethesda assay, and assessment of binding antibodies (IgG and IgM) to hFVIII was determined using ELISA. Mean change from baseline in inhibitory and binding antibodies to hFVIII was reported. SAS comprised of all subjects who received any amount of BAX 802. Here "subjects analysed" were subjects who were

evaluable for the end point. Here "99999" refers to data not available and we have added it as space-fillers.

End point type	Secondary

End point timeframe:

Baseline up to EOS (up to 44 months)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	1		
Units: BU/mL				
arithmetic mean (standard deviation)	198.67 (± 317.254)	-0.20 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Change From Baseline in Binding Antibodies to Baby Hamster Kidney (BHK) Proteins

End point title	Number of Subjects With Clinically Significant Change From Baseline in Binding Antibodies to Baby Hamster Kidney (BHK) Proteins

End point description:

The assessment of binding antibodies to BHK proteins was determined using ELISA. Clinical significance was judged by the investigator. Number of subjects with clinically significant change from baseline in binding antibodies to BHK proteins were reported.

End point type	Secondary

End point timeframe:

Baseline up to EOS (up to 44 months)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Severe Allergic Reactions

End point title	Number of Subjects With Severe Allergic Reactions

End point description:

Number of subjects with severe allergic reaction (example: anaphylaxis) after administration of study drug were reported. SAS comprised of all subjects who received any amount of BAX 802.

End point type	Secondary

End point timeframe:

Baseline up to EOS (up to 44 months)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Thromboembolic Events

End point title	Number of Subjects With Thromboembolic Events

End point description:

Thromboembolism defined as formation in a blood vessel of a clot (thrombus) that breaks loose and carried by the blood stream to plug another vessel. Number of subjects with thromboembolic events was reported. SAS comprised of all subjects who received any amount of BAX 802.

End point type	Secondary

End point timeframe:

Baseline up to EOS (up to 44 months)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Investigational Product (IP) Related Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Number of Subjects With Investigational Product (IP) Related Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs

End point description:

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. Serious AE was any untoward medical occurrence (whether considered to be related to study assigned treatment or not) that at any dose resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, resulted in a congenital abnormality/birth defect, or was an important medical event. TEAEs was defined as any adverse events (classified by preferred term) that had a start date on or after the first dose of study treatment or that had a start date before the date of first dose of study treatment, but increased in severity after the first dose of study treatment. TEAEs included both serious and non-serious TEAEs. SAS comprised of all subjects who received any amount of BAX 802.

End point type	Secondary

End point timeframe:

Baseline up to EOS (up to 44 months)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: Subjects				
IP related TEAEs	4	0		
IP related serious TEAEs	4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Change From Baseline in Vital Sign

End point title	Number of Subjects With Clinically Significant Change From Baseline in Vital Sign

End point description:

Vital sign parameters included: temperature, pulse rate, respiration rate, systolic and diastolic blood pressure. Any changes in vital signs which were deemed clinically significant was judged by the investigator. Number of subjects with clinically significant change from baseline in vital signs were reported. SAS comprised of all subjects who received any amount of BAX 802.

End point type	Secondary

End point timeframe:

Baseline up to EOS (up to 44 months)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Change From Baseline in Clinical Laboratory Values

End point title	Number of Subjects With Clinically Significant Change From Baseline in Clinical Laboratory Values

End point description:

Clinical laboratory assessment included hematology and clinical chemistry. Any changes in clinical laboratory results which were deemed clinically significant was judged by the investigator. Number of subjects with clinical significant change from baseline in clinical laboratory values were reported. SAS comprised of all subjects who received any amount of BAX 802.

End point type	Secondary

End point timeframe:

Baseline up to EOS (up to 44 months)

End point values	Major Surgeries	Minor Surgeries		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	1		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up EOS (up to 44 months)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Major Surgeries
Reporting group description:	
Male subjects with CHA with inhibitors to hFVIII undergone major surgical invasive procedures initially received loading dose BAX802 infusion, intravenously to maintain a minimum target FVIII level of >=80% approximately 1 hour prior to the surgery. Subsequent dosing was based on subject's FVIII activity levels and investigator's clinical judgement.	
Reporting group title	Minor Surgeries
Reporting group description:	
Male subjects with CHA with inhibitors to hFVIII undergone minor surgical invasive procedures initially received loading dose BAX802 infusion, intravenously to maintain a minimum target FVIII level of >=50% approximately 1 hour prior to the surgery. Subsequent dosing was based on subject's FVIII activity levels and investigator's clinical judgement.	

Serious adverse events	Major Surgeries	Minor Surgeries	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	0 / 1 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Anti factor VIII antibody positive			
subjects affected / exposed	3 / 7 (42.86%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anti factor VIII antibody increased			
subjects affected / exposed	2 / 7 (28.57%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anamnestic reaction			

subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Major Surgeries	Minor Surgeries	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	0 / 1 (0.00%)	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	3	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Skin irritation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Oral herpes			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 February 2016	Protocol Amendment 01: Study design and sample size calculation updated to ensure sufficient evidence is gathered regarding safety and effectiveness for BAX 802 in this indication. The time point Day 14 was amended to "Day 14 or discharge (whichever is earlier)", to ensure that the efficacy data was captured at the appropriate time. Clarity was added regarding the "overall perioperative" time point, to ensure that efficacy data was captured at the appropriate time. The overall study design was updated to remove the requirement for subjects who may need to undergo more than 1 surgery or 2 parallel surgeries. Primary outcome measure was updated to make the distinction between blood loss due to surgery and unrelated blood loss.
22 August 2016	Protocol Amendment 02: Inclusion criteria #1 was amended to specify only male subjects will be enrolled for consistency within the protocol.
07 February 2017	Protocol Amendment 03: "Exclusion criteria" was changed to "non-inclusion criteria" throughout, as per MoH request. Inclusion criterion #1 was revised to specify that only make subjects were to be enrolled. Inclusion criteria #3 was revised to specify entry criteria by inhibitor level.
28 June 2017	Protocol Amendment 04: The formulae to calculate the loading dose of IP for minor and major surgeries was revised to include the body-weight of the subject. More suitable statistical, clinical terminology and expected enrollment revised. The primary outcome measures were updated with the addition of pre-specified success criteria, revised assessment times, and specification individuals making the assessment. Updated secondary objectives to align with endpoints. Updated clinical trial conduct information. The study design was updated to reflect the new sample size (12 procedures in 12 evaluable subjects). Updated planned duration of subject participation, study duration and expected completion date.
08 August 2017	Protocol Amendment 05: Inclusion criterion #4 was updated to include "or medical history of high titer inhibitors (>=5 BU).
14 December 2017	Protocol Amendment 06: The initiation of the trial and the total planned duration of the trial were updated.
09 February 2018	Protocol Amendment 07: The initiation of the trial and the total planned duration of the trial was updated. The units for the BAX 802 loading dose and anti-pFVIII inhibitor titers were added, for greater clarity.
19 October 2018	Protocol Amendment 08: The definition of Study Complete was added, at the request of the Norwegian Health Authority.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study was discontinued as Takeda determined that the benefit/risk profile did not support continuation of the surgery study for this specific Congenital Hemophilia A with Inhibitors subject population.

Notes: