



ORIGINAL ARTICLE

Efficacy and safety of a recombinant factor IX (Bax326)^a in previously treated patients with severe or moderately severe haemophilia B undergoing surgical or other invasive procedures: a prospective, open-label, uncontrolled, multicentre, phase III study

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Summary. Haemostatic management of haemophilia B patients undergoing surgery is critical to patient safety. The aim of this ongoing prospective trial was to investigate the haemostatic efficacy and safety of a recombinant factor IX (rFIX) (Bax326)^a in previously treated subjects (12–65 years, without history of FIX inhibitors) with severe or moderately severe haemophilia B, undergoing surgical, dental or other invasive procedures. Haemostatic efficacy was assessed according to a predefined scale. Blood loss was compared to the average and maximum blood loss predicted preoperatively. Haemostatic FIX levels were achieved peri- and postoperatively in 100% of subjects ($n = 14$). Haemostasis was ‘excellent’ intraoperatively in all patients and postoperatively in those without a drain, and ‘excellent’ or ‘good’ at the time of drain removal and day of discharge in those with a drain

employed. Following the initial dose, the mean FIX activity level rose from 6.55% to 107.58% for major surgeries and from 3.60% to 81.4% for minor surgeries. Actual vs. predicted blood loss matched predicted intraoperative blood loss but was equal to or higher than (but less than 150%) the maximum predicted postoperative blood loss reflecting the severity of procedure and FIX requirements. There were no related adverse events, severe allergic reactions or thrombotic events. There was no evidence that BAX326 increased the risk of inhibitor or binding antibody development to FIX. BAX326 was safe and effective for peri-operative management of 14 subjects with severe and moderately severe haemophilia B.

Keywords: haemophilia B, previously treated patients, rFIX (Rixubis), surgical procedures

Introduction

Haemophilia B is an X-linked congenital bleeding disorder caused by an abnormality in the coagulation factor IX (FIX) gene and characterized by a malfunction of the coagulation system generally resulting in

uncontrolled internal haemorrhages, severe haemarthroses and arthropathies [1,2]. The benefit of recombinant replacement factor products, which are inherently free of blood-borne pathogens, allowing maintenance of satisfactory plasma levels of FIX is well documented for treatment of haemophilia B patients [3,4].

A recombinant factor IX (rFIX) Bax326 (Rixubis[®]; Baxter Healthcare Corporation, Westlake Village, CA, USA), which is comparable in structural and functional characteristics to endogenous FIX has recently been developed for prevention and control of bleeding in haemophilia B patients [5,6]. To reduce the risk of transmission of adventitious agents, BAX326 is manufactured using pathogen-free sources and two virus

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removal procedures – solvent/detergent treatment (ensuring clearance of enveloped viruses) and nanofiltration (providing a removal capacity for small non-enveloped viruses and prions) [7–9].

Due to an increased life expectancy, haemophilia patients are confronted with age-related comorbidity requiring elective or emergency surgical procedures. While coagulation factor replacement is essential in surgical intervention in haemophilia patients, limited clinical data are available on the efficacy of recombinant coagulation factors for surgical haemostasis in patients with haemophilia B, likely due to the rarity of the disease [10].

The purpose of this study was to evaluate the haemostatic efficacy and safety of Bax326 in previously treated patients (PTPs) 12–65 years old with severe (FIX level < 1%) or moderately severe (FIX level ≤ 2%) haemophilia B undergoing surgery.

Materials and methods

Study design

This prospective, controlled, multicentre study was conducted to assess the haemostatic efficacy and safety of Bax326 in PTPs with severe (FIX level < 1%) or moderately severe (FIX level ≤ 2%) haemophilia B undergoing major or minor elective or emergency surgical, dental or other invasive procedures.

The study (conducted in accordance with the Declaration of Helsinki) was initiated on 11 December 2011, was approved by local independent ethics committees for sites in four countries in Europe and is currently ongoing. All patients provided informed consent prior to enrolment. The study is registered on clinicaltrials.gov under the number NCT01507896.

The study was designed in two segments: preoperative procedures and intra/postoperative regimens. Preoperatively, a loading dose with Bax326 was administered to raise the plasma FIX level to 80–100% of normal for major surgical procedures and 30–60% for minor surgical procedures [11,12]. The required dose/units (by bolus infusion) was calculated by body weight (kg) × desired factor IX rise (%) (IU dL⁻¹) × {reciprocal of observed recovery} using the subject's most recently determined incremental recovery (IR). For major surgeries, the subject's individual half-life determined prior to surgery was also considered. The surgery started after obtaining the required FIX level and after normalizing the activated partial thromboplastin time (aPTT).

After the Bax326 loading doses, the treatment regimen was determined by the surgery type, intensity and duration of the haemostatic challenge, consistent with the standards of care for surgical management of haemophilia B patients [13–16]. To determine the adequacy of FIX replacement, blood samples drawn

pre- and post-BAX326 infusions were collected once every 24 h for measurement of plasma FIX activity and aPTT.

For major surgeries FIX levels were not to fall below 80–100% of normal until wound healing was achieved. Once adequate wound healing was achieved, FIX trough levels were maintained in a range of 30–60% of normal for 7–14 days. For minor surgeries FIX levels were not to fall below 30–60% of normal for at least a day, depending on the nature and location of the intervention.

Any modifications in the treatment regimen over the course of the peri- and postoperative period to maintain haemostatically sufficient FIX plasma levels were at the discretion of the investigator. Mechanical thrombosis prophylaxis (e.g. intermittent pneumatic compression, compression stockings and early mobilization) was permitted at the discretion of the investigator. Pharmacologic thrombosis prophylaxis (e.g. low-molecular-weight heparin) could be considered for certain surgical interventions, such as major orthopaedic surgery, only after careful evaluation of the potential risks and benefits.

Haemostatic efficacy and safety of Bax326 in the peri- and postoperative setting were the primary study objectives. The secondary objectives included assessments of intra- and postoperative haemostatic efficacy and at the time of discharge; actual intra- and postoperative blood loss at the end of surgery and until drain removal, if applicable, compared to the average and maximum blood loss as predicted preoperatively; BAX326 consumption and blood product use; and safety evaluation of product-related AEs, inhibitory and binding antibodies to FIX and thrombotic events.

Patient population

Subjects aged 12–65 years with severe or moderately severe haemophilia B, who had received treatment with Bax326 in a parent (pivotal or continuation) study and required emergency or elective major or minor surgical, dental or other invasive procedures were eligible for inclusion in the present surgery study. Newly entering subjects were eligible for elective major surgery.

Haemostatic efficacy

Prior to the surgery, the estimated volume of the average and maximum blood loss for the planned surgical intervention was predicted by the surgeons as for a haemostatically normal individual of the same sex, age and stature as the study subject for both the intraoperative procedure and the postoperative period until drain removal (if used). The use of tourniquets and suction or the placement of a postoperative drain had to be taken into account. The total amount of intraoperative blood loss consisted of the drainage volume

and the estimated blood loss into swabs and towels during the procedure. The total amount of postoperative blood loss consists of the drainage fluid.

The haemostatic efficacy of Bax326 was assessed intra- and postoperatively and on the day of discharge, according to criteria shown in Table 1.

Study subjects were also monitored for the occurrence of bleeding episodes during the entire intra- and postoperative period. Subjects with excessive bleeds were tested for plasma FIX activity, and inhibitory and binding anti-FIX antibodies.

Presurgical pharmacokinetic assessments

Presurgical pharmacokinetics were only assessed in subjects ≥ 12 years of age undergoing major elective surgery who did not undergo a pharmacokinetic assessment in the previous study and for newly entering subjects requiring major surgery. The following parameters were assessed: $AUC_{0-72\text{ h}}$ per dose (area under the plasma concentration vs. time curve from 0 to 72 h post infusion), $AUC_{0-\infty}$ per dose (area under the plasma concentration vs. time curve from time 0 to infinity), MRT (mean residence time), CL (clearance), IR (incremental recovery) at 30 min post infusion, $T_{1/2}$ (elimination phase half-life) and V_{ss} (volume of distribution at steady state).

Safety assessments

Safety was evaluated through clinical assessments of thrombotic and other adverse events (AEs), and the

occurrence of total binding and inhibitory antibodies to FIX. Samples for inhibitory and total binding antibodies to FIX were taken at screening (at least 72 h after the last dose of FIX product); on the day of discharge from the investigative site (7–16 days post surgery), or if the subject had excessive, unexplained bleeding at any time intra- or postoperatively. The presence of total binding antibodies was determined with an enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human Ig antibodies (IgG, IgM and IgA) as described by Whelan *et al.* [17] and adapted for detection of anti-FIX antibodies.

Only bleeding episodes that were unrelated to haemophilia were to be reported as AEs. Therefore, any haemophilia-related event [e.g. haemarthrosis (presenting as swelling, pain and decreased range of motion), bruising, haemorrhages, or pain at bleeding episode site] was not reported as AEs. Investigators, however, may have determined the event to be an AE if the event would also have occurred in a normal patient under the same circumstances.

Statistical analysis

The sample size was not based on statistical considerations and was determined by the number of subjects participating in previous Bax326 studies (pivotal, continuation and paediatric studies) who were undergoing surgery. The interim analysis presented here was planned after a minimum of 10 major surgeries in 10 unique subjects. The data snapshot was performed in accordance with regulatory requirements [18].

Table 1. Rating scale for intra- and postoperative efficacy assessment criteria.

Rating	Criteria
<i>Intraoperative efficacy*</i>	
Excellent	Intraoperative blood loss was less than or equal to that expected for the type of procedure performed ($\leq 100\%$)
Good	Intraoperative blood loss was up to 50% more than expected for the type of procedure performed (101–150%)
Fair	Intraoperative blood loss was more than 50% of that expected for the type of procedure performed ($>150\%$)
None	Uncontrolled haemorrhage that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of FIX concentrate
<i>Postoperative efficacy†</i>	
Excellent	Volume in drain was less than or equal than that expected for the type of procedure performed ($\leq 100\%$)
Good	Volume in drain was up to 50% more than expected for the type of procedure performed (101–150%)
Fair	Volume in drain was more than 50% of that expected for the type of procedure performed ($>150\%$)
None	Uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of FIX concentrate
<i>Postoperative efficacy assessment 72 h postoperatively‡</i>	
Excellent	Postoperative haemostasis achieved with BAX326 was as good or better than that expected for the type of surgical procedure performed in a haemostatically normal subject
Good	Postoperative haemostasis achieved with BAX326 was probably as good as that expected for the type of surgical procedure performed in a haemostatically normal subject
Fair	Postoperative haemostasis with BAX326 was clearly less than optimal for the type of procedure performed but was maintained without the need to change the FIX concentrate
None	Subject experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of FIX concentrate

*Reflects the blood loss as compared to the expected amount of blood loss estimated preoperatively for the type of procedure in a haemostatically normal individual.

†Reflects the volume in drain as compared to the volume estimated preoperatively for the type of procedure performed in a haemostatically normal individual.

‡Rating scale used to assess (approximately 72 h postoperatively) the postoperative haemostatic efficacy of BAX326 in major surgeries where no drain was employed.

The intra- and postoperative haemostatic efficacy assessment was summarized by percentage of subjects in each efficacy category ('excellent', 'good', 'fair' and 'none'). Actual intra- and postoperative blood loss, if applicable, and the difference from the expected average and maximum blood loss were summarized using descriptive statistics.

The average daily and total weight-adjusted dose of BAX326 per subject as well as the units and amount of blood product transfused were presented descriptively.

PK parameters were calculated by non-compartmental methods and were summarized using descriptive statistics.

The occurrence of product-related AEs and thrombotic events were evaluated descriptively.

Results

Patients

Baseline characteristics of the 14 enrolled and treated subjects are shown in Table 2. Thirteen of 14 subjects had been treated in the previous Bax326 study [5].

A total of 11/14 major surgeries performed included seven orthopaedic (residual femur fracture nail removal, $n = 1$; joint replacement, $n = 5$; open synovectomy, $n = 1$), two abdominal (hernioplastic), one dental surgery (third molar extraction) and one excision of neurofibroma. The 3/14 minor surgeries included two dental surgeries (first molar extraction) and one intraarticular injection.

The mean study duration was 42.5 (27.3) days (range: 4–93 days). Among subjects who underwent

Table 2. Demographic and baseline characteristics.

Parameter	Category	Subjects $N = 14$ n (%)
Gender	Male	14 (100.0)
	Female	0 (0.0)
Age	≥ 16 years	14 (100.0)
Race	White	14 (100.0)
Ethnicity	Not hispanic or latino	5 (35.7)
	Not reported	9 (64.3)
FIX activity level (%)	$<1\%$	11 (78.6)
	1–2%	3 (21.4)
FIX antigen level (%)	$<1\%$	6 (42.9)
	$\geq 1\%$	8 (57.1)
	1–2%	2 (14.3)
	<2 –5%	1 (7.1)
	$\geq 40\%$	5 (35.7)
Arthropathy at screening	Yes	14 (100.0)
Surgery type	Major*	11 (78.6)
	Minor†	3 (21.4)
	Orthopaedic	7 (50.0)
	Non-orthopaedic	7 (50.0)

*Of the 11 major surgeries: 7 were orthopaedic (1 residual femur fracture nail removal, 5 joint replacements, 1 open synovectomy); and 4 were non-orthopaedic: 1 dental (3rd molar extraction), 2 abdominal (hernioplastic); 1 neurofibroma excision).

†Three minor surgeries: two dental (1st molar extraction); one intraarticular injection.

Table 3. Pre- and postinfusion factor IX activity levels (%) by surgery type.

Period	Time point	Statistic	Major $N = 11$	Minor $N = 3$	Orthopaedic $N = 7$	Non-orthopaedic $N = 7$	All $N = 14$
Preoperative day of surgery	Pre-rFIX infusion	Mean (std)	6.55 (6.56)	3.60 (2.10)	6.26 (6.76)	5.59 (5.53)	5.92 (5.94)
		Median (min; max)	3.40 (0.5; 16.9)	4.50 (1.2; 5.1)	3.40 (0.5; 16.9)	4.50 (0.5; 16.2)	3.95 (0.5; 16.9)
Post operative day of surgery	Post-rFIX infusion	Mean (std)	107.58 (21.29)	81.43 (33.11)	116.70 (14.50)	87.26 (25.95)	101.98 (25.32)
		Median (min; max)	108.70 (65.1; 136.0)	79.20 (49.5; 115.6)	118.00 (97.6; 136.0)	83.00 (49.5; 120.9)	106.20 (49.5; 136.0)
Postoperative day 1	Pre-rFIX infusion*	Mean (std)	55.30 (18.07)	24.10 (16.00)	59.81 (19.45)	37.41 (18.45)	48.61 (21.61)
		Median (min; max)	49.90 (34.1; 89.5)	24.10 (8.1; 40.1)	56.50 (39.8; 89.5)	39.40 (8.1; 66.2)	44.00 (8.1; 89.5)
	Post-rFIX infusion	Mean (std)	129.28 (35.77)	80.20 (27.31)	142.27 (26.94)	95.26 (36.22)	118.76 (39.19)
		Median (min; max)	139.20 (79.3; 176.2)	71.50 (58.3; 110.8)	148.70 (89.9; 176.2)	87.20 (58.3; 168.5)	122.20 (58.3; 176.2)
Postoperative day 2	Pre-rFIX infusion*	Mean (std)	54.47 (22.16)	24.70 (10.89)	57.17 (20.94)	41.40 (24.89)	49.89 (23.33)
		Median (min; max)	51.90 (27.1; 91.3)	24.70 (17.0; 32.4)	55.60 (34.3; 91.3)	32.90 (17.0; 86.6)	40.20 (17.0; 91.3)
	Post-rFIX infusion	Mean (std)	128.54 (35.36)	77.00 (30.26)	144.20 (20.66)	93.08 (37.18)	120.61 (38.64)
		Median (min; max)	129.10 (65.5; 172.0)	77.00 (55.6; 98.4)	138.70 (119.1; 172.0)	86.70 (55.6; 158.1)	128.40 (55.6; 172.0)
Postoperative day 3	Pre-rFIX infusion*	Mean (std)	57.93 (22.96)	22.00 (8.49)	60.63 (22.44)	42.80 (26.37)	52.40 (25.04)
		Median (min; max)	58.80 (28.5; 88.2)	22.00 (16.0; 28.0)	70.90 (28.5; 84.4)	32.90 (16.0; 88.2)	43.90 (16.0; 88.2)
	Post-rFIX infusion	Mean (std)	125.65 (34.23)	80.15 (21.14)	143.41 (17.49)	89.75 (30.09)	118.65 (36.13)
		Median (min; max)	130.10 (57.5; 164.3)	80.15 (65.2; 95.1)	146.30 (113.5; 164.3)	83.10 (57.5; 129.9)	129.90 (57.5; 164.3)

*Recommended preinfusion target plasma FIX levels during the postoperative period are to be 80–100% until adequate wound healing and 30–60% for the subsequent 7 days. Actual mean preinfusion FIX levels were lower than the recommended range.

major surgery, study duration ranged from 16 to 93 days. For the three subjects who underwent minor surgery, study duration was 4, 10 and 28 days respectively. None of the subjects discontinued the study before or after treatment.

The mean weight-adjusted dose administered was 1265 (range: 415–2965) IU kg⁻¹ for major surgery ($n = 11$) and 291 (range: 55–601) for minor surgery ($n = 3$).

Haemostatic efficacy

On the day of surgery, the mean FIX activity level for major surgeries was raised from 6.6% preoperatively to 107.6% after the initial loading dose. On the first three postoperative days, the mean preinfusion FIX levels were below the recommended preinfusion levels of 80–100%. For minor surgeries, the mean FIX activity level was raised from 3.6% to 81.4% following the initial loading dose. The mean preinfusion FIX level on the first postoperative day for minor surgeries did not change substantially on the two following days (Table 3).

The mean intraoperative blood loss was 236.8 mL. As expected, blood loss was higher in major than in minor surgeries (mean of 300.9 vs. 1.7 mL) and was highest in orthopaedic surgeries (460.0 mL) (Table 4). The actual blood loss during major surgery largely matched the predicted blood loss: 6/11 major surgeries matched the average predicted blood loss, 2/11 matched the maximum predicted blood loss, and 1/11 was below the average predicted and maximum predicted blood loss. For all three minor surgeries, actual intraoperative blood loss was below the average predicted blood loss.

The mean postoperative blood loss for all major surgeries ($n = 7$) was 784.4 mL, and 913.3 mL in orthopaedic surgeries ($n = 6/7$; mean), which was higher than the overall mean postoperative blood loss. Actual blood loss was always less than 150%, and equal to or below the predicted maximum in 3/7 major surgeries, met the maximum predicted blood loss in 2/7 and was between the average predicted and

maximum predicted blood loss in 1/7 surgery. In 4/7 major surgeries the actual postoperative blood loss exceeded the maximum predicted blood loss but was always less than 150%. Detailed analyses showed that this was either associated with low postoperative FIX levels (34.3–40% in a subject with a joint replacement and 40–56% in a subject with a total hip replacement) or with the use of drain which was originally not considered. Intraoperative haemostatic efficacy was 'excellent' for all 14 surgeries (Table 5).

Four subjects who all underwent major orthopaedic surgery received blood product transfusions (packed red blood cells or/and fresh frozen plasma). The mean volume transfused was 725.3 mL during the intraoperative period (range: 520–1225 mL) and 575 mL during the postoperative period.

Pharmacokinetic parameters

PK parameters were available for a total of 13/14 subjects – six subjects had PK parameters assessed in a previous study and seven subjects (of whom six underwent major and one underwent minor surgery) were assessed in the present surgery study. Analysis of pre-surgical pharmacokinetic parameters for seven subjects resulted in the following mean (SD) values: half-life ($T_{1/2}$) was 21.50 ± 4.98 h, incremental recovery (IR 30 min) 1.06 ± 0.35 IU dL⁻¹: IU kg⁻¹; and AUC_{0–72 h} per dose 19.77 ± 7.88 IU h dL⁻¹: IU kg⁻¹.

Safety

None of the 14 subjects included in the interim analysis who received Bax326 for peri-operative management experienced SAEs, severe allergic reactions or thrombotic events. No patients received any mechanical or pharmacological thrombosis prophylaxis during the study. There were no treatment-related positive total binding antibodies or inhibitors to FIX observed.

Fourteen non-serious AEs unrelated to treatment with BAX326 (8 mild, 6 moderate) were reported for six (42.9%) subjects: postoperative pain ($n = 3$), pyrexia ($n = 2$), anaemia ($n = 1$), thrombocytosis ($n = 1$), postoperative anaemia ($n = 1$), postoperative

Table 4. Intraoperative and postoperative actual blood loss vs. difference to predicted maximum.

Parameter	Statistic	All	Major	Minor	Orthopaedic	Non-orthopaedic
Intraoperative	N	14	11	3	7	7
Predicted max blood loss (mL)	Mean (std)	379.6 (466.2)	480.5 (480.0)	10.0 (8.7)	728.6 (430.9)	30.7 (34.1)
Actual blood loss (mL)	Mean (std)	236.8 (341.8)	300.9 (361.6)	1.7 (1.5)	460 (369.5)	13.6 (17.4)
Difference from predicted maximum blood loss (mL)*	Mean (std)	142.9 (204)	179.5 (217.2)	8.3 (7.6)	268.6 (230)	17.1 (20)
Postoperative	N	7	7	–	6	1
Actual blood loss (mL)	Mean (std)	784.4 (420.7)	784.4 (420.7)	–	913 (269.8)	11.0 (NA)
Predicted max blood loss (mL)	Mean (std)	715.9 (358.9)	715.9 (358.9)	–	833.3 (196.6)	11.0 (NA)
Difference from predicted maximum blood loss (mL)*	Mean (std)	–68.6 (129.2)	–68.6 (129.2)	–	–80.0 (137.5)	0

*Predicted maximum blood loss minus actual blood loss.

Table 5. Haemostatic efficacy rating by surgeon/investigator.

Efficacy category	Major surgeries				All surgeries			
	Intraoperative	Drain removal*	Postoperative day 3†	Discharge from hospital	Intraoperative	Drain removal*	Postoperative day 3†	Discharge from hospital
	N = 11 n (%)	N = 7 n (%)	N = 4 n (%)	N = 11 n (%)	N = 14 n (%)	N = 7 n (%)	N = 6 n (%)	N = 14 n (%)
Excellent	11 (100)	3 (42.9)	4 (100)	8 (72.7)	14 (100)	3 (42.9)	6 (100)	11 (78.6)
Good	0 (0)	4 (57.1)	0 (0)	3 (27.3)	0 (0)	4 (57.1)	0 (0)	3 (21.4)
Fair	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
None	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

*At time of removal, if drain was used.

†At postoperative day 3 where no drain was used.

haematoma ($n = 1$), postoperative swelling ($n = 1$), arthropathy ($n = 1$), ALT increase ($n = 1$), headache ($n = 1$) and hypertension ($n = 1$). No bleeding complications were reported during the study.

Discussion

The implementation of factor concentrate therapy has largely contributed to the prolongation of life expectancy of haemophilia patients [19]. Consequently, in addition to the haemophilia-related complications, age-related morbidities requiring frequent surgical interventions have become more common [10,20]. Thus, there is an increased demand to consider reliable control over coagulation factor IX levels and effective treatment of haemophilia B patients in high-risk surgical settings.

This was the first prospective study with the recently approved rFIX Bax326 (Rixubis®, Baxter)^a in a surgical setting of PTPs (12–65 years) with haemophilia B. The study examined the haemostatic efficacy and safety of Bax326 in subjects undergoing major or minor elective or emergency surgical, dental or other invasive procedures. Bax326 was shown to be effective for peri-operative management of subjects with severe (FIX level <1%, $n = 11$) and moderately severe (FIX level 1–2%, $n = 3$) haemophilia B. Haemostasis achieved in the intraoperative period was rated as ‘excellent’ in all 14 subjects (100%). Also, postoperatively, all surgeries had a rating of either ‘excellent’ or ‘good’.

In general, the efficacy results of this study are consistent with those reported in other studies evaluating recombinant coagulation factor treatment for peri-operative management of major or minor orthopaedic, dental and general surgeries in individuals with haemophilia B. [14] Patients experienced a maximum intraoperative blood loss of 1100 mL with Bax326 in the current study vs. 1500 mL with a marketed comparator. Postoperatively, the maximum blood loss was 1270 mL with Bax326 vs. 2676 mL with a comparator rFIX. However, considering the difference in the types of surgeries, the blood loss observed during peri-operative treatment with either of the two products is considered comparable. Analogous studies testing a marketed recombinant replacement factor in haemophilia B PTPs who underwent surgical procedures (such as dental, orthopaedic, toenail removals, cyst excisions) have shown that the estimated blood loss was similar to those in individuals without a coagulation disorder [3,4]. In our study, the estimated intraoperative blood loss largely matched the actual blood loss which was, however, higher than (although less than 150%), or equal to the maximum predicted postoperative blood loss mostly reflecting the severity of procedure and related FIX requirements. The four major surgeries with an actual postoperative blood

loss exceeding the maximum predicted blood loss were either associated with low postoperative FIX levels or with the use of drain which was originally not considered. Thus, due to the nature of invasive procedures, a number of variables (e.g. major vs. minor surgeries, low vs. high preinfusion FIX levels, use of tourniquets and drains) have been identified as factors contributing to the higher than predicted postoperative blood loss and should be taken into account when estimating preoperatively the average and maximum intra- and postoperative blood loss.

Surgical studies are of particular importance as they usually document the use of very high dose of recombinant replacement factor products which can result in safety concerns [3]. This study showed that BAX326 was safe and well tolerated in 14 haemophilia B subjects who were treated for peri-operative management. No bleeding complications were observed during the intra- or postoperative period. There were no related adverse events and no severe allergic reactions. To some extent, two key concerns continue to present challenges to the current factor replacement approaches – treatment-related thrombogenicity and formation of inhibitor antibodies against FIX. Thrombosis has been reported following use of plasma derived or rFIX replacement by continuous infusion [10,21,22]. Neither the current nor the previous BAX326 study [5] showed any indication of thrombotic events. Furthermore, although it is important to emphasize that there is very limited risk of inhibitor development in this study (due to the enrolment of PTPs without history of FIX inhibitors), there have been some indications of FIX inhibitors associated with a comparator product: a low-titre, transient inhibitor in one PTP subject ($n = 56$) [4] or in two subjects ($n = 224$) [23] which are consistent with the estimated prevalence (1.5–2%) in haemophilia B patients [24]. Therefore, a crucial element of this study was the evaluation for potential inhibitor formation or treatment-related binding antibodies to FIX following

exposure to BAX326. The study results demonstrate that there was no FIX inhibitor formation or binding antibody development.

Conclusion

In summary, the results indicate that Bax326 is safe and effective for peri-operative management of 14 subjects with severe and moderately severe haemophilia B. No related AEs, no thrombotic events, nor induction of FIX inhibitors or binding antibodies and no severe allergic reactions were observed. Consequently, Bax326 allows for an effective peri-operative haemostatic management in haemophilia B patients.

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Author contributions

BA, HG and SF contributed to study conception and design, JW, TL, OS and VM contributed to study conduction and acquisition of data, BA, WW, SF, BP and MO analysed and interpreted the data, BP, BA and MC wrote the manuscript. All authors reviewed the manuscript and approved the final version.

Disclosures

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