



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research**

MEMORANDUM

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Subject: Pharmacovigilance Plan Review

Applicant: Baxter Healthcare Corporation (Baxter)

Product: Bax 855 is a recombinant antihemophilic factor VIII (Advate) PEGylated

Proposed Indication: Indicated in adolescent (12 to <18 years) and adult (≥18 years) patients with hemophilia A (congenital factor VIII (FVIII) deficiency) for:

- Control and prevention of bleeding episodes
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- Not indicated for the treatment of von Willebrand disease.

Current Indication: Not currently licensed

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1 INTRODUCTION

1.1 Product Description

BAX 855 (Antihemophilic Factor, Recombinant, PEGylated, rurioctocog alfa pegol) is an extended half-life (T_{1/2}) recombinant human coagulation factor VIII (rFVIII) modified with polyethylene glycol (PEG). rFVIII is expressed in Chinese Hamster Ovary (CHO) cells and manufactured using Baxter's Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method (rAHF-PFM); it is also the active substance in Baxter's licensed product ADVATE (antihemophilic factor recombinant). BAX 855 is a full-length form of ADVATE consisting of 2,332 amino acids (molecular weight (MW) 280 kDa) covalently conjugated with a polyethylene glycol (PEG) reagent (MW 20 kDa). The therapeutic activity of BAX 855 is derived from ADVATE, which is produced by recombinant DNA technology from the Chinese hamster ovary (CHO) cell line. The ADVATE molecule is then covalently conjugated with the PEG reagent, which targets lysine residues. The cell culture, purification process, and formulation used in the manufacture of BAX 855 do not use additives of human or animal origin. The PEG moiety increases the plasma half-life through the reduction of the LRP-1 receptor-mediated clearance of the FVIII molecule.

1.2 Rationale for Development, Indications and Usage

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 (as determined by the activated partial thromboplastin time [aPTT]). Hemophilia A is characterized by bleeding episodes predominantly in joints, but also in soft tissues (1). 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 National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC) considers prophylactic therapy with FVIII to be the optimal treatment for hemophilia A patients without inhibitors (2). Although the importance of adherence to prophylactic regimens for hemophilia A treatment has been established, the frequency of infusions still poses a challenge to patient compliance (3). On average, 3 infusions a week or one infusion every other day are required to maintain a trough FVIII level $\geq 1\%$ of normal, the level necessary to effectively prevent or reduce spontaneous bleeding episodes (4).

1.2.1 Proposed Indication

BAX 855, Antihemophilic Factor (Recombinant), PEGylated, is a PEGylated recombinant antihemophilic factor (ADVATE) indicated in adolescent (12 to less than 18 years) and adult (greater than or equal to 18 years) patients with hemophilia A (congenital factor VIII (FVIII) deficiency) for:

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

Of note, BAX 855 is not indicated for the treatment of von Willebrand's Disease.

1.3 Contraindications, Warnings, and Precautions

BAX855 is not approved for sale elsewhere. It is contraindicated in patients who have had a life-threatening hypersensitivity reaction, including anaphylaxis, to the parent molecule (ADVATE), mouse, or hamster protein, or other constituents of BAX 855.

1.4 Pertinent Regulatory History

None – BAX855 is not licensed in the United States or elsewhere.

1.5 Worldwide Distribution Data and Post-Marketing (non-study) Exposure

BAX 855 is not licensed in any country. There is no post marketing data as of the DLP of this BLA.

1.6 Objectives/Scope of the Review

The purpose of this review is to identify potential safety issues that may need to be addressed through post-marketing safety surveillance or studies should the product be licensed in the U.S., and to evaluate the pharmacovigilance plan (PVP) submitted by Baxter for the BAX 855 BLA.

2 MATERIALS REVIEWED

Date	Source	Document Type	Document(s) Reviewed
10/27/2014	Baxter	BLA Sequence 0000	125566/0.0; Module 1.16, Risk Management Plan
11/25/14	Baxter	BLA Sequence 0000	125566/0.0; Module 4.2, Non-clinical Study reports
3/27/2015	Baxter	BLA Sequence 0006	125495/0.6; Module 5.3.5.3, Integrated Summary of Safety (ISS)
3/31/2015	Baxter	BLA Sequence 0006	125566/0.6; Module 5.3.5, Reports of Efficacy and Safety Studies <ul style="list-style-type: none">• Subsection 5.3.5.1: Study Reports of Controlled Clinical Studies<ul style="list-style-type: none">➤ Study Report 261101➤ Study Report 261201• Subsection 5.3.5.2: Study Reports of Uncontrolled Clinical Studies<ul style="list-style-type: none">➤ Study Report 261204➤ Study Report 261302➤ Study Report 261204
1-3/15	Multiple	References	Medical literature review

3 PHARMACOVIGILANCE PLAN REVIEW

3.1 Non-Clinical Safety Findings

Single dose toxicity was assessed based on the data from a dose-escalation study in (b) (4) monkeys. There were no signs of toxicity at any dose level, no mortalities or changes in the endpoints of the study. Slightly elevated levels of glutamate dehydrogenase and aspartate aminotransferase were detected in single animals of the low, mid and high dose group of BAX 855, which did not result in toxicologically relevant findings. Treatment with two different batches of BAX 855 was well tolerated.

Repeat-dose toxicity studies were conducted in rats and (b) (4) monkeys. In rats, there were no drug-related clinical signs and changes to body weight, food consumption, ophthalmoscopy, clinical pathology, urinalysis, or organ weights. A specific reevaluation of brain and spinal cord was conducted with regard to determination of any vacuolization possibly caused by PEG. No findings indicative of any histopathological changes in the brain or spinal cord were reported. In a pilot repeat-dose study with (b) (4) monkeys, there were no signs of toxicity during the repeated dose phase, no mortalities, and no related changes in body weight throughout the experimental period.

Repeated doses of BAX 855 resulted in the formation of anti-drug antibodies specific for human FVIII or PEG and BAX 855 neutralizing for FVIII activity in animal models. The formation of antibodies against BAX 855 is an expected immune reaction after repeated application of heterologous human proteins to (b) (4) monkeys, (also a well known phenomenon for non-PEGylated FVIII products). Formation of anti-PEG antibodies did not result in any adverse reactions.

Local tolerance was assessed in the repeat-dose toxicity studies with rats and (b) (4) monkeys. Microscopic findings at the injection sites were comparable with controls and were consistent with a normal response expected after intravenous injection.

Nonclinical studies on reproductive and developmental toxicity of BAX 855 were not conducted because studies on reproductive and developmental toxicity are regarded to be only of minor relevance for FVIII drug products, since the majority of the hemophilia A patients would be males.

Nonclinical studies were not conducted with BAX 855 to assess its mutagenic or carcinogenic potential because BAX 855 is a recombinant protein and is not considered to be mutagenic.

3.2 Clinical Safety Database

A total of 5 studies were included in this BLA to support the safety of BAX 855. The breakdown of studies is as follows, with numbers of enrolled patients as of the DLP of this BLA (October 6, 2014);

- 1 phase 2/3 (pivotal) study (261201) with 137 subjects
- 1 phase 1 study (261101) with 19 subjects
- 1 phase 3 study (261204) in 13 surgery patients
- 1 phase 3b study (261302) with 122 subjects
- 1 phase – study (261202) in PTP pediatric patients with 0 subjects

A total of 291 subjects have been exposed to BAX 855 as of the DLP in Baxter clinical studies in the 5 trials presented in support of vaccine safety.

Table 1. Summary of Clinical Safety Studies

Study #; Region	Study Objectives (Age Range)	Study Design; Patient Population	# of Subjects	Exposure	Key Safety Findings (SAEs)
261201 (pivotal)	Evaluate efficacy, safety, PK* and HRQoL** in adolescent & adult male***PTPs with severe hemophilia A (12–17 & 18–65 yrs.)	Phase 2/3 multicenter, open label, 2-arm study, comparing the ABR between subjects receiving prophylactic dosing with on-demand treatment	138 Severe hemophilia A (FVIII <1%), adolescents and adults (12 to 58 years), PTPs with at least 150 EDs to a FVIII concentrate	<ul style="list-style-type: none"> • BAX 855/ADVATE IV bolus PK infusions 45 ±5 IU/kg • BAX 855 IV bolus Infusions for fixed prophylaxis OR On-demand treatment 	<ul style="list-style-type: none"> • 0 deaths, 0 thrombotic events, 0 allergic reactions. • 5 SAEs, none related to BAX 855.
261302 (Continuation Study)	Safety & Efficacy of BAX 855 in Prophylaxis of Bleeding in adult PTPs with Severe Hemophilia A (≤75 years)	Phase 3b	159 enrolled	137 / BAX 855 120 Prophylaxis 17 on demand	<ul style="list-style-type: none"> • Study Ongoing • 7 SAEs in 6 subjects • 0 thrombotic events • 0 deaths • 0 allergic reactions

Study #; Region	Study Objectives (Age Range)	Study Design; Patient Population	# of Subjects	Exposure	Key Safety Findings (SAEs)
261101	Primary: assess through evaluations of clinical laboratory analyses, vital signs, AEs and immunogenicity, tolerability and safety immediately post one treatment	Phase 1 prospective, open label, cross-over, dose escalation study	19 Severe hemophilia A (FVIII <1%), adults (18 to 60 years), male, PTPs with at least 150 EDs to a FVIII concentrate	BAX 855 ADVATE intravenous bolus single PK infusions: 30 ±3 IU/kg OR 40 ±6 IU/kg	<ul style="list-style-type: none"> 0 deaths, thrombosis-associated events, or allergic reactions 0 SAEs during/after treatment across cohorts 11 AEs in 8 subjects, none treatment-related.
261204 (Surgery Study)	Primary: Evaluate perioperative hemostatic efficacy of BAX 855 in subjects undergoing major or minor elective or minor emergency surgical, dental or other invasive procedures	Phase 3 prospective, uncontrolled, open-label, multicenter study	Planned: 40 subjects for 50 procedures including at least 10 major procedures	BAX 855 IV bolus infusion Presurgical PK assessment, if applicable: 60 ±5 IU/kg Dose and frequency: Major procedures: based on reaching initial FVIII target levels of 80-100% Minor procedures: based on reaching initial target FVIII levels of 30-60%	<ul style="list-style-type: none"> Study Ongoing 4 SAEs in 1 subject, none treatment related
261202	Primary: assess incidence of FVIII inhibitory antibodies	Phase 3, prospective, uncontrolled, open label, multicenter study	Planned: 60 30: <6 years AND 30: ≥6 to <12 years	BAX 855 IV bolus infusion Fixed prophylaxis: 50 ±10 IU/kg twice weekly BAX 855/ADVATE IV bolus PK infusions: 60 ±5 IU/kg	<ul style="list-style-type: none"> Study Ongoing No results as of DLP

*PK-Pharmacokinetics

**HRQoL-Health Related Quality of Life

***PTPs- Previously Treated Patients

3.2.1 Sponsor Analysis

3.2.1.1 Studies in Support of Safety

Study 261201 (Pivotal) - Completed

Objectives:

To evaluate the safety of BAX 855 for twice weekly prophylaxis in the control of bleeding episodes in terms of the occurrence of AEs and SAEs, changes in vital signs and laboratory parameters, the development of inhibitory antibodies against FVIII, and the development of binding antibodies against FVIII, PEG-FVIII, PEG and CHO.

Study design/population:

- A phase 2/3, multicenter, open label, 2-arm study in adolescent (12 to < 18 years) and adult (18 to 65 years) male PTPs with severe hemophilia A
- A total of 159 male subjects at hemophilia centers in Europe, North America and Asia were included
 - 138 subjects treated (137 treated with at least one dose of BAX 855);
 - 120 subjects received prophylactic treatment at a dose of 45 \pm 5 IU/kg twice weekly
 - 17 subjects received on-demand treatment at a dose of 10 to 50 IU/kg.

Key Safety Findings:

- 0 thrombotic events
- 0 deaths
- 0 AEs considered to be allergic reactions
- A total of 171 AEs occurred in 73 (53.3%) subjects.
 - Of these, 5 SAEs considered unrelated (osteoarthritis, herpes zoster infection neurological, humerus fracture, muscle hemorrhage, and neuroendocrine carcinoma) occurred in five (3.6%) subjects
 - No serious adverse events (SAEs) assessed as related to BAX 855
- There were 166 non-serious AEs in 70 (51.1%) subjects.
 - Of these, only 7 events in 6 subjects were assessed as related: headache (4 AEs in 3 subjects), diarrhea (1 AE in 1 subject), nausea (1 AE in 1 subject), and flushing (1 AE in 1 subject).
- There were 79 *temporally related AEs
 - headache, nasopharyngitis, and upper respiratory tract infection.
- 4.4% of subjects experienced non-serious AEs assessed as related to BAX 855 treatment;
 - Headache, diarrhea, nausea, and flushing.
- No new safety concerns identified in the evaluation of laboratory values and vitals over time or in significant shifts in toxicity grades.
- 9 subjects had pre-existing antibodies to FVIII (IgG), PEG- FVIII (IgG or IgM) or PEG (IgM) prior to the first exposure with BAX 855.
 - None of the subjects developed inhibitory antibodies to FVIII of \geq 0.6 BU or persistent binding antibody response against FVIII, PEG-FVIII, PEG or CHO proteins
 - No increased risk for previously treated patients with at least 150 EDs to develop inhibitory antibodies to FVIII after treatment with BAX 855
- No hypersensitivity reactions observed
- 77 subjects with stable HCV infection were enrolled; 1 was found to have HCV reactivation (high viral load, elevated LFTs to 3x the upper limit of normal) at the end of the study. Reactivation was assessed to be unrelated to study drug.

*A temporally associated AE was defined as an AE that began during infusion or within 24 hours of completion of infusion, regardless of causality. From these temporally related AEs, Baxter has determined that 4 were adverse reactions (diarrhea, nausea, headache, flushing) related to BAX 855.

Study 261101 (Phase I)- Completed

Objectives:

1. To assess tolerability and safety post single dose treatments of BAX855 in PTPs with severe hemophilia A; to determine the pharmacokinetic (PK) parameters of BAX855 compared in crossover with ADVATE; and to evaluate the impact of anti-PEG antibodies on PK parameters.
2. Estimate the dose necessary to maintain a FVIII level of $\geq 1\%$ for at least 5 days
3. Evaluate the influence of anti-polyethylene glycol (PEG) antibodies on the PK profile
4. Serious and non-serious AEs occurring up to 4 weeks \pm 4 days after infusion with BAX855 and ADVATE

Study design/population:

Phase 1, prospective, open label, cross-over, dose-escalation study in PTPs (male subjects) 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 distinct single dose cohorts.
- Cohort 1 consisted of 9 evaluable subjects to be infused with 30 ± 3 IU/kg ADVATE and undergo a 2-day PK evaluation; after a minimum 4-day washout period the same dose of BAX855 was given and a 7-day PK evaluation performed.
- Cohort 2 consisted of 10 evaluable subjects of whom evaluable subjects were enrolled in Japan, infused with ADVATE at $60 \text{ IU} \pm 6/\text{kg}$ and underwent a 2 day PK evaluation. After a washout period, the same dose of BAX855 was given and a 7 day PK evaluation performed.
- After infusion of their respective doses, each cohort of subjects was monitored for safety at 3 days, 2 weeks, and at the study termination visit at 4 weeks \pm 4 days for changes in vital signs, clinical laboratory assessments of hematology and chemistry, and any AEs.
- Subjects were evaluated for immunogenicity at 4 weeks \pm 4 days by testing inhibitory and binding antibodies to FVIII, BAX 855, and PEG by comparing values obtained at screening and at the study termination visit for individual subjects.

Key Safety Results:

- BAX 855 was safe and well tolerated in the 19 treated subjects.
 - 0 deaths
 - 0 thrombosis-associated events
 - 0 allergic reactions
 - 0 SAEs occurred during or after treatment across cohorts.
- A total of 11 AEs occurred in 8 subjects throughout the study across cohorts, none of which were treatment-related AEs.
- One (11.1%) AE in Cohort 1 and 1 (12.5%) AE in Cohort 2 occurred within 24 hours after infusion with ADVATE.
- Non-serious systemic AEs were reported for 3 (33.3%) subjects in Cohort 1 and 1 (12.5%) subject in Cohort 2 after infusion with BAX855
- Non-serious local AEs were reported for 1 (11.1%) subject in Cohort 1 and 1 (12.5%) subject in Cohort 2 after infusion with ADVATE alone; 1 (11.1%) subject in Cohort 1 and 1 (50.0%) subject in Cohort 2 Japan after infusion with BAX855 alone; and 1 (11.1%) subject in Cohort 1 after infusions of both ADVATE and BAX855
- The outcome of all AEs was recovered/resolved or recovering/resolving at the time of study completion
- None of the subjects developed FVIII inhibitors.

- Binding antibodies to FVIII and BAX855 were detected in a few subjects both before as well as after treatment with ADVATE and/or BAX855.
- No subjects developed binding antibodies to PEG after BAX855 infusion. Since all antibodies showed the lowest detectable titers of 1:20 or 1:40, they could not be analyzed for specificity and were therefore interpreted as “low-titer indeterminate.” Furthermore, all post-treatment antibody titer increases were <2 dilution steps and therefore considered unrelated to treatment.
- No clinically significant treatment-related changes in laboratory values or vital signs were recorded

Study 261204 (Surgery)- Ongoing

Objectives

1. To evaluate the efficacy and safety of BAX 855 in severe hemophilia A, male, previously treated patients (PTP), 2 to 75 years of age who were undergoing major or minor elective or minor emergency surgical, dental or other invasive procedures.
2. To determine the safety of BAX 855 in subjects undergoing surgery, as assessed by the occurrence of AEs and changes in vital signs and clinical laboratory parameters

Study Design/Population

- This is a phase 3, multi-center, open label, uncontrolled study to evaluate the efficacy and safety of BAX 855 in 40 PTPs with severe hemophilia A, undergoing fifty minor and major surgeries to evaluate a minimum of 10 major surgeries in at least 10 unique subjects using BAX 855 as peri-operative treatment
- Subjects are male PTPs 2–75 years of age, with severe hemophilia A (FVIII <1%)
- As of 06 October 2014, 16 subjects were enrolled. The last subject out is anticipated for November 2016.
- Safety outcomes included;
 - Development of binding antibodies to FVIII, BAX 855, CHO proteins and PEG
 - Occurrence of thrombotic events
 - Incidence of severe allergic reactions (e.g. anaphylaxis)
 - Other BAX855-related adverse events (AEs)
 - Incidence of clinically significant changes in vital signs and routine laboratory parameters (hematology, clinical chemistry)

Key Safety Findings

- Study ongoing
- Four (4) SAEs occurred in 1 subject (esophageal ulcer, emesis, urinary tract infection and constipation)

Study 261302 - Ongoing

Objectives

1. To determine the safety of BAX 855, as assessed by the occurrence of adverse events (AEs) and changes in vital signs and clinical laboratory parameters
2. To determine the immunogenicity of BAX 855

Study Design/Population

- A phase 3b continuation study of the safety and efficacy of BAX 855 in prophylaxis of bleeding in previously treated patients with severe hemophilia A

- This is a phase 3b, prospective, open label, multi-center study to evaluate the safety and efficacy of BAX 855 for prophylactic use and the control of bleeding episodes in approximately 200 pediatric and adult PTPs ≤ 75 years of age with severe hemophilia A. The study plans to include subjects from other BAX 855 studies and BAX 855-naïve subjects
- As of 06 October 2014, 124 subjects were enrolled
- An interim CSR is planned for Q1 2016 and the final CSR is planned for Q4 2017.
- Subjects will receive either a fixed dose prophylaxis with BAX 855 consisting of 45 ± 5 IU/kg for subjects aged ≥ 12 years or 50 ± 10 IU/kg for subjects aged < 12 years twice weekly or, subjects can decide to receive a pharmacokinetically tailored (PK-tailored) prophylactic BAX 855 dosing regimen based on the subject's individual PK to maintain FVIII trough levels
- The frequency of PK-tailored prophylactic BAX 855 dosing will be at least twice weekly.

Key Safety Findings:

1. A first interim safety review will be performed for marketing authorization application to the European Medicines Agency (EMA).
2. If applicable, a second interim safety review may be performed once 200 subjects have accumulated at least 100 EDs to BAX 855.

Study 261202 - Ongoing

Objectives

1. To assess the incidence of FVIII inhibitory antibodies during 6 months of twice weekly prophylactic treatment with BAX 855 or 50 exposure days (EDs), whichever occurs last
2. To compare pharmacokinetic (PK) parameters with ADVATE
3. To assess hemostatic efficacy in prophylaxis and the treatment of bleeding episodes
4. To investigate changes in health-related quality of life (HRQoL) in pediatric subjects with severe hemophilia A
5. To assess the incidence of FVIII inhibitory antibodies and all AEs and SAEs possibly or probably related to BAX 855
6. Assess clinically significant changes in vital signs (pulse, respiration, supine blood pressure, and temperature) and clinical laboratory parameters (hematology, clinical chemistry)
7. Assessment of binding antibodies to FVIII, BAX 855, PEG, and CHO.

Study Design/Population

- This study is a Phase 3, prospective, uncontrolled, multicenter, open label study in a total of 60 pediatric PTPs with severe hemophilia A
- All subjects are to receive twice weekly prophylactic treatment with 50 ± 10 IU/kg of BAX 855 over a period of 6 months or at least 50 EDs, whichever occurs last
- Two age cohorts of 30 subjects each (25 evaluable), with the following age range: < 6 years and ≥ 6 to < 12 years
- A subset of 14 subjects (12 evaluable) within each age cohort will participate in the PK portion of the study: prior to the start of the 6-month prophylactic treatment they will undergo a PK analysis with a single dose of 60 ± 5 IU/kg ADVATE followed by a single dose of 60 ± 5 IU/kg BAX 855.
- All subjects participating in the PK portion of the study will have one pre-infusion blood draw and 3 post-infusion blood draws. The latter will be randomly selected from 3 choices for each blood draw.

Key Safety Findings

- A safety review will be performed once 20 pediatric PTPs including at least 10 subjects < 6 years have completed the study and the PK studies are complete in order to start the clinical trial

3.2.2 Sponsor Integrated Analysis of Safety

There were 169 unique subjects included in the integrated safety analysis. The disposition of subjects receiving at least one dose of BAX 855 in the pooled analysis set is provided in the table below. Of 169 subjects in this integrated safety analysis, 11 discontinued in the pivotal study 261201: 4 subjects discontinued because of an AE, however none of these AEs were considered related to BAX 855. One (1) subject discontinued from the surgery study 261204, and 4 discontinued from the continuation study 261302.

The majority of subjects were from the pivotal study 261201 (137) followed by continuation study 261302 (125). The numbers of subjects in each age subgroup were as follows:

- 3 subjects <6 years (younger children)
- 1 subject 6 to <12 years (older children)
- 25 subjects 12 to <18 years (adolescents)
- 140 subjects ≥18 years (adults)

Demographics and baseline characteristics in the integrated dataset are as follows:

- Mean (SD, min-max) age was 30.1 (12.95, 3-60) years of age
- All subjects were male
- Overall, 133 (78.7%) subjects were white, 34 (20.1%) were Asian, 1 (0.6%) was black and 1 (0.6%) was "other"
- All of the children (ie <12 years) were white.

In the ISS, safety (including AEs and immunogenicity) were evaluated by age subgroups, including:

- <6 years (younger children), 6 to <12 years (older children):
 - Since there were only 3 younger children and 1 older child, an assessment of safety results in these age groups was not feasible. As of the DLP, with limited exposure to BAX 855, there were no AEs or SAEs or FVIII inhibitory antibodies reported in children.
 - Three (3) of these children had positive antibody binding tests before exposure to BAX 855 that are considered to be pre-existing antibodies and not related to the use of BAX 855
- 12 to <18 years (adolescents), and ≥18 years (adults).
 - Of the 25 adolescents included in the integrated analysis, all participated in the pivotal study and 22 continued in the continuation study. In these adolescents, a total of 2,428 EDs were accumulated with 6,934,047 IU infused overall.
 - A total of 42 AEs were reported in 15/25 (60.0%) adolescents with a rate of AEs by infusion of 1.7% (42 AEs/2435 infusions).
 - Of the 13 adverse events considered related to BAX 855, 3 occurred in 3 adolescents (2 headaches and 1 blood pressure increased)
 - Three (3) SAEs were reported in 2/25 (8.0%) adolescents
 - None of the adolescents in the integrated analysis developed FVIII inhibitory antibodies
 - Four (4) adolescents had positive antibody binding tests, 2 before exposure to BAX 855, which are considered to be pre-existing antibodies and not related to the use of BAX 855, and 2 after exposure to BAX 855, which were transient and not detectable at subsequent visits or at completion of the study

One hundred forty (140) adults were included in the integrated analysis. A total of 11,030 EDs were accumulated with 39,007,824 IU infused overall. Thirteen (13) SAEs were reported in 9 (6.4%) adults. A total of 258 AEs were reported in 81/140 (57.9%) adults with a rate of AEs by infusion of 2.3% (258 AEs/11,118 infusions). Of the 13 adverse events considered related to BAX 855 by the sponsor, 10 occurred in seven adults (6 headaches, 2 nausea, 1 diarrhoea, and 1 flushing).

Adverse Events

An overall summary of AEs in patients with BAX 855 (pooled studies) is presented below. A total of 300 AEs were reported in 96/169 (56.8%) subjects during or after treatment with at least 1 infusion of BAX 855. The overall rate of AEs by infusion was 2.2% (300 AEs/13,579 infusions), the rate of non-serious AEs by infusion was 2.1% (283 AEs/13,579 infusions), and the rate of SAEs by infusion was 0.1% (16 AEs/13,579 infusions).

Overall Summary of Treated Subjects with Adverse Events (Pooled Studies) N=169	n
Subjects with ≥1 AE	96
Subjects with ≥1 SAE	11
Subjects with treatment-related non-serious AEs	10 ^a
Subjects with treatment-related SAEs	0
Deaths	1 ^b
Subjects discontinued from the study due to an AE	4

Abbreviations: AE=adverse event; SAE=serious adverse event (during or after infusion with BAX 855).

a Relatedness was assessed by the sponsor. b One subject (521001) died of neuroendocrine carcinoma on (b) (6) after 22 EDs to BAX 855, approximately 3 weeks after withdrawal of BAX 855 on 04 Feb 2014 with the last dose on 01 Feb 2014.

Deaths and Other Significant Events

In the pivotal study 261201, one subject experienced an SAE of neuroendocrine carcinoma that resulted in death after withdrawal from the study. The subject died 21 days after discontinuing treatment with BAX 855. Of note, the subject had also received ADVATE. There were no AEs considered allergic reactions. There was 1 non-serious AE of a medical device complication considered a thrombotic event in pivotal study 261201.

SAE's

A summary of SAEs in the integrated dataset is shown by study below. There were no SAEs reported in phase 1 study 261101 or in pediatric study 261202 at the time of the data cut-off.

Overview of Serious Adverse Events of Each Study

Study Number	SAEs	SAEs of FVIII Inhibitory Antibody	SAEs Related to BAX 855
261101 Phase 1	0	0	0
261201 Pivotal	5	0	0
261202 Pediatric	0	0	0
261204 Surgery	4	0	0
261302 Continuation	7	0	0
Total	16	0	0

Throughout the 5 studies included in the integrated safety analysis, there were a total of 16 SAEs that occurred in 11/169 (6.5%) subjects treated with BAX 855, none of which were considered related:

- 1 subject with osteoarthritis
- 1 subject with neurological herpes zoster infection
- 1 subject with a humerus fracture
- 1 subject with muscle haemorrhage
- 1 subject with a neuroendocrine carcinoma (subsequently died after withdrawal from the study)
- 1 subject with abdominal pain
- 2 subjects with diabetic gastroparesis
- 1 subject with vomiting
- 1 subject with pancreatitis

- 1 subject with pneumonia
- 1 subject with postoperative abscess
- 1 subject with splenic hematoma
- 1 subject with splenic rupture
- 1 subject with traumatic fracture

Events Considered Related to BAX855

The sponsor assessed the AEs that are reported in the integrated analysis. The table below displays the events, which the sponsor either assessed as possibly or probably related to the use of BAX 855. Common adverse events considered related to BAX 855 by the sponsor (in $\geq 1\%$ of subjects) were headache and nausea.

System Organ Class	Preferred Term	Number of Related Events	Number of Subjects (%) N=169	Number Per 100 Infusions N ^b =13579	Number years N ^d =127.02
Gastrointestinal Disorders	Diarrhea	1	1 (0.6)	1 (0.01)	1 (0.008)
Gastrointestinal Disorders	Nausea	2	2 (1.2)	2 (0.01)	2 (0.016)
Investigations	Blood Pressure Increased	1	1 (0.6)	1 (0.01)	1 (0.08)
Nervous System Disorders	Headache	8	5 (3.0)	8 (0.06)	8 (0.063)
Vascular Disorders	Flushing	1	1 (0.6)	1 (0.01)	1 (0.008)
ALL	All	13	10		

a Number of sponsor-assessed, related adverse events divided by the total number of infusions, and multiplied by 100.

b Total number of BAX 855 infusions. c Number of sponsor-assessed, related adverse events divided by the total subjects' observation period for safety analysis (in days), and multiplied by 365.2425. d Total subjects' obs

Non Serious Adverse Events

Of 169 subjects included in the integrated analysis, 92 (54.4%) experienced non-serious AEs.

The rate of non-serious AEs by infusion was 2.1% (283 AEs/13,579 infusions).

The majority of non-serious AEs were mild or moderate in severity

- Mild: 183 AEs, rate of mild AEs by infusion of 1.3%
- Moderate: 94 AEs, rate of moderate AEs by infusion of 0.7%
- Severe: 5 AEs, rate of severe AEs by infusion of 0%
- Missing: 1 AE with a missing severity

Inhibitory Antibodies

Inhibitory antibodies to FVIII were measured by the (b) (4) Bethesda assay at each study visit. None of the subjects exposed to BAX 855 in the integrated analysis developed an inhibitory antibody to FVIII of ≥ 0.6 BU/mL, including:

- 120 subjects with ≥ 50 EDs (95% CI: 0.000 to 0.030)
- 48 subjects with ≥ 100 EDs (95% CI: 0.000 to 0.074)

Binding Antibodies to FVIII, PEG-FVIII, PEG, and CHO Protein

Binding IgG and IgM antibodies against FVIII, PEG-FVIII, and PEG, and CHO protein as a potential impurity were analyzed using validated ELISA assays. None of the 169 subjects in the integrated analysis developed a persistent binding antibody response against FVIII, PEG-FVIII, PEG, or CHO protein during the studies. Thirteen (13) subjects showed pre-existing antibodies against FVIII, against PEG- FVIII, or PEG prior to first exposure with BAX 855.

None of the adults in the integrated analysis developed FVIII inhibitory antibodies. Fourteen (14) adults had positive antibody binding tests, which were preexisting before exposure to BAX 855 or developed transiently at one or two consecutive study visits after exposure to BAX 855, but were not detectable at subsequent visits or at completion of the study.

Eight (8) subjects who tested as negative at screening developed transient IgG antibodies against FVIII or PEG-FVIII at one or two consecutive study visits after exposure to BAX 855. Antibodies were transient and not detectable at subsequent visits or at completion of the study. IgG antibodies against FVIII and PEG-FVIII that were not detectable at screening and completion of the surgery study or at screening for the continuation study were observed for subject 261204-322002 at the 6±1 week follow up visit. There were no subsequent evaluations done to establish the transient or persistent nature of the response. No subject had pre-existing or developed treatment related specific antibodies to CHO protein.

3.3 Safety Concerns Within the Pharmacovigilance Plan

The adverse events listed below were outlined by the sponsor as safety concerns that were either identified, potential, or had missing information.

3.3.1 Important Identified Safety Issues

None

3.3.2 Important Potential Safety Issues

- Inhibitor formation
- Hypersensitivity reaction
- Lack of effect

3.3.3 Important Missing Information

- Pediatric Patients
- Elderly patients
- Previously untreated patients
- Patients with renal impairment
- Patients with hepatic impairment
- Subpopulations with Known and relevant Polymorphisms
- Patients with moderate or mild hemophilia A (FVIII \geq 1%)
- Patients with different racial/ethnic origins

3.4 Other Potential Safety Concerns

3.4.1 Pharmacological Class Effect

Class effects are considered with respect to those adverse reactions (ARs) observed in other FVIII concentrates (e.g., ADVATE, Kogenate FS, Xyntha) and a long-acting factor VIII product, Eloctate. Adverse Reactions (AR) reported with the parent molecule (ADVATE) include FVIII inhibition, anaphylactic reaction, and hypersensitivity. ARs reported with other FVIII concentrates (e.g., Kogenate FS (Bayer) and Xyntha (Pfizer)) include FVIII inhibition, hypersensitivity reactions, infusion/injection site reactions, and central venous access device (CVAD) associated infections (Kogenate FS) and headache, pyrexia, nausea, vomiting, and diarrhea (Xyntha). ARs reported with Eloctate include malaise, chest pain, feeling cold, feeling hot, dizziness, dysgeusia, headache, joint swelling, abdominal pain lower, abdominal pain upper, hypertension, bradycardia, cough, and rash.

3.5 Sponsor's Proposed Actions and Timelines

3.5.1 Routine Pharmacovigilance Practices

Baxter has a Global Pharmacovigilance (GPV) organization that performs the Pharmacovigilance (PV) activities at the local, regional, and global levels. National Qualified Persons/Local PV responsible contacts are in place at the local level to perform PV activities at the country level. In certain geographies, a regional organization has been established that encompasses and represents multiple local country organizations. The local country organizations and/or regional staff provide information back to GPV. There are regularly scheduled meetings between the global and regional/local organizations and between regional and local organizations, respectively.

Action Plan for Safety Concerns (**see Table 3 for proposed post-licensure observational studies**). Routine pharmacovigilance will be conducted as part of the action plan for all potential risks and missing information; routine pharmacovigilance includes monthly assessment as part of the pharmacovigilance signal detection process and PAER prepared quarterly for three years and then yearly.

3.6

Table 2 (see page 50 of PVP)

Safety Issue/Area	Proposed Activity/Plan	Comments
Important Potential Risks		

Safety Issue/Area	Proposed Activity/Plan	Comments
Inhibitor formation	<p>Routine Pharmacovigilance -FVIII Inhibitor AE Questionnaire:</p> <p>Additional Pharmacovigilance -Q4 2017: Estimated date of the final CSR for Continuation study 261302 -Feb 2017: Estimated date of the final CSR for Surgery study 261204 -May 2016: Estimated date of the final CSR for Pediatric PTP study 261202 -Q2 2018: Estimated date of the final CSR for Pediatric PUP study 261203 -Nov 2017: Estimated date of the final CSR for PK guided dosing study 261303</p>	Safety & efficacy of BAX 855 based on clinical trial data from phase 1 study 261101 in 19 PTPs and data from phase 2/3 pivotal study 261201 in 137 PTPs. BAX 855 exposure limited to 2 trials and 2 ongoing studies.
Hypersensitivity Reactions	<p>Routine Pharmacovigilance</p> <p>Additional Pharmacovigilance -Q4 2017: Estimated date of the final CSR for Continuation study 261302 -Feb 2017: Estimated date of the final CSR for Surgery study 261204 -May 2016: Estimated date of the final CSR for Pediatric PTP study 261202 -Q2 2018: Estimated date of the final CSR for Pediatric PUP study 261203 -Nov 2017: Estimated date of the final CSR for PK guided dosing study *261303</p>	
Important Missing Information		
No clinical data on pediatric patients <12 y o	<p>- Identify trends in the frequency and severity of reports involving pediatric patients < 12 years of age and identify any potential safety-related issues. -Routine Pharmacovigilance</p> <p>-Additional Pharmacovigilance May 2016: Estimated date for completion of the final CSR for Pediatric PTP study 261202</p>	Safety & efficacy of BAX 855 has not been evaluated in pediatric patients <12 years of age.

Safety Issue/Area	Proposed Activity/Plan	Comments
No clinical data on use in geriatric patients ≥65 y o	<p>Identify trends in the frequency and severity of reports involving geriatric patients ≥ 65 years of age and identify any potential safety-related issues.</p> <p>Routine Pharmacovigilance</p> <p>Additional Pharmacovigilance</p> <p>-Q4 2017: Estimated date of the final CSR for Continuation study 261302</p> <p>-May 2015: Estimated date of the final CSR for Surgery study 261204</p>	The safety and efficacy of BAX 855 has not been evaluated in geriatric patients ≥ 65 years of age.
No clinical data on previously untreated patients	<p>Describe immune profile in PUPs during treatment of bleeding episodes.</p> <p>Assess safety and effectiveness of BAX 855 in PUPs in treatment of bleeding episodes.</p> <p>Additional Pharmacovigilance</p> <p>March 2018: Estimated date of the final CSR for Pediatric PUP study *261203</p>	The safety and efficacy of BAX 855 has not been evaluated in PUPs.

*See ongoing and planned studies post licensure in table below

3.6.2 Ongoing and Planned Post-licensure Studies

Table 3: Ongoing and Planned additional Pharmacovigilance studies and activities

Actions	Milestones/Exposure	Milestones/ Calendar	Study Status	Planned Date for Submission of Final Data
Pediatric PUP study 261203	First subject in Last subject out Completion of interim report Completion of final report	Q4 2015 Q1 2018 Not applicable Q2 2018	Planned	Estimated completion date of final CSR: Q2 2018
PK guided dosing study 261303	First subject in Last subject out Completion of interim report Completion of final report	Q2 2015 July 2017 October 2016 November 2017	Planned	Estimated completion date of final CSR: November 2017

4 REVIEW OF OTHER INFORMATION FROM THE MANAGED REVIEW PROCESS

4.1 Clinical Reviewer Summary

No safety issues have been identified from Clinical reviewers other than as described above. If additional safety issues are communicated to OBE/DE or identified in the reviewer's final memorandum, they will be summarized and addressed in an addendum.

4.2 Statistical Reviewer Summary

4.3 No safety issues have been identified from Statistical reviewers other than as described above. If additional safety issues are communicated to OBE/DE or identified in the reviewer's final memorandum, they will be summarized and addressed in an addendum.

5 POST LICENSURE SAFETY REVIEW

None available – BAX855 is not currently licensed in any country.

6 INTEGRATED RISK ASSESSMENT

An integrated analysis of safety data demonstrated that BAX 855 was safe and well tolerated in 169 PTPs with severe hemophilia A from 2 completed and 3 ongoing studies. Subjects were treated with BAX 855 for prophylaxis, bleeding episodes, perioperative management, or received a single-dose for a PK evaluation. One hundred and seventeen adolescent and adult subjects (117) were treated long-term with BAX 855, by initiating treatment in the pivotal study and continuing in the continuation study. No AEs considered allergic or hypersensitivity reactions were observed in any of the studies.

With regard to immunogenicity, none of the subjects developed inhibitory antibodies to FVIII of ≥ 0.6 BU/mL, and no persistent binding antibodies to FVIII, PEG-FVIII or PEG developed (Section 3.2.1.1.1). Therefore, no study subjects met the study definition of FVIII inhibitor development. Although this finding is reassuring, the limitations of the clinical safety database with regard to development of FVIII inhibitors, such as the relatively small number of subjects, absence of longer-term studies, and sparse data in young children, must be considered when interpreting these results.

With regard to the potential for HCV infection or reinfection via the product; HCV reactivation occurred in 1 subject out of 77 total subjects enrolled with stable HCV. This is a recombinant product and the sponsor reports in the product description in the PVP and draft PI that “cell culture, purification process and formulation used in the manufacture of BAX 855 do not use additives of human or animal origins”. Therefore, it seems very unlikely that the subject’s HCV reactivation could be due to new infection with HCV from the study drug. In addition, from an epidemiological perspective, we might expect additional findings in other study subjects, which was not the case. Lastly, reactivation of HCV is well described in the literature as part of the natural history of the disease. Risk factors for reactivation are not fully understood but are thought to include both host and viral factors. Host factors may include older age at the time of infection, male sex, alcohol abuse, immunosuppression, and genotype 2c (5). Thus, there appears to be an alternate explanation for reactivation in this patient (natural history of HCV in a male patient). Since, we have no biologically plausible mechanism by which the study drug might reactivate HCV, there is insufficient evidence to directly attribute reactivation of HCV to the study drug.

A total of 16 SAEs in 11 subjects were observed, none of which were considered related to BAX 855 as assessed by the investigator and the sponsor. The data submitted in support for this BLA do not identify safety issues in the use of BAX855 for the treatment of bleeding episodes, including for long-term use in adolescent and adult PTPs with severe hemophilia A. Any potential safety issues were adequately addressed by the sponsor in their risk management plan.

6 RECOMMENDATIONS

Based on the completed review of the risk management plan, OBE/DE agrees with the Risk Management Plan as proposed by the Sponsor. These include:

- Routine pharmacovigilance as proposed by the sponsor in the PVP to monitor adverse events in accordance with 21 CFR 600.80
- Periodic adverse event reports should include details of the potential risks and missing information identified in this safety review
- Study 261203, evaluation of safety and efficacy of Bax855 in PUPs, conducted as a post marketing commitment (PMC).
- The pediatric study 261202, and the pediatric patients portions of the surgery study 261204, conducted as Pediatric Research Equity Act (PREA, 21 CFR 314.81) post marketing requirement studies.

8 CONCLUSIONS

After review of the pre-licensure safety data, and the proposed pharmacovigilance plan, the OBE/DE reviewer has not identified any new safety concerns that warrant a post-marketing requirement study (PMR) or a Risk Evaluation and Mitigation Strategy (REMS) Study. If any further safety concerns are identified, FDA may recommend further modification of the pharmacovigilance activities.

9 REFERENCES

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