Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2016), **22**, e251–e258 DOI: 10.1111/hae.12963

ORIGINAL ARTICLE *Clinical haemophilia*

Efficacy and safety of pegylated full-length recombinant factor VIII with extended half-life for perioperative haemostasis in haemophilia A patients

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Introduction: BAX 855 is a pegylated full-length recombinant factor VIII (rFVIII) with an extended half-life, built on a licensed rFVIII (ADVATE®). BAX 855 demonstrated efficacy and safety in prophylaxis and the treatment of bleeding episodes in previously treated patients (PTPs) with severe haemophilia A. **Aim:** This phase 3 surgery study evaluates the haemostatic efficacy and safety of BAX 855 for perioperative haemostasis in PTPs with severe haemophilia A undergoing surgery. **Methods:** Elective procedures were prospectively classified as major or minor. The dose and frequency of BAX 855 administered perioperatively were to be guided by each patient's pharmacokinetic profile for major procedures or BAX 855 incremental recovery for minor procedures. Haemostatic efficacy was evaluated using a predefined scale. Blood loss was compared to the expected average and maximum blood loss predicted preoperatively. **Results:** A total of 15 male patients (aged 19–52 years) underwent 15 procedures (11 major and four minor). The overall intra- and perioperative haemostatic efficacy of BAX 855 was 'excellent' in all 15 subjects (100%). Postoperatively, evaluated at postoperative Day 1, all treatments were 'excellent' except for one minor (dental) procedure which was rated 'good'. No related adverse events, allergic reactions, thrombotic events, nor signs of immunogenicity in terms of induction of binding antibodies to FVIII, PEG or PEG-VIII, or FVIII inhibitors were observed. **Conclusion:** These results demonstrate that BAX 855 is safe and haemostatically effective in patients with severe haemophilia A undergoing surgery.

Keywords: extended half-life, haemophilia A, pegylated recombinant factor VIII, perioperative haemostasis

Introduction

Haemophilia A is an X-chromosome-linked recessive, congenital bleeding disorder characterized by deficiency of clotting factor VIII (FVIII) manifested by clinical symptoms such as bleeding in joints, muscles, soft tissues and the central nervous system, as well as haemorrhages and prolonged healing times following trauma and surgery [1,2]. Over the last several decades the life expectancy of haemophilia patients has progressively become similar to that of the general population [3] which has led to an increase in age-related surgical conditions [4,5]. For example, in Italy the median life expectancy of haemophiliacs increased from 62 years between 1990 and 1999 to 71 years during 2000–2007 [6]. Early surgical intervention is also important in young haemophiliacs for slowing disease progression and preventing lasting joint damage [7,8]. Individuals with severe haemophilia A (FVIII <1% of normal) require intensified FVIII replacement during surgery, as well as during the immediate postoperative recovery period until wound healing is complete (>10 days in major surgery) [9,10]. Current FVIII products have a half-life of 10–14 h [11–14], which necessitates frequent infusions also in the postoperative period, particularly during rehabilitation on prophylactic regimens (every 2–3 days) to maintain levels above which spontaneous bleeding is less likely (>1%). A full-length pegylated recombinant FVIII, rurioctacog alfa pegol (BAX 855),

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Accepted after revision 25 March 2016

has been developed based on the manufacturing platform utilized for ADVATE®, a full-length, unmodified rFVIII (Baxalta, Westlake Village, CA, USA) [15]. BAX 855 is expected to combine the efficacy [16,17] and established safety profile [18] of ADVATE® with the prolonged half-life achieved by controlled covalent binding of PEG moieties.

The efficacy and safety of BAX 855 in prophylaxis and treatment of bleeding episodes, and its prolonged FVIII half-life in the circulation by up to 1.5 times compared to ADVATE® have been demonstrated in previous trials [19].

The purpose of this study is to evaluate the haemostatic efficacy and safety of BAX 855 for perioperative haemostasis in previously treated patients (PTPs) with severe haemophilia A.

Materials and methods

Study design

This prospective, open-label, single-arm, uncontrolled, multicentre study was designed to evaluate the efficacy and safety of BAX 855 in male PTPs with severe haemophilia A undergoing major or minor elective surgery; minor emergency surgical, dental or other invasive procedures. Major surgeries were defined as those requiring moderate or deep sedation, general anaesthesia, or major nerve conduction blockade for patient comfort and comprise major orthopaedic (e.g., joint replacement), major abdominal, intracranial, cardiovascular, spinal and any other surgery which has a significant risk of large volume blood loss or blood loss into a confined anatomical space; minor surgeries comprised surgeries which can be safely and comfortably performed on a patient who has received local or topical anaesthesia, without more than minimal preoperative medication or minimal intraoperative sedation [20,21].

Initiated on 20 December 2013, this ongoing study (clinicaltrials.gov, NCT01913405) is being conducted in accordance with the Declaration of Helsinki and was approved by local independent ethics committees for all participating sites. All patients provided informed consent prior to enrolment.

The study was composed of preoperative procedures and intra/postoperative regimens. Based on the category and type of surgery, the investigator outlined the expected FVIII substitution plan with target peak and trough levels covering the perioperative procedure until expected wound healing. A pharmacokinetic study was required for major surgery [22,23]. Preoperatively, a loading dose of BAX 855 was administered to ensure FVIII levels of 80–100% for major surgeries and 30–60% for minor procedures [22,23]. The required dose (IU) was calculated using the formula *body weight (kg) × desired FVIII rise (%) (IU dL^{-1}) × {reciprocal of observed recovery}* using the subject's individual PK parameters for major surgeries and the most recent incremental recovery (IR) value for minor surgeries.[1]

Factor VIII levels and activated partial thromboplastin time (aPTT) were assessed within 30 min prior and 15 ± 5 min after the loading dose, and a re-bolus was administered if needed to raise FVIII to the desired level. The surgery could begin only once aPTT had normalized. For major surgeries, the postoperative preinfusion FVIII levels were to remain at a minimum of 80% for the first 72 h and at least 50% on postoperative Days 4–7. From Day 8 until discharge the FVIII levels were to remain above 30%. For minor surgeries, the postoperative, preinfusion FVIII level was to be kept at 30–60% for the first 24 h or longer as deemed necessary by the investigator. The treatment intervals were tailored in order not to exceed supra-physiological peak FVIII levels of 180%. The dose was to be administered in 1–3 infusions over 24 h, most commonly in two infusions. Adjunct fibrinolytic agents such as tranexamic acid or topical haemostatic agents were permitted.

Mechanical thromboprophylaxis was permitted. Pharmacological thromboprophylaxis could be considered for certain surgical interventions after a risk-benefit evaluation by the investigator.

Perioperative haemostatic efficacy of BAX 855 determined at postoperative Day 14 or at discharge, whichever occurred first, was the primary study objective.

The secondary objectives included intra- and postoperative blood loss compared to the predicted blood loss; volume of blood products transfused; occurrence of unexpected bleeding episodes and additional need for surgical intervention; and BAX 855 consumption per subject. Safety was evaluated in terms of AEs and immunological assessments.

Patient population

Patients aged 2–75 years with severe haemophilia A, who required major or minor elective or minor emergency surgical, dental or other invasive procedures were eligible for inclusion in this study. Eligible subjects were participating in or had completed participation in parent studies [19], or were newly recruited. Enrolment of subjects <12 years of age was limited to those who had received treatment with BAX 855 in a parent (paediatric or continuation) study.

Haemostatic efficacy

The primary haemostatic efficacy outcome measure was assessed using three ratings (Table 1). Prior to surgery, the

[1]If no individual IR is available (e.g. in emergency surgeries), the dose should be based on the empirical finding that one 1 IU of BAX 855 per kg body weight increases the plasma factor VIII level by 2 IU dL^{-1} of plasma.

surgeon estimated the volume of the average and maximum blood loss for the planned surgical intervention as for a haemostatically normal individual of the same sex, age and stature as the subject; the actual intra- and postoperative blood loss volumes were compared to the estimated values. 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 anaesthesiologist's record. Postoperatively, blood loss was determined by the drainage volume collected. Intraoperative and postoperative (on Day 1) haemostatic efficacy were assessed by the surgeon; overall perioperative haemostatic efficacy was evaluated by the investigator at discharge or on postoperative Day 14 (whichever occurred first).

Subjects were also monitored for the occurrence of bleeding episodes, additional need for surgical intervention, transfusion requirements and daily and total weight-adjusted consumption of BAX 855 during the intra- and postoperative period.

Presurgical pharmacokinetic assessments

The following presurgical FVIII PK assessments were performed: IR (within 45 days prior to surgery in subjects undergoing minor surgeries), IR following the initial bolus infusion prior to surgery, area under the plasma concentration vs. time curve from time 0 to infinity ($AUC_{0-\infty}$/dose), area under the plasma concentration vs. time curve from 0 to 96 h ($AUC_{0-96\ h}$/dose), mean residence time (MRT), clearance (CL), elimination phase half-life ($T_{½}$) and volume of distribution at steady state (V_{ss}).

Safety assessments

Safety was evaluated through clinical assessments of the occurrence of thrombotic and other adverse events, incidence of severe allergic reactions, FVIII inhibitors, binding antibodies to FVIII, BAX 855, PEG and host cell [Chinese hamster ovary (CHO)] proteins, and changes in vital signs and clinical laboratory parameters following BAX 855 administration. The presence of FVIII inhibitors was assessed using the Nijmegen modification of the Bethesda assay. Binding antibodies to FVIII, PEG-FVIII, PEG and CHO proteins were measured using an enzyme-linked immunosorbent assay (ELISA) employing polyclonal anti-human Ig antibodies (IgG, IgM and IgA) [24].

Statistical analysis

The sample size of approximately 50 major and minor surgeries or other invasive procedures in approximately 40 subjects to evaluate at least 10 major surgical/invasive procedures in at least five subjects was determined by the number of subjects requiring major or minor procedures, and was not based on statistical

Table 1. Haemostatic efficacy assessment scale.

Rating	Score	Criteria
Intraoperative efficacy assessment scale (assessed at the time of discharge from the OR)		
Excellent	3	Intraoperative blood loss was less than or equal to that expected for the type of procedure performed in a non-haemophilic population (≤100%).
Good	2	Intraoperative blood loss was up to 50% more than expected for the type of procedure performed in a non-haemophilic population (101–150%).
Fair	1	Intraoperative blood loss was more than 50% of that expected for the type of procedure performed in a non-haemophilic population (>150%).
None	0	Uncontrolled haemorrhage that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy
Postoperative efficacy assessment scale (postoperative Day 1)		
Excellent	3	Postoperative blood loss was less than or equal to (≤100%) that expected for the type of procedure performed in a non-haemophilic population.
Good	2	Postoperative blood loss was up to 50% more (101–150%) than expected for the type of procedure performed in a non-haemophilic population.
Fair	1	Postoperative blood loss was more than 50% (>150%) of that expected for the type of procedure performed in a non-haemophilic population.
None	0	Significant postoperative bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy.
Perioperative efficacy assessment scale (discharge visit or Day 14, whichever is first)		
Excellent	3	Perioperative blood loss was less than or equal to (≤100%) that expected for the type of procedure performed in a non-haemophilic population. Required blood components for transfusions were less than or similar to that expected in non-haemophilic population
Good	2	Perioperative blood loss was up to 50% more (101–150%) than expected for the type of procedure performed in a non-haemophilic population. Required blood components for transfusions were less than or similar to that expected in non-haemophilic population
Fair	1	Perioperative blood loss was more than 50% of that expected for the type of procedure performed in a non-haemophilic population (>150%). Required blood components transfusions were greater than that expected in non-haemophilic population
None	0	Significant perioperative bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy. Required blood components for transfusions were substantially greater than that expected in non-haemophilic population.

Table 2. Subject baseline characteristics.

Baseline characteristics	
	Median (min-max)
Age (years)	34 (19–52)
Weight (kg)	68 (48–131.2)
	N (%)
Gender (%)	
Male	17 (100%)
Female	0 (0%)
Race	
White	16 (94.1%)
Asian	1 (5.9%)
Haemophilia severity [*n* (%)]	
Severe (FVIII <1%)	16 (94.1%)
Not severe*	1 (5.9%)
Type of surgery (*N* = 15)	
Major†	11 (73.3%)
Minor‡	4 (26.7%)

*One subject (major surgery, gastric band insertion) had a baseline FVIII level ≥1% (1 U dL^{-1} measured by 1-stage clotting assay, and <3 U dL^{-1}, measured by chromogenic assay). However, the subject had a documented history of severe haemophilia A, which is defined as a FVIII activity level <1%.

†Major surgeries: six orthopaedic procedures (*n* = 3 knee replacements, *n* = 2 arthroscopic synovectomies, *n* = 1 elbow cyst extirpation) and five non-orthopaedic procedures [*n* = 3 dental (multiple tooth extractions including one radicular cyst removal), *n* = 1 cardiovascular (mediport placement), *n* = 1 abdominal (gastric band insertion)].

‡Minor surgeries (*n* = 1 synoviorthesis, *n* = 1 radiosynovectomy, *n* = 1 tooth extraction, *n* = 1 dermatological surgery).

considerations. The interim analysis presented here was planned after a minimum of 10 major surgeries in 10 unique subjects were performed. PK parameters were calculated by non-compartmental methods and were summarized using descriptive statistics.

Results

Patients

A total of 15/17 recruited subjects (aged 19–52 years, median age 34 years) in this interim analysis underwent surgical procedures, including 11 major surgeries (Table 2). Subjects were enrolled from study sites in Bulgaria (1), Lithuania (1), Russia (1), Spain (2), Switzerland (1), UK (1) and USA (4).

Five subjects were previously treated in parent studies [16], and 12 subjects were newly recruited.

Haemostatic efficacy

Perioperative and intraoperative haemostatic efficacy were rated 'excellent' for all 15 surgical procedures (Table 3). The postoperative efficacy of BAX 855 (postoperative Day 1), was rated 'excellent' for 13 procedures. Treatment of one minor surgery was rated 'good' due to oozing from the gums during the night following surgery and another minor surgery was not rated.

The median intraoperative actual blood loss (Table 4) was lower than the predicted average: 10.0 mL vs. 50.0 mL for major surgeries and 2.5 mL vs. 2.5 mL for minor surgeries. The actual maximum intraoperative blood loss of 180 mL for major and 50 mL for minor surgeries was also lower than the predicted maximum of 300 mL for major and 200 mL for minor surgeries.

Postoperative blood loss was reported for five major surgeries up to postoperative Day 1 (arthroscopic synovectomy), Day 2 (two knee replacements), Day 4 (abdominal surgery) and Day 5 (one knee replacement).

The preoperatively estimated blood loss varied widely between study sites and according to the surgery performed with a maximum of 1500 mL for major surgeries. Three subjects who underwent knee replacement had an overall perioperative blood loss in the range 1210–1430 mL, which was lower than predicted. Two subjects undergoing major surgeries received three blood transfusions [packed red blood cells (PRBC)], with a mean volume of 307.7 mL due to low haemoglobin. Another subject, undergoing major abdominal surgery, received two PRBC transfusions of 300 mL each on postoperative Day 2 and 3, experiencing a total blood loss of 305 mL.

No unexpected bleeding episodes were reported and no additional surgical intervention became necessary.

The mean (SD) presurgical FVIII levels following the loading dose were 146.25% (57.67) in those five subjects with available FVIII results. Postoperative mean (SD) FVIII trough levels during major surgery varied between 72.06% (27.66%) (Day 1), 80.72% (25.48%) (Day 2) and 72.57% (30.57%) (Day 3) which was close to the minimum required 80%. From postoperative Day 4–7, the mean (SD) FVIII trough level was in accordance with the required 50% at

Table 3. Haemostatic efficacy ratings.

	Major surgeries (*N* = 11) *n* (%)			All surgeries (*N* = 15) *n* (%)		
Assessment	Intra-operative	Postoperative*	Perioperative	Intraoperative	Postoperative*	Perioperative
Excellent	11 (100)	11 (100)	11 (100.0)	15 (100)	13 (86.7)	15 (100.0)
Good	0 (0)	0 (0)	0 (0.0)	0 (0)	1 (6.7)	0 (0.0)
Fair	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)
Not done	0 (0)	0 (0)	0 (0.0)	0 (0)	1 (6.7)	0 (0.0)

*Postoperative Day 1 (i.e. the day following the day of surgery).

Table 4. Intraoperative and postoperative blood loss.

Parameter	Median (range)		
	All	Major	Minor
Intraoperative	15	11	4
Actual blood loss (mL)	7.5 (0–180)	10 (0–180)	2.5 (0–50)
Predicted average blood loss (mL)	20 (0–200)	50 (0–200)	2.5 (0–200)
Predicted max blood loss (mL)	100 (0–300)	150 (0–300)	2.5 (0–200)
Postoperative (Day 1)	15	11	4
Actual blood loss (mL)	65 (0–1200)	65 (0–1200)	None
Predicted average blood loss (mL)	25 (0–700)	30 (0–700)	0 (0–200)
Predicted max blood loss (mL)	50 (0–1200)	50 (0–1200)	0 (0–200)

52.71% (25.63%), but considerably lower than 30% [10.65% (0.49)] after postoperative Day 7 (Table 5).

Factor VIII trough levels of one subject undergoing knee replacement with a postoperative blood loss at Day 1 of 900 mL and receiving one PRBC were only 34.6%. The dose was subsequently adjusted and FVIII trough levels were within the expected range. Another subject also undergoing knee replacement had FVIII trough levels around 55% up to postoperative Day 4 and experienced a blood loss of 1100 and 100 mL at postoperative Days 1 and 2 respectively. The dose was not adjusted. The third subject undergoing knee replacement with a blood loss of 1200 and 200 mL at postoperative Days 1 and 2 had FVIII trough levels ranging from 30% to 46% without dose adjustments.

The median (range) total weight-adjusted consumption of BAX 855 was 362 IU kg^{-1} (236–863) in major surgeries and 97 IU kg^{-1} (73–119) in minor surgeries. Analyses of the daily weight-adjusted consumption of BAX 855 over the first seven postoperative days demonstrate a decrease in consumption for major surgeries over the treatment period (Fig. 1). Four of the subjects undergoing major surgery (multiple teeth extraction [2], cyst exstirpation elbow [1], gastric band insertion [1]) also received antifibrinolytics or Etamsylate for the perioperative period.

Pharmacokinetic parameters

Pharmacokinetic (PK) parameters were available for 15 subjects (one of the 15 subjects only underwent the PK assessment). The PK assessment for two subjects was performed in a parent study.

Analysis of presurgical PK parameters resulted in the following range values: $T_{1/2}$ was 8.81–18.06 h. A $T_{1/2}$ <10 h (8.81 h) was calculated for one subject who underwent knee replacement. His FVIII trough levels were below target at postoperative Day 3 (62.5%), but increased above target at Day 4 (82.0%). IR at Cmax (all 15 subjects) was 1.48–2.9% IU kg^{-1}; $AUC_{0-\infty}$/dose was 1382.94–4898.75 (IU*h) dL^{-1}, MRT was

Table 5. FVIII levels after preoperative, intra- and postoperative infusions with BAX 855.

Statistic	Pre-Op	Day of surgery	Postoperative				
			Day 1	Day 2	Day 3	Day 4–7	Day >7
Total number of subjects infused							
N	11	9	11	11	11	11	4
Total number of infusions							
N	11	10	18	18	15	46	18
Average number of infusions per subject and day							
Mean	1.0	1.1	1.6	1.6	1.4	1.2	1.0
Weight-adjusted dose(IU kg^{-1}) per infusion							
Mean (SD)	67.49 (18.52)	32.66 (13.95)	39.35 (13.69)	32.28 (14.24)	31.14 (16.64)	29.91 (10.55)	26.58 (11.40)
Median (min–max)	64.63 (35.9–99.2)	30.09 (18.3–54.7)	35.87 (18.3–64.6)	31.04 (9.1–62.8)	24.71 (11.4–62.8)	28.67 (16.4–62.8)	21.51 (13.0–47.1)
Peak FVIII (%) postinfusion							
N	5	2	10	10	10	8	2
Mean (SD)	146.25 (57.67)	137.35 (42.64)	152.23 (36.14)	153.74 (52.04)	136.12 (48.76)	127.50 (41.45)	127.45 (26.66)
Median (min–max)	110.00 (100.0–229.5)	137.35 (107.2–167.5)	144.80 (115.1–202.7)	150.45 (86.5–229.7)	137.70 (62.5–209.3)	114.45 (84.2–221.2)	127.45 (108.6–146.3)
Trough FVIII (%) preinfusion							
N	5	1	10	10	10	8	2
Mean(SD)	3.07 (3.37)	71.70 (NA)	72.06 (27.66)	80.72 (25.48)	72.57 (30.57)	52.71 (25.63)	10.65 (0.49)
Median (min–max)	2.00 (0.5–9.0)	NA (NA)	66.65 (35.7–112.5)	80.25 (45.6–118.2)	69.55 (29.6–128.7)	53.35 (8.3–98.4)	10.65 (10.3–11.0)

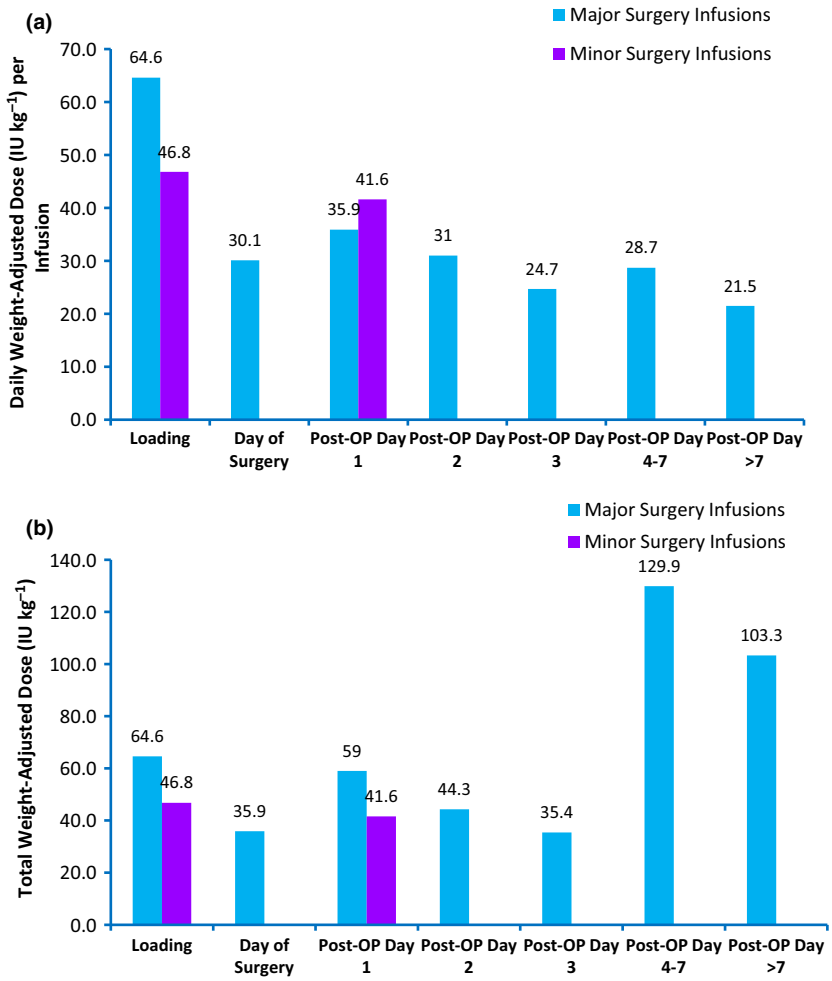

Figure 1. Median Total Dose per Patient (IU kg^{-1}). (a) Daily weight-adjusted consumption of BAX 855; (b) total weight-adjusted consumption of BAX 855.

10.25–24.26 h; CL was 0.01–0.04 mL (kg h^{-1}) $^{-1}$ and V_{ss} was 0.27–0.68 dL kg^{-1}.

Safety

None of the subjects exposed to BAX 855 for perioperative control of haemostasis experienced SAEs, severe allergic reactions or thrombotic events. One subject had FVIII peak levels >200% (maximum 229.7%) over 5 days and three additional subjects showed singular FVIII peak levels ≥180% up to postoperative Day 3. One of these subjects who had a singular FVIII peak level of 215.5% at postoperative Day 2 received postoperative thrombosis prophylaxis with low-molecular-weight heparin (LMWH). No other subject received pharmacological thromboprophylaxis. None of the subjects developed inhibitory antibodies to FVIII or persistent binding antibodies to FVIII, BAX 855 or PEG. There were no binding antibodies to CHO proteins observed.

No trends over time were observed for clinical chemistry and haematology parameters.

Discussion

Coagulation factor replacement is essential in surgical procedures in haemophilia patients. A factor concentrate therapy that provides the optimal dose and administration frequency for the most effective bleed management during surgery in haemophilia A patients would offer an advancement in the control of surgical bleeding and lead to a positive postoperative clinical outcome [25]. Less frequent dosing could enable shorter hospital stays, improve rehabilitation and therefore reduce costs. Only limited clinical data are available on the efficacy of recombinant FVIII products with extended half-life for surgical haemostasis [26,27].

This report presents the first prospective study of the newly developed recombinant FVIII with prolonged half-life (BAX 855) in PTPs with haemophilia A for use in surgical procedures, confirming previous data on the haemostatic efficacy and safety of BAX 855 when administered for prophylaxis or on-demand [19].

BAX 855 was shown to be effective for perioperative bleed management of haemophilia A subjects, with haemostatic efficacy rated as 'excellent' intra-operatively and at postoperative Day 14 or at discharge (whichever occurred earlier) in all 15 subjects (100%). At postoperative Day 1, all treatments were rated either 'excellent' (11 major surgeries and 2/3 minor surgeries) except for 1 minor (dental) procedure which received a postoperative rating of 'good' due to a small amount of oozing and for one minor procedure which was not rated at the time of the analysis (Table 3). The efficacy results of this study are comparable with those reported in a trial evaluating longer lasting recombinant FVIII treatment for surgical management in individuals with haemophilia A where the haemostatic response during the perioperative period was rated as excellent (n = 8/9) or good (n = 1/9) [26].

In a large scale surgery study including 22 major surgeries, Negrier *et al.* (2008) reported a higher median total weight-adjusted consumption of rFVIII (ADVATE®) (910 IU kg^{-1}; range: 228–1825) compared to the median consumption of BAX 855 (362 IU kg^{-1}; range: 236–863) observed in this study, however, this was presumably due to the relatively high number of orthopaedic surgeries included (21/22), which require increased coagulation factor consumption [28]. A recent study with another commercially available FVIII product in 15 major, mainly orthopaedic surgeries reported a median consumption of 684 (219–1512 IU kg^{-1}) [29]. However, comparison of data across studies is difficult due to the different surgery types, duration of rehabilitation, consumption analysis periods and treatment outcome definitions. The daily weight-adjusted consumption of BAX 855 decreased from postoperative Day 1 to discharge for major surgeries (Fig. 1), consistent with the decrease in FVIII trough levels which were close to the required 80% during the first 72 h postoperatively and 50% from postoperative Days 4–7, but below the required 30% after postoperative Day 7 until discharge (10.65 ± 0.49%). Supra-physiological FVIII levels >180% were observed in four subjects, without any clinical signs of thrombosis. Furthermore, the actual maximum intraoperative blood loss for major and minor surgeries was lower than the estimated maximum blood loss. In the five major surgeries with postoperative blood loss, the actual blood loss did not exceed the maximum predicted blood loss. Compared to the outcome of the large scale surgery study with rFVIII (ADVATE®), these results demonstrated that BAX 855 can achieve optimal control of bleeding providing an additional treatment option for haemophilia A patients in surgical settings [28].

Surgical studies are of general interest due to the use of recombinant replacement factor products at high doses, which can be associated with safety concerns [30]. BAX 855 was safe and well tolerated in all 15 haemophilia A subjects treated for perioperative management, without any bleeding complications observed during the intra- or postoperative period. There were no related adverse events, and no thrombotic or severe allergic reactions. In addition to the administration of FVIII concentrates by continuous infusion which has been suggested to contribute to a higher incidence of inhibitors perioperatively, one of the putative factors that may influence inhibitor development in (minimally) previously treated patients is the activation of the immune system after surgery [31]. In this study, there was no evidence of increased immunogenicity with BAX 855, as none of the subjects developed FVIII inhibitors, persistent binding antibodies to FVIII, PEG- FVIII, PEG or CHO proteins. The results further showed that the BAX 855 safety profile was consistent with that of its base molecule ADVATE®, and can be safely administered during major and minor surgeries in patients with haemophilia A.

Conclusion

In summary, the results indicate that BAX 855 is safe and effective for perioperative management of patients with severe haemophilia A. No related adverse events, no thrombotic events, no signs of immunogenicity in terms of FVIII inhibitors or persistent binding antibodies to FVIII, PEG-FVIII or PEG, and no severe allergic reactions were observed.

Acknowledgements

The authors thank the following individuals for their contributions to the conduct of the trial at the investigative sites: Elaine Eyster, Brian Wicklund, Liana Gercheva, Margarita Timofeeva, Saturnino Haya Guaita and Pratima Chowdary. The authors also thank the BAX 855 clinical study team: Bruce Ewenstein, Barbara Valenta-Singer, Feriandas Greblikas, Monika Fuerlinger, Eli Taube, Judit Koranyi, Nicole Baumgartner, Alfreda McCulloch-Bayr and Tschung-I (Jenny) Ho, as well as Frank Horling for immunological assessments. We gratefully acknowledge the participating patients for their commitment to the study.

Author contributions

BB, BA and TD contributed to study conception and design; BB, RG, TW, LG and MFLF to study conduction and acquisition of data; TD, MC, BP and BA analysed and interpreted the data; BP, BA and MC wrote the manuscript. All authors reviewed the manuscript and approved the final version.

Funding

The study was funded by Baxalta.

Disclosures

TD, MC, BP and BA are employees of Baxalta. BB, RG, TW, LG and MFLF received honoraria as an investigator in the trial. TW received research funding as a clinical trial investigator from Pfizer.

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