

# CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology  
Office of Blood Review & Research

BLA 125566/0

Product:	Factor VIII (Recombinant), PEGylated lyophilized powder for solution for intravenous injection
Sponsor:	Baxter Healthcare Corporation
Indication:	Control and prevention of bleeding episodes, and routine prophylaxis to prevent or reduce the frequency of episodes in adolescent and adult patients with hemophilia A
CBER Received:	November 25, 2014
Reviewer:	Carl-Michael Staschen, M.D., Ph.D.
RPM:	Yu Do/Edward Thompson
Through:	Bindu George, M.D.

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## Introduction/Background

FVIII is a critical component of the intrinsic coagulation pathway. Hemophilia A is an X-chromosome linked recessive, congenital bleeding disorder characterized by a deficiency of functional coagulation FVIII, resulting in a prolonged patient plasma clotting time. Hemophilia A leads to bleeding episodes predominantly in joints and in soft tissues. FVIII concentrates (either plasma derived or recombinant) are used in hemophilia A patients to normalize the aPTT by providing a hemostatic FVIII level sufficient to treat and prevent bleeding episodes over the effective dosing period. The optimal effective treatment of the disorder is replacement of FVIII using FVIII concentrate either obtained by fractionation of human plasma or manufactured by recombinant DNA technology.

Prophylactic therapy with FVIII is considered to be the optimal treatment for hemophilia A patients without inhibitors. Due to the short circulating FVIII half-life (12 to 14 hours), 2-3 infusions a week are required to maintain a FVIII level of at least 1% of normal to effectively prevent or reduce spontaneous bleeding episodes. A longer-acting FVIII concentrate would reduce the frequency of infusions. Modification with polyethylene glycol (PEG) is a well established method to improve the pharmacokinetic (PK) profile and prolong half-life and circulation of therapeutic proteins. Hence, chemical modification of FVIII by PEG polymers might achieve a longer-acting FVIII.

The investigational product, BAX 855, is manufactured by covalently binding a branched PEG reagent with a molecular weight of 20 kDa to Baxter's rFVIII (ADVATE®). BAX 855 is intended for intravenous (i.v.) use. It is available as a lyophilized powder in single-use vials. Each vial contains nominally 250, 500, 1000 or 2000 International Units (IU) of FVIII potency. After

reconstitution with sterile Water for Injection (sWFI), BAX 855 contains approximately 50, 100, 200 and 400 IU/mL of human FVIII. One IU corresponds to the activity of FVIII contained in one mL of normal human plasma determined using a standardized one-stage clotting assay.

Baxter is seeking approval in the U.S. for the following indication:

BAX 855 is indicated for use in adolescent (12 to <18 years) and adult ( $\geq 18$  years) patients with hemophilia A (congenital FVIII deficiency) for:

- Control and prevention of bleeding episodes
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

The Clinical Pharmacology has been assessed in two submitted clinical studies (No. 261101 and No. 261201). These studies were designed to evaluate the PK characteristics of BAX 855 as well as to compare BAX 855 to ADVATE® with respect to PK in previously treated patients (PTPs) with severe hemophilia A (FVIII levels <1%).

**1. Study Title:** BAX855 (PEGylated Recombinant Factor VIII): A Phase 1, prospective, open label, cross-over, dose-escalation study in previously treated patients with severe (FVIII < 1%) hemophilia A (Study Report No. 261101).

**2. Study Title:** A Phase 2/3, multi-center, open label study of efficacy, safety, and pharmacokinetics of pegylated recombinant factor FVIII (BAX 855) administered for prophylaxis and treatment of bleeding in previously treated patients with severe (FVIII < 1%) hemophilia A (Study Report No. 261201).

**1. Study Title:** BAX 855 (PEGylated Recombinant Factor VIII): A Phase 1, prospective, open label, cross-over, dose-escalation study in previously treated patients (PTPs) with severe (FVIII < 1%) hemophilia A (Study Report No. 261101).

Objectives:

The objectives of this study were

- to assess tolerability and safety post single dose treatments of BAX 855 in PTPs with severe hemophilia A
- determine the pharmacokinetic (PK) parameters of BAX 855 compared in crossover with ADVATE (to compare the pharmacokinetic (PK) parameters of BAX 855 with ADVATE)
- to evaluate the impact of anti-PEG antibodies on PK.

Study Design:

This was a Phase 1, prospective, open label, cross-over, dose-escalation study in previously treated male patients (PTPs), with severe hemophilia A (FVIII levels < 1%) to evaluate safety and PK parameters of single doses of BAX 855 compared to single doses of ADVATE.

The study consisted of 2 cohorts. The target population was 18 evaluable adult male PTPs with severe hemophilia A (FVIII < 1%). Cohort 1 had 8 evaluable subjects. Cohort 2 had 10 evaluable subjects, 2 were enrolled in Japan. Subjects in Cohort 1 received single doses of ADVATE and BAX 855 at 30 IU/kg, and subjects in Cohort 2 received single doses of ADVATE and BAX 855 at 60 IU/kg.

Blood samples for PK analysis were drawn at following time points:

- ADVATE: 15, 30, 60 min, 4 h, 9 h, 12 h, 24 h, and 48 h post infusion
- BAX 855: 15, 30, 60 min, 4 h, 9 h, 12 h, 24 h, 48 h, 56 h, 72 h, 80 h, 96 h, 120 h, Day 6, and Day 7.

Bioanalytical assay and data analysis method:

FVIII activity and IP activity levels were measured using a specific 1-stage clotting assay (LLOQ = (b) (4)) as the primary assay, and a chromogenic assay to provide supportive data. Data were analyzed using non-compartmental methodology (b) (4) or later).

Results:

Pharmacokinetic parameters of BAX 855 and ADVATE based on one-stage clotting assay are presented in Table 1. The 2 patients (Group 2) enrolled in Japan were not included in the PK analysis because of major protocol violations and assay problems.

**Table 1.** Mean ( $\pm$ SD) PK Parameters for BAX 855 and ADVATE using the one-stage clotting assay.

	<b>Cohort 1: 30 IU/kg Dose Level N = 8</b>		<b>Cohort 2: 60 IU/kg Dose Level N = 8</b>	
<b>Parameter</b>	<b>BAX855</b>	<b>ADVATE</b>	<b>BAX855</b>	<b>ADVATE</b>
<b>AUC<sub>0-t</sub></b> (IU•h/dL)	1501.87 $\pm$ 417.069	836.04 $\pm$ 270.744	3054.11 $\pm$ 752.179	1910.69 $\pm$ 560.848
<b>AUC<sub>0-∞</sub></b> (IU•h/dL)	1540.64 $\pm$ 432.443	913.04 $\pm$ 314.282	3096.08 $\pm$ 736.259	2055.58 $\pm$ 597.858
<b>AUMC<sub>0-∞</sub></b> (IU•h <sup>2</sup> /dL)	29548.48 $\pm$ 12849.025	12430.25 $\pm$ 6251.361	69664.82 $\pm$ 26899.235	32276.94 $\pm$ 14800.882
<b>AUC<sub>0-120h</sub></b> (IU•h/dL)	1501.87 $\pm$ 417.069	-	3045.18 $\pm$ 744.413	-
<b>T<sub>1/2</sub></b> (h)	13.60 $\pm$ 2.786	9.90 $\pm$ 1.702	16.64 $\pm$ 3.597	11.11 $\pm$ 1.835
<b>TD<sub>1/2</sub></b> (h)	8.19 $\pm$ 2.202 <sup>a</sup>	6.55 $\pm$ 4.571 <sup>b</sup>	13.36 $\pm$ 4.354 <sup>c</sup>	7.47 $\pm$ 2.302 <sup>d</sup>
<b>MRT</b> (h)	18.41 $\pm$ 3.875	12.88 $\pm$ 2.894	21.86 $\pm$ 3.791	15.14 $\pm$ 2.882
<b>CL</b> (dL/(kg•h))	0.0215 $\pm$ 0.00721	0.0377 $\pm$ 0.01538	0.0198 $\pm$ 0.00408	0.0315 $\pm$ 0.00915
<b>V<sub>ss</sub></b> (dL/kg)	0.3760 $\pm$ 0.06854	0.4533 $\pm$ 0.09936	0.4223 $\pm$ 0.04747	0.4609 $\pm$ 0.09544
<b>C<sub>max</sub></b> (IU/dL)	82.88 $\pm$ 16.479	78.38 $\pm$ 20.325	146.75 $\pm$ 23.057	141.00 $\pm$ 32.523
<b>T<sub>max</sub></b> (h)	0.60 $\pm$ 0.263	0.58 $\pm$ 0.174	1.11 $\pm$ 1.219	0.75 $\pm$ 0.257
<b>IR</b> (IU/dL: IU/kg)	2.73 $\pm$ 0.586	2.58 $\pm$ 0.658	2.49 $\pm$ 0.378	2.34 $\pm$ 0.543

While no formal statistical comparisons were made for FVIII activity, direct comparisons of the relevant PK parameters (using the one-stage-clotting assay) of BAX 855 and ADVATE at the same doses (30 and 60 IU/kg) showed the following (Mean  $\pm$  SD):

- Plasma half-life (T<sub>1/2</sub>, h) was 1.4-fold to 1.5-fold longer for BAX 855 compared to ADVATE (Cohort 1: 13.6  $\pm$  2.8 h versus 9.90  $\pm$  1.7 h; Cohort 2: 16.6  $\pm$  3.6 h versus 11.1  $\pm$  1.84 h).
- Systemic clearance (CL, (dL/kg)/h) was smaller for BAX 855 compared to ADVATE (Cohort 1: 0.0215  $\pm$  0.0072 versus 0.0377  $\pm$  0.0154; Cohort 2: 0.0198  $\pm$  0.0041 versus 0.0315  $\pm$  0.0092).
- Incremental in-vivo recovery (IR, IU/dL per IU/kg) was higher for BAX 855 compared to ADVATE (Cohort 1: 2.73  $\pm$  0.59 versus 2.58  $\pm$  0.66; Cohort 2: 2.49  $\pm$  0.38 versus 2.34  $\pm$  0.54).

The PK parameters assessed using the chromogenic assay were similar to those from the one-stage-clotting assay. Differences in PK parameter estimates between the two assays were less than 20 %.

No neutralizing antibodies against BAX 855 were detected both before as well as after treatment.

In summary, the PK analyses indicated that the mean terminal plasma half-life of BAX 855 is prolonged by approximately 1.4- to 1.5-fold in comparison to ADVATE and in line with this drug mean clearance decreased by approximately 40%.

**2. Study Title:** A Phase 2/3, multi-center, open label study of efficacy, safety, and pharmacokinetics of pegylated recombinant factor FVIII (BAX 855) administered for prophylaxis and treatment of bleeding in previously treated patients (PTPs) with severe (FVIII < 1%) hemophilia A (Study Report No. 261201).

#### Objectives

The purpose of the study was:

- To assess efficacy and safety, including immunogenicity of BAX 855, administered as prophylaxis and as on-demand therapy in adolescent (12 to < 18 years) and adult (18 to 65 years) PTPs with severe hemophilia A
- To determine the PK parameters of BAX 855 in adolescents (12 to < 18 years) and in adults (18 to 65 years) following single and repeat dosing after at least 50 exposure days (ED), and compare results to ADVATE PK parameters

#### Study Design:

This study was a Phase 2/3, multicenter, open-label, 2-arm study with a total of 119 adolescent (12 to < 18 years) and adult (18 to 65 years) male PTPs with severe hemophilia A to evaluate efficacy, safety, and pharmacokinetics (PK) of BAX 855 and Health-Related Quality of Life in subjects receiving BAX 855. Subjects were enrolled to receive either prophylactic treatment with BAX 855 at a dose of 45 IU/kg twice weekly (Arm A) or on-demand therapy with BAX 855 at a dose of 10 to 60 IU/kg dose (Arm B).

The initial PK assessment was performed with ADVATE (PK 1) followed by a PK assessment with BAX 855 (PK-2). To evaluate the impact of long-term exposure of BAX 855, a PK assessment was repeated after the subjects had completed prophylactic treatment for several months (PK3). A dose of 45 IU/kg, both for ADVATE and for BAX 855, was used for PK determination. A PK evaluation was performed in approximately 25 subjects assigned to receive

twice weekly prophylactic treatment with BAX 855 with at least 6 subjects between age 12 to < 18 years. Blood samples for the 3 PK evaluations (PK1, PK2, and PK3) were taken at pre-dose, 10, 30, 60 min, 3, 6, 9, 24, 32, 48, and 56 hours after dose. For BAX 855 two blood samples at 72 and 96 hours were added.

Bioanalytical assay and data analysis method:

FVIII activity levels were measured using a specific 1-stage clotting assay as the primary assay, and a chromogenic assay to provide supportive data. PK was assessed using non-compartmental methodology ((b) (4) or later).

Results:

The following summary statistics were computed for the full analysis dataset for PK assessments using the one-stage-clotting assay (Table 1). Comparing the PK results of BAX 855 (PK-2) with ADVATE (PK-1), the mean T1/2 was 1.4 fold prolonged, respectively, with a mean T1/2 for BAX 855 of 14.3 h (SD = 3.8 h), confirming the results of the Phase 1 clinical study (Report No. 261101). IR-values of BAX 855 and ADVATE were comparable (ratio of 1.093 for BAX 855/ADVATE). The mean IR remained unchanged over time for both the adolescents and adults (one-stage clotting assay). Similar results were observed based on the chromogenic assay.

None of the subjects developed inhibitory antibodies to FVIII  $\geq 0.6$  BU at any time during the study.

In summary, the PK analyses demonstrated that the mean terminal half-life of BAX 855 was prolonged by approximately 1.4- to 1.5-fold in comparison to ADVATE. The PK parameters estimated after repeated dosing with BAX 855 were consistent with the initial PK parameter estimates after a single dose.

**Table 1.** Mean (SD) pharmacokinetic results based on the one-stage clotting assay.

Parameter	Statistics	PK-1 ADVATE	PK-2 BAX 855 (Initial dose)	Ratio PK- 2/PK-1	PK-3 BAX 855 (After ≥50 EDs)	Ratio PK- 3/PK-2
$T_{1/2}$ (h)	N	26	26	26	22	22
	Mean (SD)	10.40 (2.244)	14.30 (3.838)	1.382 (0.2535)	16.02 (4.922)	1.181 (0.4730)
MRT (h)	N	26	26	26	22	22
	Mean (SD)	12.86 (3.044)	19.56 (5.315)	1.515 (0.1786)	20.65 (4.821)	1.101 (0.2567)
CL (dL/(kg·h))	N	26	26	26	22	22
	Mean (SD)	0.04551 (0.021725)	0.02760 (0.020288)	0.6128 (0.27532)	0.02474 (0.008225)	1.0041 (0.26671)
IR (IU/dL·IU/kg)	N	26	26	26	22	22
	Mean (SD)	2.372 (0.5357)	2.493 (0.6944)	1.093 (0.3624)	2.297 (0.6377)	0.961 (0.2249)
$AUC_{0-\infty}$ (IU·h/dL)	N	26	26	26	22	22
	Mean (SD)	1168.0 (425.40)	2073.3 (778.41)	1.897 (0.9132)	2008.7 (631.53)	1.088 (0.5045)
$V_{ss}$ (dL/kg)	N	26	26	26	22	22
	Mean (SD)	0.5487 (0.20213)	0.4715 (0.14602)	0.902 (0.2926)	0.4970 (0.15756)	1.075 (0.2843)
$C_{max}$ (IU/dL)	N	26	26	26	22	22
	Mean (SD)	108.45 (26.250)	113.68 (30.259)	1.117 (0.4708)	103.34 (29.311)	0.949 (0.2277)
$T_{max}$ (h)	N	26	26	26	22	22
	Mean (SD)	0.296 (0.1662)	0.397 (0.2632)	1.597 (1.0692)	0.467 (0.6044)	1.640 (2.4797)

### REVIEWER'S COMMENTS

- In general, the PK results of the clinical Phase 1 study and Phase 2/3 study are acceptable from a Clinical Pharmacology perspective.
- The PK parameter differences between the one-stage clotting assay and the chromogenic assay were less than 20% and appear not to be of clinical significance.

## CLINICAL PHARMACOLOGY LABELING COMMENTS

### 12. CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

DRUG NAME, is a pegylated ~~conjugate form of the FDA-approved~~ recombinant antihemophilic factor (ADVATE), temporarily replaces the missing coagulation factor VIII needed for effective hemostasis ~~in congenital hemophilia A patients~~ [see *Description (11)*].

#### 12.2 Pharmacodynamics

Hemophilia A is a disorder characterized by a deficiency of functional coagulation factor VIII, resulting in a prolonged, patient plasma clotting time as measured by the activated partial thromboplastin time (aPTT). Treatment with DRUG NAME normalizes the aPTT over the effective dosing period. ~~The administration of DRUG NAME increases plasma levels of factor VIII, and can temporarily correct the coagulation defect in these patients.~~

#### 12.3 Pharmacokinetics

The pharmacokinetics (PK) of DRUG NAME was evaluated in a ~~Phase 2/3~~ crossover study with ADVATE in 26 subjects ~~(18 adults and 8 adolescents)~~ and in 22 subjects ~~(16 adults and 6 adolescents)~~ after 6 months of treatment with DRUG NAME. A single ~~nominal~~ dose of  $45 \pm 5$  IU/kg was ~~administered to patients~~ for both products. The PK parameters, as shown in Tables 3 ~~and 4~~, were based on plasma ~~coagulation~~ factor VIII activity measured by the one-stage clotting assay and are presented by age groups (adults and adolescents).

~~The terminal plasma half-life of DRUG NAME was 1.4 to 1.5-fold longer than ADVATE. Compared to ADVATE, DRUG NAME demonstrated has an 1.4 to 1.5 fold increase extended in terminal plasma half life of 1.4 to 1.5 fold, based on the one stage clotting assay, and the chromogenic assays, respectively. An increase in AUC and a decrease in clearance as compared to the parent molecule, ADVATE, were also observed. Incremental recovery was comparable between with both products. The change in PK parameters was similar in both the adult and adolescent populations and between one stage clotting and chromogenic substrate assays. The PK data demonstrate that DRUG NAME has a prolonged circulating half life. The PK parameters after repeated dosing with DRUG NAME were consistent with the initial parameter estimates following a single dose.~~

FDA comment:

Please consolidate the results in Table 3 (adults) and Table 4 (adolescents) in one Table. The columns in Table 3/Table 4 displaying data of ADVATE and DRUG NAME > 50 EDs should be deleted because they are already described in the text. Please add a description of C<sub>max</sub> and T<sub>max</sub> to the legend of Table 3.



**Table 3: Pharmacokinetic Parameters in Adolescents (12 to 17 yr) and Adults (≥ 18 yr)**  
**(greater than or equal to 18 years)**  
**(Arithmetic Mean ± SD)**

PK Parameters	ADVATE Upon Initial Dose N=18	DRUG NAME Upon Initial Dose N = 18	DRUG NAME ≥ 50 EDs N=16
Terminal half-life [h]	10.83 ± 2.08	14.69 ± 3.79	16.39 ± 5.28
MRT [h]	13.41 ± 3.00	20.27 ± 5.23	21.09 ± 4.73
CL [mL/(kg·h)]	3.88 ± 1.24	2.27 ± 0.84	2.37 ± 0.77
Incremental Recovery [(IU/dL)/(IU/kg)]	2.57 ± 0.43	2.66 ± 0.68	2.33 ± 0.55
AUC <sub>0-Inf</sub> [IU·h/dL]	1286 ± 390	2264 ± 729	2062 ± 575
Vss [dL/kg]	0.50 ± 0.11	0.43 ± 0.11	0.49 ± 0.17
Cmax [IU/dL]	117 ± 20	122 ± 29	105 ± 25
Tmax [h]	0.33 ± 0.19	0.46 ± 0.29	0.38 ± 0.18

Abbreviations: CI: confidence interval; Cmax: maximum observed activity; AUC: area under the curve; MRT: mean residence time; CL: clearance; Vss: body weight adjusted volume of distribution at steady-state

**Table 4: Pharmacokinetic Parameters in Adolescents (12 to less than 18 years)**  
**(Arithmetic Mean ± SD )**

PK Parameters	ADVATE Upon Initial Dose (95% CI) N = 8	DRUG NAME Upon Initial Dose (95% CI) N = 8	DRUG NAME ≥ 50 EDs (95% CI) N = 6
Terminal half-life [h]	9.45 ± 2.45	13.43 ± 4.05	15.06 ± 4.08
MRT [h]	11.63 ± 2.94	17.96 ± 5.49	19.47 ± 5.32
CL [mL/(kg·h)]	6.07 ± 3.05	3.87 ± 3.31	2.75 ± 0.96
Incremental Recovery [(IU/dL)/(IU/kg)]	1.94 ± 0.52	2.12 ± 0.60	2.22 ± 0.88
AUC <sub>0-Inf</sub> [IU·h/dL]	902 ± 400	1642 ± 752	1868 ± 807
Vss [dL/kg]	0.67 ± 0.31	0.56 ± 0.18	0.51 ± 0.13
Cmax [IU/dL]	89 ± 29	95 ± 25	100 ± 42
Tmax [h]	0.21 ± 0.04	0.26 ± 0.10	0.71 ± 1.16

Please add:

***Pediatric Pharmacokinetics:***

Pharmacokinetic profiles of DRUG NAME have not been established in pediatric patients less than 12 years old.

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