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BLA Clinical Review Memo

Application Type	Efficacy Supplement
STN	125566/607
CBER Received Date	May 15, 2020
PDUFA Goal Date	June 14, 2021
Division / Office	DCEPT /OTAT
Priority Review	No
Reviewer Name(s)	Poornima Sharma Poornima Sharma -S
Review Completion Date / Stamped Date	June 14, 2021
Supervisory Concurrence	Tejashri Purohit Sheth MD
Applicant	Baxalta US Inc.
Established Name	Antihemophilic Factor (Recombinant), PEGylated
Trade Name	BAX 855
Pharmacologic Class	Coagulation factor
Formulation(s), including Adjuvants, etc.	Lyophilized powder in single-use vials
Dosage Form(s) and Route(s) of Administration	250, 500 ,1000 or 2000 international units (IU) for intravenous use
Dosing Regimen	On-demand treatment and control of bleeding episodes & perioperative management: Estimated Increment of factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg); Dose (IU) = Body Weight (kg) x Desired factor VIII Rise (IU/dL or % of Normal) x 0.5 (IU/kg per IU/dL); Routine prophylaxis: Administer (b) (4) IU per kg body weight 2 times a week (40-60 IU per kg body weight in patients <12 years of age).
Indication(s) and Intended Population(s)	On-demand treatment and control of bleeding episodes; Perioperative management; Routine prophylaxis to reduce the frequency of bleeding episodes for adults and children
Orphan Designated (Yes/No)	No

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Glossary

AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMV	cytomegalovirus
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
DIS	Division of Inspections and Surveillance
eCTD	electronic Common Technical Document
ELISA	Enzyme-Linked Immunosorbent Assay
ES	Executive Summary
FDAAA	Food and Drug Administration Amendments Act of 2007
GRMP	good review management principles
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ISE	integrated summary of efficacy
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NDA	new drug application
NME	new molecular entity
OBE	Office of Biostatistics and Epidemiology
OCOD	Office of Communication Outreach and Development (CBER)
OSE	Office of Surveillance and Epidemiology
PD	pharmacodynamics
PeRC	Pediatric Review Committee (CDER)
PI	package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PSA	prostate-specific antigen
REMS	risk evaluation and mitigation strategy
RMS/BLA	regulatory management system for the biologics license application
RTF	refuse to file
SAE	serious adverse event
PTP	previously treated patient

1. EXECUTIVE SUMMARY:

Adynovate or BAX 855 (Antihemophilic Factor (Recombinant), PEGylated; rFVIII, PEGylated) is a lyophilized protein manufactured in Chinese Hamster Ovary (CHO) cells. The fusion protein consists of a full-length form of recombinant antihemophilic factor (b) (4) to the marketed Antihemophilic Factor (Recombinant) product, ADVATE) covalently conjugated to a polyethylene glycol (PEG) reagent. The product consists of a

mixture of rFVIII molecules with varying degrees of PEGylation (varying ratios in the number of molecules of PEG moiety conjugated covalently to each rFVIII moiety) with the mean ratio of (b) (4) The PEG enables an increase of the plasma half-life through the reduction of receptor-mediated clearance of the factor VIII molecule. As a result, BAX 855 is longer-acting and was developed for intravenous replacement therapy or prophylaxis on a less frequent basis than standard regimens in hemophilia A. The elimination half-life of BAX 855 is 14.3 hours compared to an average half-life of 8-12 hours in non-fusion protein plasma derived for recombinant FVIII products.

BAX 855 was initially approved for the adolescent and adult patients (12 years or older) with hemophilia A for on-demand treatment and control of bleeding episodes and routine prophylaxis to reduce the frequency of bleeding episodes on November 13, 2015. The indication was expanded for on-demand treatment and routine prophylaxis in children (<12 years of age) and for perioperative management in children and adults on December 25, 2016.

On May 15, 2020, the Applicant submitted an efficacy supplement which included labeling changes based on data from the three completed studies including post marketing commitment studies (PMC) and post-marketing requirement study (deferred pediatric PREA PMR) see Table 1. On September 2020, a major amendment was issued to the BLA after the Applicant submitted final datasets to replace draft datasets that were erroneously submitted for two studies included in the submission (Studies 302 and 303).

The studies included in the BLA submission are summarized below:

Table 1

Study Name	Study Description	PMC/PMR	Regulatory status
PROPEL Study (303)	A phase 3, prospective, randomized, multicenter clinical study comparing the safety and efficacy of BAX 855 [BAX 855] following PK-guided prophylaxis targeting two different FVIII trough levels in subjects with severe Hemophilia A	Ages 12 to < 17 years: PREA PMR Adult component: PMC	PMC or PMR not fulfilled
Study 302	A phase 3b, prospective, open label, and multi-center continuation study of safety and efficacy of BAX 855 in the routine prophylaxis of bleeding to reduce the frequency of bleeding episodes in PTPs	PMC	Fulfilled on August 4,2020
Study 204	A phase 3, prospective, open label, multicenter study of efficacy and safety of BAX 855 in the perioperative management of bleeding in PTPs age 2-75 years.	Adult component: PMC	Fulfilled on January 15,2019

Following approval of this submission, the Applicant will have a single outstanding PMC study remaining, which is a phase 3, multi-center, open label study to investigate safety and immunogenicity of BAX 855 in previously untreated patients (PUPs) [clinical study

261203]. This study will evaluate on-demand treatment, routine prophylaxis, and perioperative management of bleeding in PUPs.

Based on the results of Study 303, the Applicant proposed to (b) (4)

The Applicant also proposed to (b) (4) However, Sections 6.2.1 and 14 of the prescribing information were updated based on the clinical review and the supplement pursuant to the official withdrawal as per above is recommended for approval.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Demographics for Study 303:

Parameter		Low Target Trough Arm n=57	High Target Trough arm N=58	N=115
Age (years)	Mean (SD)	31(13.7)	31(12)	31(12.9)
	Min, Max	12;61	13;61	12;61
	≥12 to <18 years	10 (18%)	7 (12%)	17(15%)
	≥18 years	47 (82%)	51 (88%)	98 (85%)
Race	White	40 (70%)	36 (62%)	76 (66%)
	Asian	14 (25%)	18 (31%)	32(28%)
	Other	3 (5%)	4 (7%)	7(6%)

Demographics for Study 302:

Parameter	Category	Age <6 n (%)	Age ≥6 to <12 n (%)	Age ≥12 to <18 n (%)	Age ≥18 n (%)	Total n (%)
Number of Subjects in Study Group	N	32	33	30	121	216
Gender	Male	32 (100.0)	32 (97.0)	30 (100.0)	121 (100.0)	215 (99.5)
	Female	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (0.5)
Race	Asian	7 (21.9)	9 (27.3)	5 (16.7)	37 (30.6)	58 (26.9)
	Black or African American	1 (3.1)	2 (6.1)	1 (3.3)	0 (0.0)	4 (1.9)
	White	22 (68.8)	22 (66.7)	24 (80.0)	84 (69.4)	152 (70.4)
	Other	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
	Mixed	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Ethnicity	Hispanic or Latino	1 (3.1)	2 (6.1)	0 (0.0)	7 (5.8)	10 (4.6)
	Not Hispanic or Latino	31 (96.9)	31 (93.9)	30 (100.0)	114 (94.2)	206 (95.4)
Previous BAX 855 study participated in	None	6 (18.8)	4 (12.1)	0 (0.0)	0 (0.0)	10 (4.6)
	At least one previous BAX 855 study	26 (81.3)	29 (87.9)	30 (100.0)	121 (100.0)	206 (95.4)
	BAX 855 phase 1 study (261101)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)	2 (0.9)
	BAX 855 phase 2/3 pivotal study (261201)	0 (0.0)	0 (0.0)	20 (66.7)	97 (80.2)	117 (54.2)
	BAX 855 pediatric study (261202)	24 (75.0)	29 (87.9)	4 (13.3)	0 (0.0)	57 (26.4)
	BAX 855 PUP study (261203)	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)
	BAX 855 surgery study (261204)	0 (0.0)	0 (0.0)	1 (3.3)	14 (11.6)	15 (6.9)

Source: BLA 125566/383 Section 5.3 5.2, Clinical Study Report: Study 302, Page 77

Study 204:

Demographic data for the 22 subjects that were enrolled indicated that all subjects were males between 16 and 61 years of age with mean age (SD) of 35(13.4) years. The majority were white (20/22) with one Asian and one Black or African American.

Reviewer's comment: The limited representation of Blacks and Hispanics makes it challenging to reach conclusions about the efficacy of BAX 855 in these races. Since the predilection for clinical bleeding is primarily dependent on the degree of factor VIII deficiency, race-related differences in efficacy of BAX-855 are expected to be minimal. Therefore, it is reasonable to extrapolate the efficacy data from Whites and Asians to the other ethnic groups.

1.2 Patient Experience Data

Table 2: Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	Section 6
☐	Observer-reported outcome	
☒	Clinician-reported outcome	Section 6
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A (HA) is a rare hereditary blood disorder caused by deficiency or dysfunction of Factor VIII (FVIII) resulting in bleeding. The hemophilia A gene is located on the X chromosome with an X-linked recessive inheritance pattern and spontaneous gene mutation in 30% of cases, affecting 1 in 10,000 male births, with approximately 20,000 affected males in the United States. The relationship of bleeding severity correlates with clotting factor level. Patients with <0.01 IU/ mL or <1% of functional FVIII are categorized as severe with spontaneous bleeding into joints or muscles. Moderate severity and mild severity have clotting factor levels of 1-5% and 5 to<40%, respectively. To prevent joint destruction, the standard of care for severe HA is primary prophylaxis with infusions of FVIII. These regular infusions are initiated at the time of the first bleeding episode in a joint or earlier aiming to prevent joint damage. However, inhibitory

antibodies to infused FVIII products develop in a substantial percentage of patients treated with either plasma derived or recombinant FVIII products, making usual treatment with FVIII complicated. Prophylaxis has been shown to prevent complications later in life and to decrease the incidence of inhibitor formation.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently, there are over ten licensed recombinant FVIII products some of which are full-length FVIII products and others that are beta domain deleted (BDD) products. These products are indicated for adults and children with Hemophilia A for the control and prevention of bleeding episodes, and/or perioperative management, and/or routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage. These include: Recombinate, Kogenate, Refacto, Advate, Xyntha, Novoeight, Eloctate, Obizur, Nuwiq, Afstyla, Kovaltry, JIVI and Eloctate.

2.3 Safety and Efficacy of Pharmacologically Related Products

BAX 855 or Adynovate is a fusion protein that consists of a full-length form of recombinant antihemophilic factor (b) (4) to the marketed recombinant Antihemophilic Factor product (ADVATE), covalently conjugated to a polyethylene glycol (PEG) reagent. ADVATE was FDA approved in 2003. Safety concerns as stated in the prescribing information for ADVATE include hypersensitivity and Factor VIII inhibitors. ADVATE is indicated for the control and prevention of bleeding episodes, perioperative management and routine prophylaxis to prevent and reduce the frequency of bleeding episodes. The rFVIII products are genetically engineered and manufactured from animal cell lines, thus minimizing the risk of transmission of human pathogens. Full- length and modified rFVIII have been produced in Chinese hamster ovary (CHO) or baby hamster kidney (BHK) cells. In addition to the risk of pathogen transmission, the development of neutralizing antibodies, or inhibitors, has been and remains the most concerning safety issue following the administration of FVIII concentrates. The etiology of the development of inhibitors is thought to be a host immune response triggered by non-human proteins contained in the final recombinant FVIII product. Purification steps in the manufacturing processes of successive generations of rFVIII aim to reduce both the transmission of pathogens and the development of inhibitors, which occurs in up to 30% of patients with severe Hemophilia A1.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Human subjects were exposed for the first time to BAX 855 under IND 15299 and the original BLA 125566/0. BAX 855 is currently licensed in the USA and various countries worldwide including EU, Canada, South America, UAE and Australia.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The evidence for safety and effectiveness for this product was collected under IND 15299. No pre-BLA meeting request was submitted for this BLA supplement.

Pre-submission Regulatory activity:
Study 204 (Perioperative trial): The interim study report was submitted on February 25, 2016 under efficacy supplement 125566/51 and results from this interim study supported approval of the perioperative indication in the pediatric and adult population. This approval on December 22, 2016 resulted in fulfillment of PREA PMR for the perioperative indication. The final study report with datasets was submitted on May 11, 2017 under amendment 234. A PMC fulfilled letter was issued on January 15,2019.

Study 302 (Extension Study) was designed to be in compliance with EMA/CHMP/BPWP recommendations for the study of FVIII in severe Hemophilia A. The final study report with datasets was submitted on October 1, 2018 under amendment 383. A PMC fulfilled letter was issued to the Applicant on August 4, 2020.

Study 303 (Randomized Phase 3 trial evaluating PK directed dosing targeting different FVIII trough levels) A pre-IND meeting (CRMTS#8603) was held on September 19, 2012 to discuss the study proposal. Subsequently, the Phase 3 clinical protocol was submitted under amendment 26 for IND 15299. Review team provided feedback regarding handling of missing data, sample collection for PK analysis and statistical analysis plan. A final study report with datasets was submitted on October 4, 2019 under amendment 526.This was reviewed as a final study report since no efficacy supplement was submitted. Therefore, per PeRC and clinical review team a PMC/PMR fulfilled letter was not issued.

Post-submission Regulatory Activity:

- On September 2020, a major amendment was issued to the BLA after the Applicant submitted final datasets to replace draft datasets that were erroneously submitted for two studies included in the submission (Studies 302 and 303).
- March 29, 2021, Agency recommended that Applicant withdraw request to modify Indication and Dose and Administration sections of the submission. The Applicant accepted Agency's recommendation.

2.6 Other Relevant Background Information

Since Study 303 evaluated a new dosing regimen (PK directed dosing targeting a FVIII trough level of 8-12%);the pediatric portion (12 to <17 years) of the study is considered PREA PMR, while the adult portion (≥17 years) of the study is considered a PMC.
Study 302: This is a PMC study to confirm the long-term safety and efficacy of the approved twice weekly prophylactic regimen of BAX 855. This PMC has been fulfilled.
Study 204:The perioperative indication was granted in December 2016 based on interim results of Study 204. The completion of the adult portion of the study is PMC as it confirmed the efficacy of BAX 855 in the perioperative setting. This PMC has been fulfilled.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

Final study report and related datasets submitted under BLA 125566 for each study included in the submission is outlined below:
Study 204 : Amendment 234
Study 302: Amendment 526

Study 303: Amendment 383

3.2 Compliance With Good Clinical Practices And Submission Integrity

A bioresearch monitoring audit process and report was not requested from the Division of Inspections and Surveillance (DIS) given the prior regulatory history of BIMO inspections without major findings that impacted the review.

3.3 Financial Disclosures

Covered clinical study (name and/or number): Studies 204,302 and 303		
Was a list of clinical investigators provided:	Yes ☒	No (Request list from applicant)
Total number of investigators identified: 240		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 11		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 11 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes	No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes	No (Request explanation from applicant)

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls:

No new CMC data were submitted with this supplement.

4.2 Assay Validation

Please refer to the CMC review memo from the original BLA for complete details.

4.3 Nonclinical Pharmacology/Toxicology

No new Pharmacology/Toxicology data were submitted with this supplement. Please see Pharmacology/Toxicology review memo from the original BLA for complete details.

4.4 Clinical Pharmacology

Please refer to the Clinical Pharmacology review memo for this efficacy supplement for complete details.

4.4.1 Mechanism of Action

BAX 855 temporarily replaces the missing clotting factor VIII needed for effective hemostasis in patients with hemophilia A. Upon activation of the clotting cascade, FVIII is converted to activated FVIII and acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X on phospholipid surfaces, which ultimately converts prothrombin to thrombin and leads to the formation of a fibrin clot.

4.4.2 Human Pharmacodynamics (PD)

N/A

4.4.3 Human Pharmacokinetics (PK)

See Clinical Pharmacology review memo for full details regarding the pharmacokinetics data for the studies. (b) (4)

4.5 Statistical

Please refer to the Statistical review memo for full details.

4.6 Pharmacovigilance

The analyses of the safety data did not identify new safety issues that warrant additional pharmacovigilance over routine pharmacovigilance.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Review of this supplement was based on clinical data provided in BLA 125566/607.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Documents pertinent to this review were provided in 125566/607, 234, 383, 526, 51 and IND 15299, including the clinical summary, overview, and clinical study reports. Studies 261303, 261302, and 261204 form the basis of this supplement review.

5.3 Table of Studies/Clinical Trials

The completed, in-progress, and planned post-marketing clinical trials are summarized in Table 3 below:

Table 3

Study Number	Short Study Title and Description	Study Status Report (if Available)	Sample Size[a]	Main Criteria for Inclusion	Dose Range and Frequency
261101	**BAX 855 Dose-escalation Safety** Phase 1, first-in-human, prospective, open label, crossover, dose-escalation study to evaluate safety and PK parameters of single doses of BAX 855 compared to single doses of ADVATE	Complete CSR 261101	19	PTPs[b] 18 to 65 years FVIII <1%	Two sequential dose cohorts: Cohort 1: Single administration of 30 IU/kg BW of ADVATE followed by administration of the same dose of BAX 855 after a wash-out period >96 h Cohort 2: Single administration of 60 IU/kg BW of ADVATE followed by administration of the same dose of BAX 855 after a wash-out period >96 h Acute bleeding episodes: treated with ADVATE
261201	**BAX 855 Pivotal** Phase 2/3, multicenter, open label, 2-arm study to evaluate efficacy, safety, and PK parameters of BAX 855 and HRQoL	Complete CSR 261201	138	PTPs[b] 12 to 65 years FVIII <1%	Prophylaxis: 45 ± 5 IU/kg BW twice weekly for ≥50 EDs[c] or 6 months ± 2 weeks, whichever occurs last On-demand: 10 - 60 ± 5 IU/kg BW for an approximate duration of 6 months Acute bleeding episodes: treated with BAX 855 PK evaluation: ADVATE and BAX 855 at prophylactic dose level
261202	**BAX 855 Pediatric** Phase 3 prospective, uncontrolled, multicenter study to evaluate PK, efficacy, safety, and immunogenicity of BAX 855	Complete CSR 261202	66 2 age groups (32 aged <6 years and 34 aged 6 to <12 years)	PTPs[b] <12 years FVIII <1%	Prophylaxis: 50 ±10 IU/kg BW over a period of 6 months, or at least 50 EDs[c] Acute bleeding episodes: treated with BAX 855 PK evaluation: ADVATE and BAX 855 at 60 ± 5 IU/kg

Study Number	Short Study Title and Description	Study Status Report (if Available)	Sample Size[a]	Main Criteria for Inclusion	Dose Range and Frequency
261204	**BAX 855 Surgery** Phase 3, prospective, open label multicenter study of efficacy and safety of BAX 855 in surgical or other invasive procedures	Complete CSR 261204	21 unique subjects who underwent 21 major and 5 minor surgeries; 22 subjects evaluable for safety	PTPs[b] 2 to 75 years FVIII <1%	Surgical prophylaxis: dose tailored to achieve FVIII target levels of 80 - 100% of normal for major and 30 - 60% of normal for minor surgeries
261302	**BAX 855 Continuation** Phase 3b, prospective, open label, multicenter continuation study of safety and efficacy of BAX 855 in the prophylaxis of bleeding	Complete CSR 261302	216	PTPs[b] who completed another BAX 855 study or BAX 855 naïve ≤75 years FVIII <1%	Fixed-dose prophylaxis[d] depending on age, given twice weekly OR PK-tailored prophylaxis to maintain trough FVIII level ≥3% For at least 100 EDs
261303	**BAX 855 PK-tailored Dosing** Phase 3, prospective, randomized, open-label multi-center clinical study to compare the safety and efficacy of PK-tailored BAX 855 dosing targeting 2 different FVIII trough levels	Complete CSR 261303	121, 57 in the 1-3% trough arm, 58 in the 8-12% trough arm, 6 not randomized	PTPs[b] who completed another BAX 855 study; or BAX 855 naïve; 12 - 65 years of age with FVIII <1%	PK-tailored BAX 855 dose to maintain FVIII target trough levels of 1 - 3% or 8 - 12% FVIII trough level 1 - 3%: approximately twice weekly FVIII trough level 8% - 12%: every other day

Table 3a

Study Number	Short Study Title and Description	Study Status Report (if Available)	Sample Size[a]	Main Criteria for Inclusion	Dose Range and Frequency
261203	**BAX 855 PUPs** Phase 3, multi-center, open-label study to investigate safety, immunogenicity and efficacy of BAX 855 in PUPs	Ongoing	120 (100 evaluable)	PUPs <6 years, FVIII <1%, who have undergone <3 EDs[e] with ADVATE, BAX 855 or plasma	Prophylaxis: to be initiated before the age of 3 years or once the subjects has experienced 2 joint bleeds before the age of 3 years, whichever occurs first; at least once weekly dosing of 25 – 50 IU/kg, which may be increased to 80 IU/kg On-demand: only if subject is <3 years of age and has less than 2 joint bleeds; 10 – 80 IU/kg depending on bleeding severity In case of FVIII inhibitors: high-dose regimen of 100 - 200 IU/kg daily or low-dose regimen of 50 IU/kg 3 x/week with or without bypassing agents

Source: BLA 125566/607: Clinical Overview Addendum, In text Table -1, Pages 11-13

5.4 Consultations:

No consultations were requested by the review team.

5.4.1 Advisory Committee Meeting (if applicable)

Not applicable

5.4.2 External Consults/Collaborations:

Not applicable

5.5 Literature Reviewed:

1. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020: 26(Suppl 6): 1-158. https://doi.org/10.1111/hae.14046

6.1 Study 1: 261303

Study 261303, a Phase 3, prospective, randomized, open-label, multicenter study compared the safety and efficacy of a PK-tailored BAX 855 dose regimen targeting 2 different FVIII trough levels of 1-3% and approximately 10% (8-12%) in adolescent and adult PTPs ≥12 years to <65 years of age with severe hemophilia A (<1% FVIII).

6.1.1 Objectives:

Primary Objective:

The primary objective of the study was to compare 2 prophylactic dosing regimens of BAX 855 targeting 2 different FVIII trough levels, by comparing the proportions of subjects achieving a total annualized bleeding rate (ABR) of 0 in the second 6-month study period.

Secondary Objectives:

Efficacy:

1. To compare the 2 prophylactic dosing regimens of BAX 855 targeting 2 different FVIII trough levels with respect to the following:
   - □ The proportion of subjects in each prophylactic dosing arm achieving a spontaneous ABR and spontaneous annualized joint bleeding rate (AJBR) of 0 in the second 6-month study period
   - □ The proportion of subjects in each prophylactic dosing arm with a total, spontaneous ABR and AJBR <2
   - □ The total, spontaneous, and trauma-related ABRs in the 12-month study period
   - □ The reduction in ABR between the 2 prophylactic dosing arms and the historical ABR prior to study enrollment
   - □ The total weight-adjusted consumption of BAX 855 for each prophylactic regimen
   - □ The joint status using the hemophilia joint health score (HJHS) and over time
   - □ Health-related quality of life (HRQoL) and pharmacoeconomic outcomes
2. To determine the hemostatic efficacy of BAX 855 in the control of bleeding episodes.
3. To evaluate the efficacy of BAX 855 for perioperative management, if surgery was required.

Safety: To determine immunogenicity and safety of BAX 855

PK: To determine the PK parameters of BAX 855 at baseline and at steady state and to determine IR over time.

PRO: To determine the difference in the SF-36 physical domain, component change scores and change of days of physical activity participation from baseline and during follow up between subjects in 10% and 1-3% trough arm.

6.1.2 Design Overview

This was a Phase 3, prospective, randomized, open-label, multicenter study to compare the safety and efficacy of PK guided BAX 855 prophylaxis targeting FVIII trough levels of 1-3% and 10%(8-12%). The study was planned in a total of 96 evaluable adolescent and previously treated adults with severe hemophilia A.
Subjects were screened and after confirmation of eligibility, underwent initial PK assessment following a single administration of BAX 855 at 60+/-5IU/kg. Thereafter, subjects were randomized to one of the two dosing regimens: the standard prophylaxis arm targeting FVIII trough levels of 1-3% or the second, intensified prophylaxis arm targeting FVIII trough level of 10% (8-12%). Subjects were followed in the study for 12 months. During the first six months on the study, subjects underwent dose adjustment based on FVIII trough levels determined at each study visit. During the second 6 months (Days 182-364), dose adjustments could only be performed if FVIII trough levels were considerably below 1% and 8% for the low and high target trough arms, respectively. The primary endpoint was evaluated during the second 6-month period.
Randomization was stratified according to subjects' pre-study treatment regimen and the annualized bleed rate; and prophylaxis with ABR <5 vs. prophylaxis with ABR ≥5 vs. on-demand.

6.1.3 Population

Key Inclusion criteria:

- Subject could have completed end of study visit of a BAX 855 study or transitioned from continuation Study 302 or be a new subject who is BAX 855 naïve.
- 12-65 years old with severe hemophilia A (FVIII clotting activity <1%).
- ≥150 exposure days to any FVIII product.
- Subject receiving on-demand or prophylaxis with an ABR ≥2 during the past 12 months
- If subject is HIV positive, then CD4+ count ≥200 cells/mm3
- Subject should be hepatitis C negative (HCV-) or HCV+ with chronic stable hepatitis.

Key exclusion criteria:

- Confirmed inhibitory antibody to FVIII with titer of ≥0.6BU during the course of previous BAX 855 study.
- Any acquired hemostatic defect, platelet count <100,000/ml
- Serum creatinine >1.5 times ULN.
- Active hepatic disease with ALT and/or AST ≥5xULN.
- Subject is to receive systemic immunomodulating drug
- Weight is <35kg or >100kg.
- Known hypersensitivity towards mouse or hamster proteins, PEG or tween 80.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Prophylaxis regimen:
The two PK tailored dosing regimens are outlined below:

- FVIII target trough levels of 1-3% with twice daily dosing: BAX 855 was administered twice weekly, with alternating 3 days and 4 days interval. Dosing was different for the two intervals. Alternatively, an infusion may be administered every 3.5 days.

- FVIII target trough levels of ~10% (8-12%) with dosing every other day: more frequent dosing (including daily dosing for high trough arm) could be considered if single doses of ≥80IU/kg are required or regular FVIII peak levels of 200% would be reached. The required dose and frequency was provided by sponsor. Subjects requiring treatment for a breakthrough bleeding episode could resume their PK tailored prophylaxis as soon as bleeding was resolved. If a dose was missed, it had to be documented and the next dose was to be taken as soon as possible after which the regularly scheduled regimen had to be resumed. The days of week on which the treatment was administered could be selected by the subject or his physician which would provide maximum coverage for physical activity.

Adjustment of BAX 855 dose and /or frequency adjustment:

In the first 6 months of the study: FVIII trough level was determined at each study visit. Before dose adjustment, a confirmatory FVIII trough level determination at an additional study visit within 2 weeks was performed. After receipt of the repeat FVIII activity, dose adjustments were performed. A repeat FVIII trough level was determined 2 weeks after dose adjustment.
The following were triggers for dose adjustment during the first 6 months:

- If the lower FVIII trough activity level is < 1% and < 8% respectively
- If the upper FVIII trough activity level exceeds 3% and 12% respectively

In the second 6-month period:
Dose adjustment was performed if:

- FVIII trough levels are considerably below 1% and 8% respectively .
- FVIII trough levels are considerably above 3% and 12% respectively.

Guidance for dose adjustment:

- In case of FVIII levels < 1% in the low dose arm, the dose was increased by approximately 30%.
  - For FVIII levels > 3% in the low dose arm, or FVIII levels > 12% or < 8% in the high dose arm, the adjusted dose was calculated using the formula below:

    $Dose_{adj} = (TL_{target} / TL_{predicted}) Dose_{current}$ where TL_{target} is the target trough level (1.7% or 10%) and $TL_{predicted}$ is the TL predicted under the current dose.

  - For low FVIII levels, the BAX 855 dosage could be increased up to maximum of 80+/-5IU/kg and or the dosing frequency may be increased as long as FVIII peak did not exceed 200%.

Treatment of Bleeding episodes: Please refer to Table 4 below:

Table 4:

BAX 855 Treatment Guidelines for Bleeding Episodes

Type of Bleeding Episode	**FVIII Level Required (%)** *Dose (IU/kg)*	**Frequency of Dosing**
Minor Early hemarthrosis, mild muscle bleeding, or mild oral bleeding, including, epistaxis	20 to 40% *10 to 20 (±5) IU/kg*	Repeat infusions every 12 to 24 h for 1 to 3 days or until the bleeding episode is resolved
Moderate Moderate bleeding into muscles, bleeding into the oral cavity, definite hemarthrosis, and known trauma	30 to 60% *15 to 30 (±5) IU/kg*	Repeat infusions every 12 to 24 h for 3 days or more until the pain and acute disability/ incapacity are resolved
Major Significant gastrointestinal bleeding, intracranial, intra-abdominal, or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces or iliopsoas sheath, fractures, head trauma	60 to 100% *30 to 60 (±5) IU/kg* In case of life-threatening bleeds, a dose of 80 (±5) IU/kg may be considered	Repeat infusions every 8 to 12 h until the bleeding episode/threat is resolved

The required units will be calculated according to the following formula:

body weight (kg) x desired FVIII rise (%) (IU/dL) x {reciprocal of observed recovery}

Source: BLA 125566/526,Section 5, Appendix 16.1.1: Clinical protocol Study 303,Amendment 3, Section 8.7.7.

If possible, subjects' most recent individual IR should be used. In its absence, an anticipated recovery of 2.5IU(IU/dl)/IU/kg based on the PK data with BAX 855 should be assumed using the following formula:

body weight (kg) x desired FVIII rise (% or (IU/dL) x 0.4 dL/kg

- Treatment of a bleed was to be initiated as soon as possible after occurrence of the bleeding episode. When bleeding was controlled, additional infusions of BAX 855 to maintain hemostasis were permitted if required and these additional infusions were documented in e CRF. If 2 or more responses to treatment of unique bleeding episodes were rated "fair", the investigator may re-evaluate the dosing regimen and the time from bleeding onset to the start of treatment.

Reviewer's comment:

The dosing recommendations for the on-demand treatment of bleeding episodes are similar to dosing evaluated in the licensing study, 201(10-60IU/kg+/-5 IU/kg), and the approved dosing for the on-demand treatment of bleeding episodes, which is 10-50IU/kg. The protocol allowed for a slightly higher dose (30-60 IU/kg) than currently approved by the label (30-50 IU/kg) for the management of major bleeding episodes with a dose of up to 80IU/kg for the treatment of life-threatening bleeding, which is reasonable.

Prior and concomitant therapy: Administration of any pegylated medication was not permitted within 30 days before study entry and during the course of the

study. Hemostatic agents such as tranexamic acid, were permitted as clinically indicated to treat mucosal bleeding or perioperative management. The use of commercial ADVATE was permitted for a short period for administrative reasons.

6.1.6 Sites and Centers

A total of 87 study sites from 23 countries participated in the study. Sixty-two study sites in 19 countries enrolled a total of 135 subjects.

6.1.7 Surveillance/Monitoring

All study procedures were to be performed under direct supervision of the Investigator at the study site.
Table 5

Study Procedures and Assessments

Procedures/ Assessments	Screening Visit	PK Assessment[a] Pre infusion, 15-30 min, 3 ±0.5 h, 8 ±0.5 h, 24 ±2 h, 48 ±4 h, 72 ±4 h & 96 ±4 h Post- Infusion	Baseline Visit	Study Visits								Completion/ Termination Visit[c] 12 Mo (53 ±1 Wk)
				Visit 4Wk ±5d	Visit 8Wk ±1Wk	Visit 3 Mo ±2Wk	Visit 4.5 Mo ±2Wk	Visit 6 Mo ±1Wk (26 ±1Wk)	Phone Visit 7.5 Mo ±2Wk[b]	Visit 9 Mo ±2Wk + optional PK	Phone Visit 10.5 Mo ±2 Wk[b]	
Washout	N/A	72-96 h		Consistent with the infusion interval according to the treatment regimen provided to the subject and immediately before the next planned regular prophylactic infusion.								
Informed consent[d]	X											
Eligibility criteria	X											
Medical and medication history[e]	X*											
Concomitant medications[f]	X*	X	X	X	X	X	X	X	X	X	X	X
Non-drug therapies[f]	X*	X	X	X	X	X	X	X	X	X	X	X
Physical exam[g]	X*	X	X			X		X	(X)[b]	X	(X)[b]	X
Vital signs[h]	X*	X	X	X	X	X	X	X	(X)[b]	X	(X)[b]	X
Adverse events[f]	*	X	X	X	X	X	X	X	X	X	X	X
Bleeding episodes and their treatment[f,i]	*			X	X	X	X	X	X	X	X	X
Assessment of target joints[j]	X		X			X		X	(X)	X	(X)	X
Joint score (HJHS)			X									X
X-ray of impaired joint			X[k]	(X)[k]								
Subject diary[l]	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments[m]	X*	X	X	X	X	X	X	X	(X)[b]	X	(X)[b]	X
IP treatment[n]		X	X	X	X	X	X	X	(X)[b]	X	(X)[b]	X

Source: BLA 125566/526,Section 5, Appendix 16.1.1: Clinical protocol Study 303,Amendment 3, Section 21.3, Schedule of Study Procedures and Assessments.

Note: The study did not have a data safety monitoring board.
For each subject, BAX 855 infusions to perform PK, IR and the first individualized prophylaxis dose administered at the baseline visit was administered in the hospital/clinic setting under medical supervision. All other treatments may be self-administered, administered by parent or caregiver, or administered in clinic or hospital setting. Subject compliance with BAX 855 individualized treatment regimens were monitored by review of subject diaries and study drug accountability.
Subjects and/or their legally authorized representatives were trained on the use of the diary. Diary was provided in electronic or paper format. The following information was recorded in e-diary: infusion record for BAX 855, details of bleeding episodes and response to treatment, physical activity within 8 hours prior to bleeding episode, type

and duration of physical activity with a risk category of 2.5 or higher or contact sport with duration of ≥15 minutes.
The following information about the bleeding event was recorded: location, type, severity of bleeding event and treatment administered.

- Hemostatic efficacy at 8 hours after initiation of treatment and at resolution of bleeding event.
- Physical activity within 8 hours of the occurrence of the bleeding event. Adverse events and PRO were recorded in e-dairy. The investigator reviewed the diary for completeness and missing information.

For subjects without bleeding episodes, visit 6 and 8 (7.5 months and 10.5 months) were phone visits. If subject has a bleeding episode, then these two visits were in person to assess FVIII trough levels, IR and to re-evaluate the PK guided regimen, subject's physical activity and compliance.
Reviewer's comment: Overall plan outlined in protocol for surveillance is acceptable.

6.1.8 Endpoints and Criteria for Study Success

The primary end point was the presence or absence of any bleeding episode in the second 6-month study period (observation day 183 to 364).
The secondary outcome measures were:
Efficacy:
1. Spontaneous, and traumatic ABR, and spontaneous AJBR
2. Total weight-adjusted consumption of BAX 855
3. Overall hemostatic efficacy rating at 8 (±1) hours after the initiation of treatment and at resolution of bleed
4. Number of BAX 855 infusions needed for the treatment of bleeding episodes
5. Hemophilia Joint Health Score
6. Intra-, post-, and perioperative hemostatic efficacy in case of surgery
7. Intra- and postoperative blood loss in case of surgery

Safety:
I. Occurrence of AEs and SAEs
II. Clinically significant changes in vital signs and clinical laboratory parameters (hematology, clinical chemistry, and lipids)
III. Inhibitory antibodies to FVIII, and binding antibodies to FVIII, PEG-FVIII, PEG, and CHO protein

Patient reported outcomes:
Physical domain and component scores of the SF-36 Health Survey
PK endpoints: Defer to Clinical Pharmacology review memo for details.

Bleeding events were captured by the subject or caregiver in the subject's diary and /or in physician, nurse or clinic notes. A bleeding event was defined as a subjective or objective evidence of bleeding which was treated or untreated. Bleeding events occurring at the same anatomical location with the same etiology (spontaneous versus traumatic) within 72 hours of onset of the first bleed were to be considered a single bleed. A new bleed was defined as a bleed occurring >72 hours after stopping treatment for the original bleed for which treatment was initiated and had an initial moderate to excellent response to treatment.

Bleeding occurring at multiple locations related to the same injury (e.g., knee and ankle bleeds following a fall) was to be counted as a single bleeding episode.

Hemostatic efficacy rating for the treatment bleeding episodes is summarized below:

Table 6: Hemostatic Efficacy Rating Scale

Table 2 **Efficacy Rating Scale for Treatment of Bleeding Episodes**	
Excellent	Full relief of pain and/or cessation of objective signs of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution.
None	No improvement or condition worsens.

Source: BLA 125566/526,Section 5, Appendix 16.1.1: Clinical protocol Study 303,Amendment 3, Section 11.1.1.

The subject or their caregiver rated the severity of the bleeding episode. Efficacy rating was performed at 8 hours after the initiation of treatment and at the resolution of bleed using a 4-point efficacy scale. If multiple infusions are administered for the treatment of a bleeding episode, then the overall response to all infusions combined was recorded at the resolution of the bleed. If more than one infusion was given to treat a bleeding episode, and the treatment was rated "excellent", additional information should be provided about the severity of the bleeding episode.
Reviewer's comment: It was confirmed during the BLA review via IR that both treated and untreated bleeding events were captured in the primary efficacy analysis. Overall, the protocol definitions of a single and new bleeding episode are considered acceptable. The hemostatic efficacy rating scale is identical to the scale used in the licensing study 201.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Primary efficacy analysis:
The proportion of subjects with ABR=0 in the two prophylaxis treatment regimens in the second 6-months period were compared using the chi-square test with continuity correction at a two-sided 5% level of significance. All data analyses followed the intent to treat principle regardless of the compliance with the treatment regimen. Bleedings observed in the observation period were used in the analyses irrespective of compliance with the treatment regimen of the protocol. The null hypothesis that there is no difference in the proportion of subjects with ABR=0 between the prophylaxis regimens was tested against a two-sided alternative.
Missing data:
Missing data was not to be imputed in general, with the following key exception:
Handling of incomplete observation periods for ABR: The primary endpoint required complete data for the second 6 months of prophylaxis (Day 183-364). The multiple imputations technique was used for the analysis of the primary endpoint and estimation of ABRs for missing bleeding event data. The multiple imputations technique was used

to handle an observation period shorter than 6 months(182 days). For details regarding the multiple imputation technique, please refer to statistical review memo.

Sample size:

Approximately 40% of subjects in the BAX 855 regimen targeting trough levels of 1-3% were expected to be bleed-free as shown in the ADVATE Prophylaxis study and the BAX 855 pivotal Study 261201. For the BAX 855 regimen targeting approximately 10% (8-12%) trough level, an increase to 70% bleed-free subjects was expected based on modeling of the bleeding rates per FVIII level as noted in the BAX 855 pivotal study, 261201. Under these assumptions, 48 subjects per study arm were needed to reject the null hypothesis of no difference between the study arms against a two-sided alternative at the 5% level of statistical significance with 80% power. Assuming a drop-out rate of close to 10%, and 10-15% of subjects being non-compliant, approximately 116 subjects were planned to be randomized between the two BAX 855 regimens with an allocation ratio of 1:1.

Observation period:

In addition to the observation period for efficacy, the protocol specified an extended observation period for efficacy (e OPF) for subjects who did not complete the full second 6-month efficacy period (defined as observation day 364). Post-discontinuation bleeding event data for subjects who prematurely transitioned to continuation Study 302 were included to augment bleed data for any missing observation efficacy period in the study. Bleed data up to the nominal observation Day 364 was obtained as RAW data export from the continuation study to STDM dataset with a flag that identified these data as post-PROPEL for the applicable subject. For the purpose of statistical analyses, these post-PROPEL data were treated as if captured during the PROPEL study.

For subjects that had missing observation period in PROPEL for which there was no post-PROPEL bleed information provided, imputation of the bleeds was performed as outlined above for the calculation of ABR.

6.1.10 Study Population and Disposition

6.1.10.1 Key Populations Enrolled/Analyzed

Full Analysis Set (FAS): This set comprised of all subjects who were randomized and who were treated with BAX 855 prophylactically for any period of time. The primary efficacy analysis was performed on FAS.

Per protocol analysis set: This set comprised of all subjects who were randomized and completed the second 6 months of prophylactic treatment and had no major deviations from the protocol affecting the study results.

Safety analysis set (SAS): This set was comprised of all subjects treated with at least 1 BAX 855 dose. Safety analysis was performed on SAS.

6.1.10.1.1 Demographics
Table 7

Parameter		Low Target Trough Arm n=57	High Target Trough Arm N=58	Total N=115
Age (years)	Mean (SD)	31(13.7)	31(12)	31(12.9)
	Min, Max	12; 61	13; 61	12; 61
	≥12 to <18 years	10 (18%)	7 (12%)	17(15%)
	≥18 years	47 (82%)	51 (88%)	98 (85%)
Race	White	40 (70%)	36 (62%)	76 (66%)
	Asian	14 (25%)	18 (31%)	32(28%)
	Other	3 (5%)	4 (7%)	7(6%)

All subjects were males.

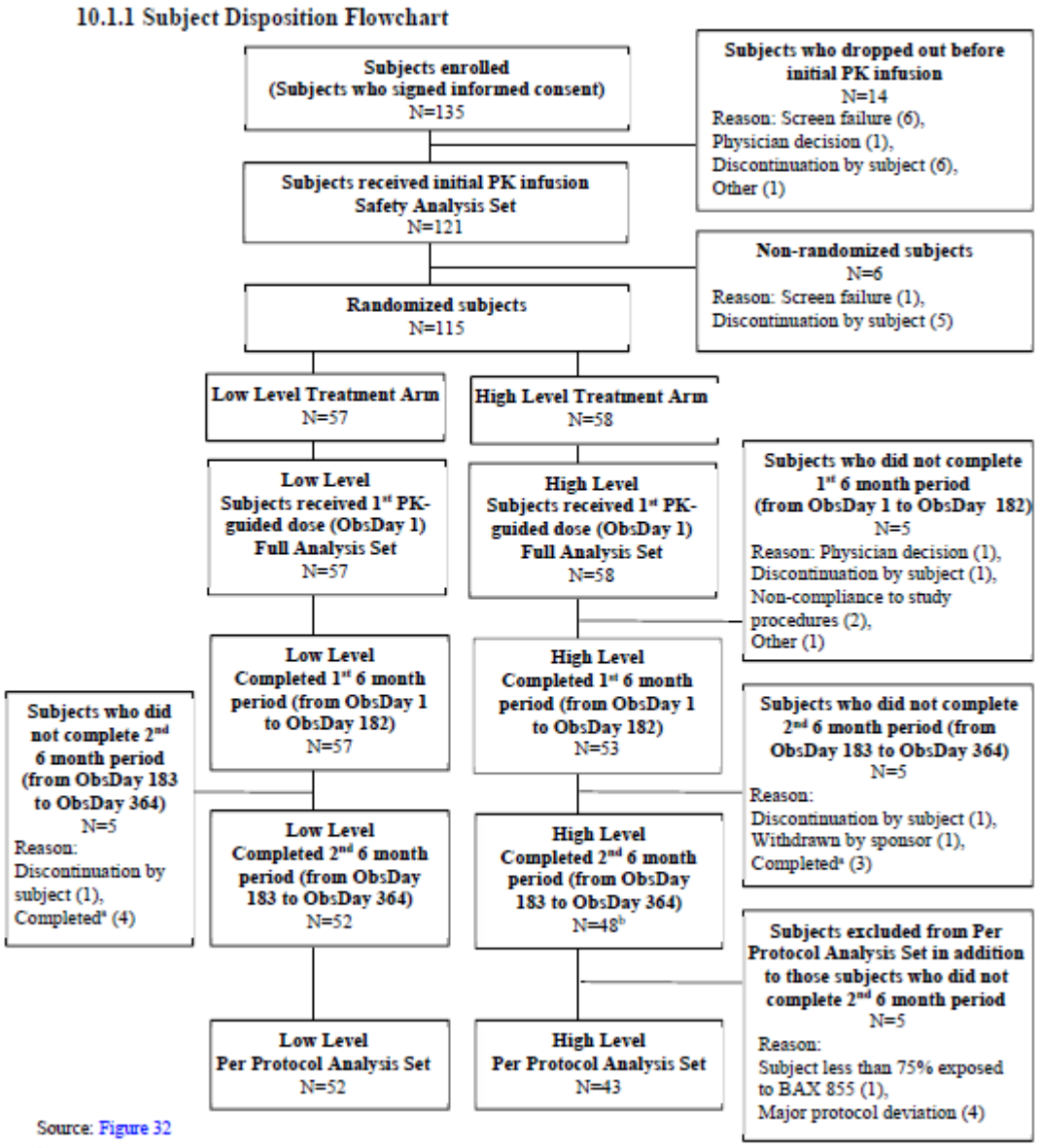
Reviewer's comment: Baseline demographic characteristics were fairly similar between the two dosing arms. The proportion of adolescent subjects was higher in the low trough arm compared to the high trough arm (18% versus 12%). However, the size of the adolescent population was limited and contributed only 15% to the FAS.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Table 8

Parameter		Low Target Trough Arm N=57	High Target Trough Arm N=58
Prophylaxis		43 (75%)	42 (72%)
	ABR<5	21 (37%)	23 (40%)
	ABR≥5	22 (39%)	19 (33%)
On-Demand		14 (25%)	16 (28%)
	Mean ABR	19.6	26
	Median ABR (Min, Max)	12.5 (2, 60)	19 (2, 100)
Target joints	Yes	40 (70%)	44 (76%)
	≥4 target joints	5 (9%)	10 (17%)
	No	17 (30%)	14 (24%)
Hemophilic arthropathy	Yes	7 (12%)	15 (26%)
	No	50 (88%)	43 (74%)

Reviewer's comment: The proportion of patients with ≥4 target joints and hemophilic arthropathy was higher in the high target trough arm compared to the low target trough arm. Of the patients receiving on-demand therapy, mean and median ABR was higher in the high target trough arm compared to the low target trough arm. Overall, the imbalances in the baseline characteristics were in favor of the standard of care arm indicating that the outcome of the investigational arm was not influenced by any favorable prognostic disease characteristics.

6.1.10.1.3 Subject Disposition: Figure 1



Source: Clinical study report: 261303: BLA 125566/607

Five subjects (9%) randomized to the low target trough arm did not complete second 6-month observation period for efficacy compared to the high target trough arm in which a total of ten subjects (17%) were unable to complete the efficacy period [five subjects did not complete the first six month observation period (observation duration ≤182 days) and additional five subjects did not complete the second six month extended observation period (183 to 364 days) in the study]. The primary reason for the inability to complete the study was poor compliance.

Post-PROPEL bleed data:
In the low trough arm, two subjects were rolled over to the continuation study, 302 at 361 and 363 observation days respectively immediately after participation in the PROPEL study. For these subjects, the efficacy period was extended with observations in the continuation study, allowing for the extended observation period to reach 364. Bleed data from completion in Study 303 to Day 364 (from continuation Study 302) revealed no additional bleeds for the extended observation period for these two subjects. For the high target trough arm, none of the subjects had "Post-PROPEL" bleed data incorporated into the complete observation period for efficacy.

Per protocol analysis Set:
In addition to the ten subjects who were randomized to the high target trough arm that did not complete the efficacy observation period (second six month period of efficacy), an additional five subjects were excluded from the per-protocol analysis as they had major protocol deviations during the study which are outlined below Table 9:

Table 9: Major Protocol Deviations

Treatment Arm	Subject ID	Reason for exclusion
High target trough arm	(b) (6)	Subject exposure to BAX 855 was less than 75%.
	(b) (6)	Subject was not compliant with study medication (did not administer BAX 855 for 50 days due to negligence).
	(b) (6)	Subject did not follow dose adjustment from 51IU/kg to 35 IU/kg due to intense physical activity.
	(b) (6)	Subject was not compliant with study medication.
	(b) (6)	Subject was not compliant with study medication.

Reviewer's comment:
More subjects in the high target trough arm were unable to complete the 364 days of extended observation for efficacy compared to the low dose arm (17% vs. 9%). This relates to the more frequent dosing modifications, more frequent dose administration and more frequent e-diary entry required in the high target trough arm compared to the low target trough arm. Therefore, imputation for missing periods of bleeding information for subjects who prematurely discontinued the study was performed in more subjects and for longer duration in the high target trough arm compared to low target trough arm (17% vs. 9%). Please see Appendix A; Table 2a and 2b for details regarding imputation. This study demonstrates the practical challenges that may be encountered with the high target trough dosing that requires more frequent administration and compliance which may limit its applicability to the wider hemophilia population. Inclusion of post-PROPEL bleed data for subjects who were prematurely transitioned to the continuation study, 302, prior to completion of the observation period for efficacy was prespecified and is acceptable. Overall, this was used in two subjects and only limited amount of data was included that should not impact the study result.

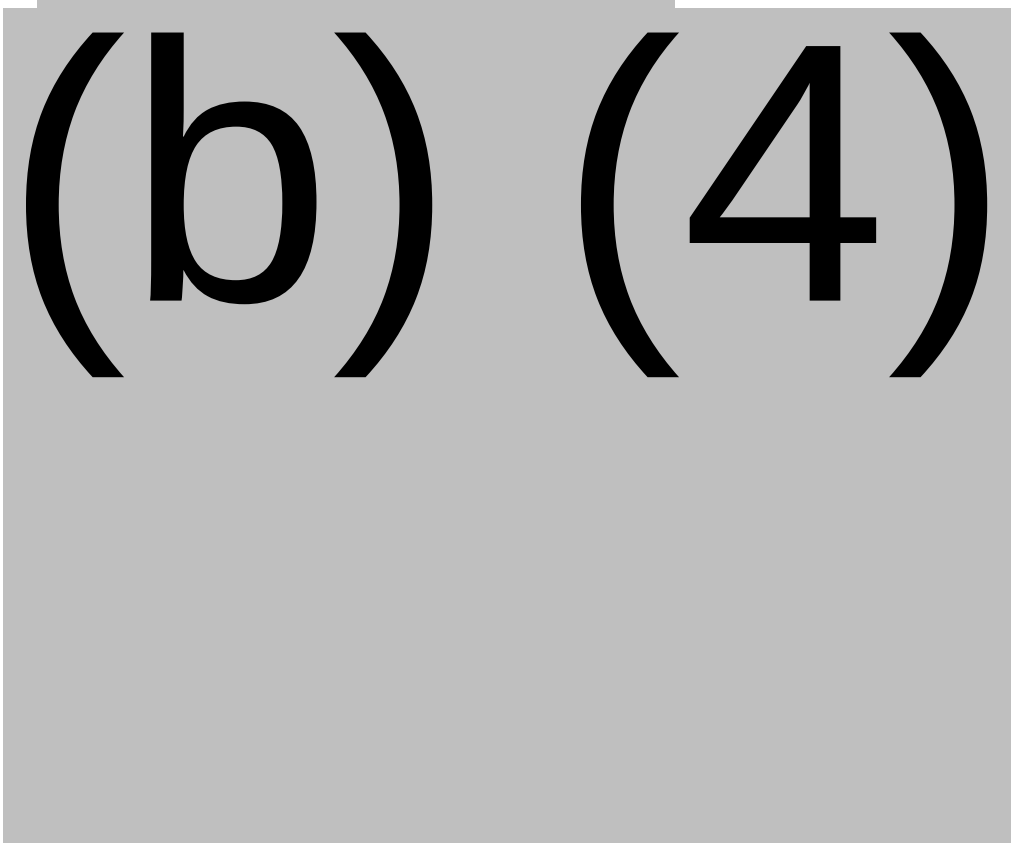
6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

(b) (4)

2 pages have been determined to be not releasable: (b)(4)

(b) (4)



(b) (4)

6.1.12 Safety Analyses

6.1.12.1 Methods

The safety population comprised of 121 subjects who received at least one infusion of BAX 855 during the study. This includes the 115 subjects that were randomized and received at least one prophylactic infusion and six subjects were not randomized but received one PK infusion each.

6.1.12.2 Overview of Adverse Events

Table 13. Adverse Events Possibly Related to BAX 855

Adverse Event	Low Target Trough N =57	High Target Trough N=58	Total N= 121*
Headache	4 (7%)	6 (10%)	10 (8%)
Dizziness	1 (1.7%)		1 (0.8%)
Diarrhea	3 (5%)	2 (3.4%)	5 (4%)
Infusion related reaction		2 (3.4%)	2 (1.6%)
FVIII inhibitor		1(1.7%)	1 (0.8%)
Ocular hyperemia	1(1.7%)		1 (0.8%)
Rash		1(1.7%)	1 (0.8%)
Urticaria		2 (3.4%)	2 (1.6%)

*Denominator includes the six subjects that received infusion only for PK analysis

Adverse events were reviewed and were considered possibly related based on temporal association, plausibility given the mechanism of action, AEs reported with similar class of products and lack of an alternative etiology. In addition, adverse events previously observed with BAX 855 were taken into consideration. No significant difference in safety profile was noted between the two arms.

No deaths occurred in the study. None of the study subjects discontinued the study due to adverse events. Majority of the AEs were mild or moderate in nature. The newly identified AEs of urticaria, ocular hyperemia and infusion related reaction were mild in severity. These will be included in the label.

There were 12 SAEs that occurred in 10 /121 subjects (8.3%).The number of SAEs that occurred were similar between the two treatment arms. Three SAEs occurred prior to randomization. Post -randomization, there were 4 SAEs that occurred in the low target trough arm (7%) and 5 SAEs occurred in the high target trough arm (8.6%). The only SAE that was related to BAX 855 was development of a transient low titer FVIII inhibitor that developed in the high target trough arm (See under immunogenicity). All other SAEs were deemed unrelated to BAX 855, which these included infections, injuries, fracture, cerebellar hematoma, and synovitis.

6.1.12.5 Adverse Events of Special Interest (AESI)

Immunogenicity: One adult subject (ID (b) (6) from UK with history of hepatitis C and HIV randomized to the high target trough arm developed low titer (0.6 Bethesda Unit) inhibitory antibody to FVIII at Week 8 and Month 3. His neutralizing antibody test was negative at screening, baseline and Week 4. Neutralizing antibody testing was negative at 3 subsequent unscheduled visits at Month 4, Month 6, Month 9 and the completion visit. His PK parameters were within target at 6 and 9 months. This subject did not develop any bleeding episodes during the study and prophylaxis was not interrupted indicating limited significance of this low titer FVIII inhibitor.

Binding Antibodies to PEG-FVIII, FVIII,PEG and CHO protein:

Low target trough arm:

- 2/57 subjects (3.5%) developed binding IgG antibodies to PEG-FVIII.
  One subject had a single positive result at screening and the second subject had a single positive result at baseline.
- 1/57 (1.8%) subject had a single positive result for binding IgM antibodies to PEG at screening.

High target trough group:

- 7/58 (12%) subjects had binding IgG antibodies to PEG-FVIII
- 3/58 (5%) subjects had binding IgM antibodies to PEG
- 3/58 (5%) subjects had binding IgG antibodies to FVIII
- 1/58 (2%) subjects had binding IgM antibodies to PEG-FVIII

In summary, a total of 9 individual subjects in the high target trough arm had positive binding antibodies for any parameter. All 9 subjects had positive binding antibodies at screening/baseline. In 8/9 subjects, binding antibodies were transient. One subject was positive for binding IgG antibodies to PEG-FVIII from screening through study completion.

Thromboembolism: No thromboembolic events were reported in the study.

Reviewer's comments: In all subjects with binding antibodies during the study period, binding antibodies were present at screening/baseline. Binding antibodies were not associated with impaired treatment efficacy or adverse events, indicating limited clinical significance at this time. Based on Clinical Reviewer's discussion with the clinical pharmacology reviewer regarding the impact of the binding antibodies on the PK profile of BAX 855, there is no indication that PK was affected by binding antibodies as determined by FVIII incremental recovery and trough values.

6.1.13 Study Summary and Conclusions

(b) (4)

One subject treated in the high target trough arm developed a low titer transient FVIII inhibitor which did not impact hemostatic efficacy. No thrombotic events or deaths were reported in the study. Binding antibodies to PEG-FVIII, PEG and to FVIII that were

identified in the study were not associated with impaired treatment efficacy or adverse events. No new significant safety signals were identified from this study.

(b) (4)

6.2 Study 2: 261302

Study 261302, a Phase 3b, prospective, open label, multi-center study that evaluated the long-term safety and efficacy of BAX 855 for prophylactic use and the control of bleeding episodes.

6.2.1 Objectives:

The co-primary objectives of the study were:
1. To determine the safety of BAX 855 based on the incidence of FVIII inhibitory antibody development.
2. To determine the efficacy of BAX 855 based on the annualized bleed rate (ABR) of spontaneous bleeding episodes.

Secondary Objectives:
Efficacy:
1. To determine the total ABR (spontaneous and traumatic bleeding episodes)
2. To determine the overall hemostatic efficacy rating of BAX 855 for treatment of breakthrough bleeding episodes
3. To determine the length of intervals between bleeding episodes
4. To characterize the hemostatic efficacy of BAX 855 for treatment of bleeding episodes by the number of BAX 855 infusions for treatment
5. To determine total weight-adjusted consumption of BAX 855 for prophylaxis and for treatment of bleeding episodes
6. To assess Patient Reported Outcomes (PROs) over time for subjects receiving BAX 855

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

6.2.2 Design Overview

This is a Phase 3, prospective, open-label, multicenter study designed to evaluate safety and efficacy of BAX 855 for prophylaxis and the control of bleeding episodes in

approximately 200 pediatric and adult PTP (previously treated patients) ≤ 75 years of age with severe hemophilia A. Study included subjects from other BAX 855 studies and BAX 855 naïve subjects. Subjects were treated on the specified prophylactic treatment regimen until they reached 100 exposure days as accumulated across all BAX 855 studies. Following 100 exposure days, subjects were given the option to continue until the study was terminated. Subjects were treated with either a fixed dose prophylaxis with BAX 855 or PK tailored prophylactic dosing regimen based on individual PK to maintain FVIII trough level of ≥3%. Prior to implementation of amendment 4, subjects treated with prophylaxis or on-demand from previous BAX 855 studies with a spontaneous ABR =0 could be treated with an extended dosing regimen of 30-80IU/kg (+/-5IU/kg) every 5 days. After 6 consecutive months of treatment, the BAX 855 dosing could be further extended to 30 to 80(+/-5) IU/kg every 7 days depending on the subject's bleeding rate.

6.2.3 Population

Key Inclusion Criteria:
1, ≤75 years of age at screening.
2. Males with severe hemophilia A (FVIII clotting activity <1%) confirmed by central laboratory at screening.
3. Previous exposure to plasma derived or recombinant FVIII concentrate for ≥ 150 exposure days.
4. HIV negative; HIV positive subjects must have CD4+ count ≥200 cells/mm3.
5. Hepatitis C negative by antibody or PCR testing

Key Exclusion Criteria: 1.Detectable FVIII inhibitory antibodies (≥ 0.4 BU using the (b) (4) Bethesda assay) as confirmed by central laboratory at screening.
2. Subject with inherited or acquired hemostatic defect other than hemophilia A.
3. Severe hepatic dysfunction; ALT ≥ 5XULN or INR >1.5.
4. Severe renal impairment; serum creatinine >2mg/dl
5. Life threatening or gastrointestinal bleeding episode within 3 months prior to study entry.
6. Recent use (<30 days) of any other pegylated drug prior to study participation.

6.2.4 : Study Treatments or Agents Mandated by the Protocol

Prophylaxis Regimen for the study is outline below in Table 14.
Subjects were treated on a specified prophylaxis regimen for 6-month periods until they reach 100 exposure days (ED) across all Baxalta studies. The regimen choice was based on subject's previous treatment regimen and spontaneous ABR (s ABR) outcome outlined below. The prophylaxis twice weekly dosing is the approved dose included in the label.

Table 14: Dosage and Infusion Schedule

Table 1
BAX 855 Dosage and Infusion Frequency Schedule and Recommended Adjustments

Subjects	0-6 Months	6-12 Months	12-18 Months	≥18 Months
Subjects treated on-demand subjects from the phase 2/3 pivotal with sABR > 0 Subjects from the surgery study BAX 855 naïve subjects	Fixed dose: 45 ± 5 IU/kg twice weekly	sABR > 0: 45 to 80 (± 5) IU/kg[a] twice weekly	sABR > 0: 45 to 80 (± 5) IU/kg[a] twice weekly	sABR > 0: 45 to 80 (± 5) IU/kg[a] twice weekly
		sABR = 0: 30 to 80 (± 5) IU/kg[a] q5d[b]	sABR > 2: 45 to 80 (± 5) IU/kg[a] twice weekly	
			sABR ≤ 2: 30 to 80 (± 5) IU/kg[a] q5d[b]	
			sABR = 0: 30 to 80 (± 5) IU/kg[a] q7d[b]	sABR > 4: 45 to 80 (± 5) IU/kg[a] twice weekly
				2 < sABR ≤ 4: 30 to 80 (± 5) IU/kg[a] q5d[b]
				sABR ≤ 2: 30 to 80 (± 5) IU/kg[a] q7d[b]
Subjects from the phase 2/3 pivotal study	sABR > 0: 45 to 80 (± 5) IU/kg[a] twice weekly	sABR > 0: 45 to 80 (± 5) IU/kg[a] twice weekly	sABR > 0: 45 to 80 (± 5) IU/kg[a] twice weekly	sABR > 0: 45 to 80 (± 5) IU/kg[a] twice weekly
Subjects from the, pediatric PTP study	sABR = 0: 30 to 80 (±5) IU/kg[a] q5d[b]	sABR > 2: 45 to 80 (± 5) IU/kg[a] twice weekly		

Table 14 (continued)

Table 1
BAX 855 Dosage and Infusion Frequency Schedule and Recommended Adjustments

Subjects	0-6 Months	6-12 Months	12-18 Months	≥18 Months
Subjects from other BAX 855 studies		sABR ≤ 2: 30 to 80 (± 5) IU/kg[a] q5d[b]		
		sABR = 0: 30 to 80 (± 5) IU/kg[a] q7d[b]	sABR > 4: 45 to 80 (± 5) IU/kg[a] twice weekly	
			2 < sABR ≤ 4: 30 to 80 (± 5) IU/kg[a] q5d[b]	
			sABR ≤ 2: 30 to 80 (± 5) IU/kg[a] q7d[b]	

Abbreviations: sABR = spontaneous annualized bleed rate; PTP = previously treated patients; q5d = every 5 days; q7d = every 7 days.

a. From the recommended dosage range, the investigator will determine prescribed dosage, allowing ± 5 IU/kg.

b. Infusion frequencies of q5d or q7d will be at investigators discretion.

Source :BLA 125566/383, Section 5, Appendix 16.1.1, Clinical Protocol, Amendment 3.Section 8.6.3, Description of Treatment.

- The fixed-dose prophylactic treatment regimen with BAX 855 was age dependent as outlined below:
  - ≥ 12 years of age: 45+/-5 IU/kg twice weekly which may be increased to 80IU/kg.
  - <12 years of age: 50+/-10 IU/kg twice weekly which may be increased to 80IU/kg.

Additional guidelines for dosing modifications are outlined below:

- A subject may receive a BAX 855 dosage < 45 IU/kg if he has a known PK profile from another BAX 855 study that will maintain his FVIII trough level above 1%.
- For subjects receiving twice weekly prophylaxis and with spontaneous ABR > 2, dosing of BAX 855 may be adjusted to a FVIII trough level of up to 10% for 6 months period, at investigators' discretion and with approval by the sponsor's medical director.
- Subjects meeting any of the following criteria during prophylaxis may have their BAX 855 dosage and/or infusion frequency increased (dose increased up to 80 +/-5 IU/kg) before completion of the 6-month treatment period:
  a) Two or more spontaneous bleeding episodes in the same target joint within any 2-month period.
  b) One or more spontaneous bleeding episodes in a non-target joint within any 2-month period.
  c) FVIII trough level < 1% and investigator's estimate that the subject has an increased risk of bleeding.

Reviewer's comment:
The dose of 45+/-5 IU/kg twice weekly for prophylaxis is based on the dosing that was evaluated in the licensing study, 201, for prophylaxis and the dose that was approved for prophylactic use in the label. The pediatric dosing for prophylaxis is similar to the approved dosing in the label for <12 years (55IU/kg twice weekly with a maximum dose of 70 IU/kg).
The criteria for dose adjustment outlined above are similar to the licensing study, Study 201. Overall, 9% of the FAS population treated with the twice weekly prophylaxis required dose escalation based on protocol specified criteria.
According to the protocol, subjects enrolled from another BAX 855 study with a spontaneous ABR =0 or subjects with sABR =0 on twice weekly dosing after 6 months on this study could switch to every 5-day regimen at the investigator's discretion. Subjects with sABR =0 on every 5-day dosing schedule for 6 months could switch to every 7 days regimen at the investigator's discretion. The decision to assign or switch subjects with sABR of zero to extended dosing regimen was discretionary based on patient's preference and investigator's judgement.
PK criteria were not used to select subjects for extended dosing regimen.
This could introduce selection bias which may influence the efficacy results for this subset of study population. Approximately 50% of the subjects eligible for the every 5-day extending dosing, actually received this dosing regimen.
The absence of protocol specified selection criteria for the extended dosing regimen will make it challenging to specify the indicated population for this regimen from a (b) (4) .

Treatment of Bleeding Episodes:

BAX 855 was used for the treatment of breakthrough bleeding episodes according to the guidelines outlined in Table 15 below:

Table 15: Treatment Guidelines for Bleeding Episodes

Table 2
BAX 855 and ADVATE Treatment Guidelines for Bleeding Episodes

Type of Bleeding Episode	Dose	Frequency of Dosing
Minor Early hemarthrosis, mild muscle bleeding, or mild oral bleeding, including, epistaxis	10 to 20 (±5) IU/kg	Repeat infusions every 12 to 24 h for 1 to 3 days until the bleeding episode is resolved
Moderate Moderate bleeding into muscles, bleeding into the oral cavity, definite hemarthroses, and known trauma	15 to 30 (±5) IU/kg	Repeat infusions every 12 to 24 h for 3 days or more until the pain and moderate disability/incapacity are resolved
Major Significant gastrointestinal bleeding, intracranial, intra-abdominal, or intrathoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces or iliopsoas sheath, fractures, head trauma	30 to 60 (±5) IU/kg	Repeat infusions every 8 to 12 h until the bleeding episode is resolved

NOTE: Subjects with life-threatening or gastrointestinal bleeding should be withdrawn from the study.

Source: BLA 125566/383, Section 5, Appendix 16.1.1, Clinical Protocol, Amendment 3.Section 8.6.3.1,Treatment of Bleeding Episodes.

Reviewer's comment:
The dose outlined in Table 15 above for the treatment of bleeding episode is similar to the dose evaluated in Study 201 for treatment of bleeding episodes and included in the approved label.

6.2.6 Sites and Centers

A total of 218 subjects were enrolled in the study at 86 sites in 23 countries worldwide.

6.2.7 Surveillance/Monitoring

Table 16: Study Monitoring

20.3.1 Subjects Transitioning from Other BAX 855 Studies on Fixed Dose Prophylactic Treatment Regimen

Procedures/Assessments	Screening Visit[a]	Follow-Up Visits		End of Study Visit[b]
		6 ± 1 Weeks Following Screening	Every 3 Months ± 2 Weeks Following Screening	
Informed consent[c]	X			
Eligibility criteria	X			
Confirmation of eligibility		X		
Medical history	*			
Medication history	*			
Concomitant medications[d]	*	X	X	X
Non-drug therapies[d]	*	X	X	X
Physical exam	*	X	X	X
Adverse events[d]	*	X	X	X
Laboratories[e]	*	X	X	X
Vital signs[f]	*	X	X	X
Bleeding episodes and their treatment[d]	*	X	X	X
Pregnancy test[g]	X			X
PROs[h]	X		X[i]	X
Patient e-diary[j]	X	X	X	X
IR determination[k]	X	X	X	X
Dispense IP	X[k]	X	X	

a. The screening visit coincides with the end of study visit of the previous BAX 855 study. The procedures/assessments marked with an asterisk (*) will be transcribed from the end of study visit of the previous BAX 855 study. The following assessments are not part of the end of study assessments of the previous BAX 855 study and must be performed at screening to ensure eligibility: Performance score (Karnofsky or Lansky), viral serology (see Section 20.4.1), and pregnancy test if female of childbearing potential. Additionally, for subjects transitioning from the surgery study (Study 261204), FVIII assays and lipid panel (see Section 20.4.1) should also be performed.

b. Including cases of withdrawal or discontinuation.

Source: BLA 125566/383, Section 5, Appendix 16.1.1, Clinical Protocol, Amendment 4.Section 20.3,Schedule of Study Procedures and Assessments

6.2.8 Endpoints and Criteria for Study Success

Primary outcome measure:
Safety: Development of inhibitory antibodies to FVIII.
Efficacy: Spontaneous mean ABR (treated and untreated) using a generalized linear model for subjects who have ≥100 EDs

Secondary outcome measures:
Efficacy:

- Mean total ABR (spontaneous and traumatic)
- Overall hemostatic efficacy rating of BAX 855 for the treatment of bleeding episodes
- Number of BAX 855 infusions to treat bleeding episodes

- Time intervals between bleeding episodes
- Weight adjusted consumption of BAX 855

Safety:

- Occurrence of AEs and SAEs
- Change in vital signs and clinical laboratory parameters
- Immunogenicity: Binding antibodies to FVIII, BAX 855, and PEG, anti-CHO antibodies

Patient reported outcomes:
Bleed and pain severity as measured using the Haemo-SYM questionnaire
HRQoL as assessed using the SF-36/PedsQL questionnaires.

Assessment of efficacy:

1. ABR was assessed from bleeding episodes that were recorded in the subject's diary or recorded in the physician, nurses, and clinic notes. A bleeding episode was defined as subjective or objective evidence of untreated or treated bleeding event. Bleeding episode occurring at the same anatomical location with the same etiology within 24 hours of onset of the first episode was considered a single bleeding event. Bleeding events occurring at multiple locations related to the same injury was counted as one bleeding event.
2. Hemostatic efficacy: The subject or caregiver rated the severity of the bleeding episode and the overall treatment response at 24 hours after treatment initiation using a 4-point hemostatic efficacy rating scale. If multiple infusions were administered, then the overall response to all infusions combined was incorporated in the efficacy rating. The 4-point hemostatic efficacy rating tool is outlined below:

Table 17: Assessment of Hemostatic Efficacy

Table 4 **Efficacy Rating Scale for Treatment of Bleeding Episodes at 24 ± 2 Hours from the Initiation of Treatment and at Resolution of Bleed**	
Excellent	Full relief of pain and cessation of objective signs of bleeding (eg, swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution.
None	No improvement or condition worsens.

Source: BLA 125566/383, Section 5, Appendix 16.1.1, Clinical Protocol
Reviewer's comment: The definition of bleeding event used in the continuation study, 302, is identical to the licensing Study 201. The time point of hemostatic efficacy assessment (at 24 hours after treatment initiation) and the 4-point rating scale is identical to the licensing Study 201. Therefore, if the hemostatic efficacy data from this

continuation study recapitulates results from Study 201, it will be confirmatory of the hemostatic efficacy of BAX 855.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample size and Power calculations:
In accordance with the EMA guidance, the plan was to enroll 250 subjects to ensure that 200 evaluable subjects have a minimum of 100 exposure days to BAX 855.
Handling of missing data: Missing data was not imputed.

Primary outcome measure:
Safety: The number and proportion of subjects (Clopper-Pearson exact 95% CI) that were exposed to BAX 855 and develop inhibitory antibodies to FVIII was the primary safety endpoint.
Efficacy: The spontaneous ABR was assumed to have a negative binomial distribution, and the mean ABR (95% CI) was estimated using a general estimating equation (GEE) model framework with treatment regimen as a fixed effect, subject effect as random effect, age at baseline as continuous covariate, and the logarithm of follow up as an offset. Only subjects that had ≥100 ED were included in the model. The model was analyzed separately for each of the every 5 day and every 7-day regimens.

Secondary outcome measure:
Efficacy:
Total ABR
The hemostatic efficacy of BAX 855
The median number of BAX 855 infusions to control bleeding, total weight adjusted dose of BAX 855 administered for prophylaxis and for treatment of bleeding episode per subject.
Median time interval (95% CI) between bleeding episodes
The results of the efficacy parameters are descriptive with no formal hypothesis testing.
The safety secondary outcomes are characterized and presented descriptively.
Reviewer's comment:
The statistical plan is acceptable for a continuation study.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed
Safety Analysis Set: The safety analysis set comprised all subjects treated with at least 1 BAX 855 infusion. All safety analyses were performed on the safety analysis set.
Full Analysis Set: The full analysis set is the same as the safety analysis set. All efficacy analyses were performed on the full analysis set.
Per Protocol Analysis Set: The per protocol (PP) analysis set comprised all subjects from the full analysis set who had no major deviations from the protocol affecting the study results.
Analysis Cohorts:
In addition to the overall subject group, subgroups of subjects on (1) fixed dose prophylactic treatment regimen and (2) PK-tailored prophylactic treatment regimen were analyzed separately.

6.2.10.1.1 Demographics

Table 18: Participation in BAX 855 studies and baseline disease characteristics:

Parameter	Category	Age <6 n (%)	Age ≥6 to <12 n (%)	Age ≥12 to <18 n (%)	Age ≥18 n (%)	Total n (%)
Number of Subjects in Study Group	N	32	33	30	121	216
Gender	Male	32 (100.0)	32 (97.0)	30 (100.0)	121 (100.0)	215 (99.5)
	Female	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (0.5)
Race	Asian	7 (21.9)	9 (27.3)	5 (16.7)	37 (30.6)	58 (26.9)
	Black or African American	1 (3.1)	2 (6.1)	1 (3.3)	0 (0.0)	4 (1.9)
	White	22 (68.8)	22 (66.7)	24 (80.0)	84 (69.4)	152 (70.4)
	Other	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
	Mixed	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Ethnicity	Hispanic or Latino	1 (3.1)	2 (6.1)	0 (0.0)	7 (5.8)	10 (4.6)
	Not Hispanic or Latino	31 (96.9)	31 (93.9)	30 (100.0)	114 (94.2)	206 (95.4)
Previous BAX 855 study participated in	None	6 (18.8)	4 (12.1)	0 (0.0)	0 (0.0)	10 (4.6)
	At least one previous BAX 855 study	26 (81.3)	29 (87.9)	30 (100.0)	121 (100.0)	206 (95.4)
	BAX 855 phase 1 study (261101)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)	2 (0.9)
	BAX 855 phase 2/3 pivotal study (261201)	0 (0.0)	0 (0.0)	20 (66.7)	97 (80.2)	117 (54.2)
	BAX 855 pediatric study (261202)	24 (75.0)	29 (87.9)	4 (13.3)	0 (0.0)	57 (26.4)
	BAX 855 PUP study (261203)	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)
	BAX 855 surgery study (261204)	0 (0.0)	0 (0.0)	1 (3.3)	14 (11.6)	15 (6.9)

BLA 125566/383, Section 5,Clinical Study Report Study 302, Intext Table 9, Page 77.

Reviewer's comment:
All except one subject treated in the study were male, which is consistent with the sex distribution for Hemophilia A. The majority of subjects were Whites followed by Asian and Black or African American. Only three subjects were less than 2 years of age indicating that the long-term efficacy and safety data are limited in the very young population. As anticipated, majority of the study population (95%) had participated in another BAX 855 study. Only 5% of the subjects (all <12 years) were BAX 855 naïve.

Table 19: Baseline Disease Characteristics

In-text Table 9. Demographic, Baseline, and Disease Characteristics by Age Group (EU Categories) – Categorical Data (Study 261302: Safety Analysis Set)

Parameter	Category	Age <6 n (%)	Age ≥6 to <12 n (%)	Age ≥12 to <18 n (%)	Age ≥18 n (%)	Total n (%)
	BAX 855 PROPEL study (261303)	0 (0.0)	0 (0.0)	5 (16.7)	11 (9.1)	16 (7.4)
Number of target joints at screening	0	30 (93.8)	24 (72.7)	18 (60.0)	34 (28.1)	106 (49.1)
	1	2 (6.3)	3 (9.1)	6 (20.0)	26 (21.5)	37 (17.1)
	2	0 (0.0)	5 (15.2)	3 (10.0)	26 (21.5)	34 (15.7)
	3	0 (0.0)	1 (3.0)	2 (6.7)	13 (10.7)	16 (7.4)
	≥4	0 (0.0)	0 (0.0)	1 (3.3)	22 (18.2)	23 (10.6)
Hemophilia arthropathy	Present	0 (0.0)	2 (6.1)	7 (23.3)	84 (69.4)	93 (43.1)
	Absent	32 (100.0)	31 (93.9)	23 (76.7)	37 (30.6)	123 (56.9)
Treatment Regimen Prior to Current Study	Prophylactic	30 (93.8)	33 (100.0)	29 (96.7)	99 (81.8)	191 (88.4)
	On-demand	2 (6.3)	0 (0.0)	1 (3.3)	22 (18.2)	25 (11.6)

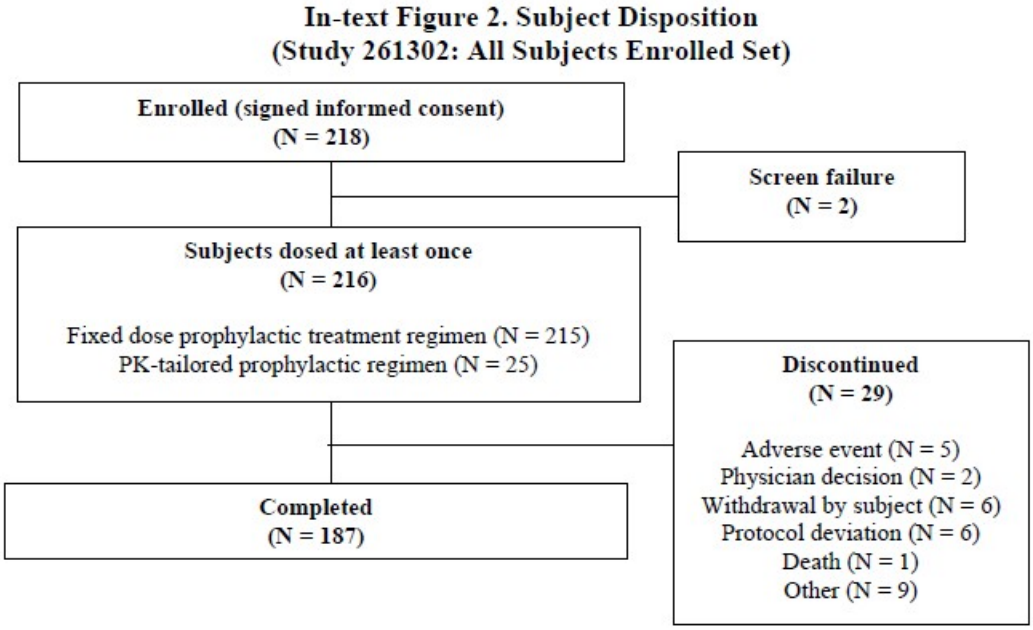
Abbreviations: n = number of subjects in each category; N = total number of subjects in the relevant analysis set, age group and study group; % = Percentage of subjects in each category relative to the number of subjects in the relevant analysis set, age group and study group.
Source: Table 13

Source: BLA 125566/383, Section 5, Clinical Study Report Study 302, Intext Table 9, Page 78.

The historical mean (SD) spontaneous ABR for subjects based on therapy prior to enrollment on the study is outlined below:
Prophylaxis (N=191): Mean ABR (SD)= 1.6 (4.7).
On-demand (N=25): Mean ABR (SD)= 28 (24).

Reviewer's comment:
Hemophilic arthropathy was present in 43% of the study population, 51% of the subjects had target joints and majority (88%) of the study population were receiving prophylactic therapy at the time of screening. Overall, the enrolled population was fairly representative of the real-world hemophilia population. The significantly higher mean spontaneous ABR noted in the on-demand population is expected given that treatment of active bleeding episodes does not prevent the occurrence of spontaneous bleeding events.

Figure:2: Subject Disposition for Study 302.



Source: Study 261302: Clinical Study Report

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The primary efficacy of spontaneous mean ABR analyzed using generalized estimating equations (GEE) was determined for fixed-dose prophylaxis administered twice weekly, every 5 days, every 7 days and for PK tailored prophylaxis. Subjects had to complete ≥100 EDs across all studies to be included in the analysis. Subjects receiving treatment in multiple regimens were included in summaries for multiple regimens. This is described in Table 20 below:

Table 20: Annualized spontaneous ABR; Full analysis set

Regimen	Age Group	Number of subjects	ABR (point estimate)	95% CI
Twice weekly	All	186	1.2	0.92, 1.6
	Age < 6 years	31	0.66	0.39, 1.1
	Age ≥6 to <12 years	31	0.76	0.44, 1.3
	Age ≥12 to <18years	23	1.77	1.1, 2.8
	Age ≥18 years	101	1.26	0.8, 1.8

(b) (4)

Reviewer's comment:

The population included in the efficacy analysis included subjects who have completed 100 exposure days as was prespecified in the protocol. The mean(SD) number of prophylactic EDs to BAX 855 was 195 (101). The annualized spontaneous ABR for the

twice weekly regimen in this continuation study was similar to the sABRs noted in the licensing studies (201 and 202). In Study 201, the mean (SD) sABR with twice weekly prophylactic regimen for ≥12 years of age was 2.9 (7.1). It was 2.9 (4.2) for ages 12 to <18 years and 2.9 (7.7) for ages 18-65 years. Similarly, in the pediatric Study 202, the mean (SD) s ABR rate was 1.2 (2.3) for subjects <12 years of age. It was 1.0 (2.0) for ages <6 years and 1.3(2.5) for ages 6 to <12 years.

6.2.11.2 Analyses of Secondary Endpoints:
Table 21: ABR (spontaneous and traumatic) using GEE:

Regimen	Age Group	Number of subjects	ABR (point estimate)	95% CI
Twice weekly	All	186	2.2	1.8, 2.7
	Age < 6 years	31	1.5	1.0, 2.2
	Age ≥6 to < 12 years	31	2.0	1.3, 3.0
	Age ≥12 to <18years	23	3.1	2.3, 4.4
	Age ≥18 years	101	2.1	1.6, 2.8

(b) (4)

Reviewer's comment:
In the pivotal study 201, total ABR for population ≥12 years of age was 4.3 (95% CI:3.4, 5.5); for ages 12 to <18 years, it was 5.0 (95% CI: 3.2, 7.7) and for ages 18-65 years it was 4.1(95% CI 3.1, 5.5).
For the pediatric study (<12 years of age), the total ABR was 3.0 (95% CI: 2.2, 4.2); it was 2.4 (95% CI:1.5, 3.8) for ages <6 years and 3.7 (95% CI: 2.4, 5.8) in ages 6 to <12 years.
The ABRs during long term administration of BAX 855 using twice weekly regimen in the continuation Study 302 is comparable to the ABRs in the pivotal study 201 and pediatric study 202 confirming its hemostatic efficacy.

Treatment of Bleeding episodes:
A total of 180 out of the 216 subjects (83%) had one or more bleeding episode during the study. A total of 1064 bleeding episodes occurred during the study. A total of 910 bleeding events (86%) that occurred in 165 subjects were treated with BAX 855 and150 bleeding events (14%) were not treated.
Hemostatic efficacy of 910 bleeding episodes treated with BAX 855 is outlined below:

Table 22: Hemostatic Efficacy

Parameter		N=910 (%)
Hemostatic efficacy	Excellent	438 (48%)
	Good	368 (40%)
	Fair	48 (5%)
	None	4 (0.4%)
	Not reported	52 (5.7%)
No. of infusions for treatment	One	673 (74%)
	Two	140 (15%)
	Three	39 (4%)
	Four	17 (2%)
	≥ Four	22 (2.4%)
	Not reported	19 (2%)
No. of infusions administered per bleeding episode	Mean	1.4 infusions
	Median	1 infusion

Table 23: Characteristics of treated bleeds in study 302 : N=910 bleeds

	Major/Severe	Moderate	Minor/ Mild	Not reported
Severity of Bleeding event N (%)	101 (11%)	464 (51%)	338 (37%)	7 (0.8%)
	Spontaneous	Traumatic	Unknown	Not reported
Type of Bleeding event N (%)	375 (41%)	446 (49%)	88 (10%)	1 (0.1%)

Table 24: Number of bleeding events treated with BAX 855 and the hemostatic efficacy for each age group.

	Age < 6 yrs.	Age ≥6 to <12 yrs.	≥12 to <18 yrs.	≥18 yrs.	Total
No. of bleeding events	72 (8%)	126 (14%)	202 (22%)	510 (56%)	910
Hemostatic efficacy					
Excellent	37	74	104	223	438
Good	26	43	76	223	368
Fair	3	2	8	35	48
None	0	0	1	3	4
Not reported	6	7	13	26	52
Overall hemostatic efficacy	87.5%	93%	89%	87%	88.5%

Reviewer's comments:
BAX 855 demonstrated hemostatic efficacy of 88.4% in the treatment of bleeds which is comparable to the efficacy that was observed in the licensing study 201 which had a

success rate of 95%. The hemostatic efficacy of >85% was observed across all age groups as noted in Table 24 above.

Eighty-nine percent (89%) of the bleeding events were treated with 1-2 infusions of BAX 855 which is similar to Study 201 in which 95% of the bleeding episodes were treated with 1-2 infusions of BAX 855.

Weight adjusted consumption of BAX 855:
The weight-based consumption of BAX 855 for the FAS based on the age groups in Study 302 and licensing study 201 is outlined below:

Average dose IU/kg per prophylactic infusion administered twice weekly:
Study 302:
Age < 6 years : Mean (SD)= 53 IU/kg (7.6) , Median= 52 IU/kg
Age ≥6 to <12 years: Mean (SD)=54IU/kg (8.2), Median= 51 IU/kg
Age ≥ 12 years: Mean (SD)=48 IU/kg (6.9), Median =46 IU/kg

Studies 201 and 202:
Age <6 years: Mean (SD)=51IU/kg (4.9), Median= 52 IU/kg
Age ≥6-<12 years: Mean (SD)= 51 IU/kg (6), Median=50 IU/kg
Age ≥12 years: Mean(SD)= 45 IU/kg (4.5), Median=45 IU/kg

Reviewer's comment:
The mean weight- based consumption of BAX 855 for twice weekly prophylaxis was comparable across all age groups between the licensing studies 201 and 202 and continuation study 302. However, the mean dose/kg that was administered per bleeding episode was higher in Study 302 compared to licensing study 201. For Study 302, the mean dose (SD) for the treatment of bleeding events was 70IU/kg (82) for 12 to <18 years and 61IU/kg (61) in ≥18 years of age. In the licensing study 201, the mean (SD) dose was 42 IU/kg (31) for 12 to <18 years of age and it was 37 IU/kg (28)in >18 years.

Applicant clarified in an IR that the higher dose/kg administered for treatment of bleeding episode in Study 302 was on account of some subjects continuing to use their prophylaxis dose (including the higher every 5, 7 day and PK driven dose) for the treatment of bleeding episode as opposed to the protocol specified dose for treatment of bleeding events. In the licensing study 201, most bleeding events occurred in the on-demand subjects who were not on prophylaxis and therefore, these subjects had higher compliance with the protocol specified dose for treatment of bleeding episode. Therefore, this difference in the dose used for treatment of bleeding episodes may be driven by the difference in the behavior of the study population across studies. Dose used for treatment of bleeding episodes within the prophylaxis subset was comparable across the two studies.

Extended 5-day dosing regimen:
(b) (4)

1 page has been determined to be not releasable: (b)(4)

6.2.12 Safety Analyses

The safety population included 216 subjects that received prophylaxis in the study. The mean (SD) observation period per subject was 2.2 (1.1) years.

Table 26: AEs Considered Related to BAX 855

AE	Number of Subjects N=216
Nausea	5 (2.3%)
Dizziness	1 (0.5%)
Eosinophil count increased	2 (0.9%)
Urticaria	2 (0.9%)
Rash	4 (1.8%)
Headache	14 (6%)
Drug eruption	1 (0.5%)
Diarrhea	11 (5%)
Ocular hyperemia	1 (0.5%)
Hypersensitivity reaction	1(0.5%)

AEs of dizziness, increased eosinophil count, urticaria, drug eruption and ocular hyperemia were not previously reported and will be included in the PI. Majority of these events were low grade and of limited duration.

Deaths:

Subject (b) (6) 15-year-old Asian male died from cerebral hemorrhage from Hemophilia A which was not related to BAX 855. This subject was previously treated on the pivotal Study 201. This subject did not develop inhibitory or binding antibody to FVIII. He had no reported AEs to BAX 855. He had 271 EDs on twice weekly prophylaxis. This events is related to underlying disease as opposed to the treatment.

No thromboembolic AE was reported on the study.

Discontinuation: Five subjects (5/216=2%) discontinued the study due to adverse events that were not related to BAX 855 including increased transaminases, ileus, traumatic fracture, hematomas, and injury.

Thirty-three out of the 216 (15%) subjects treated with BAX 855 developed 52 SAEs. This includes two cases of pancreatitis and one case of skin rash (moderate severity) was considered as possibly related to the BAX 855 and included in the label to inform providers.

FVIII inhibitor:

The analysis for development of inhibitory antibodies to FVIII included 204 subjects who had ≥100 exposure days.

Subject (b) (6), a 3-year-old Black/African American male, had a single positive FVIII inhibitor result of 0.6 BU in the (b) (4) assay performed at the central laboratory at 24 months. He did not return for a confirmatory testing within 2-4 weeks as was specified in the protocol. He underwent repeat FVIII inhibitor testing approximately 2.5 months later at the end of study visit (>100EDs) which was negative. During the observation period of 2.2 years in the study, this subject only experienced a spontaneous minor skin bleeding episode which resolved with one BAX 855 infusion.

Five subjects had IgG binding antibodies to FVIII at any time post baseline. Eight subjects had IgG binding antibodies to PEG-FVIII at any time post-baseline. Binding antibodies to FVIII and PEG-FVIII were transient in all but one subject. This subject (Subject (b) (6)) had transitioned from pivotal Study 201 and had pre-existing binding IgG antibodies to PEG-FVIII at the time of entry to the pivotal Study 201 prior to first exposure to BAX 855 which persisted throughout the studies. No safety or efficacy issues were reported for this subject during the study.

Exposure during pregnancy:

There were 4 case reports of drug exposure during pregnancy in the trial involving 3 female partners of 3 male participants. One case resulted in fetal death due to cystic hygroma in a 35-year-old female with h/o Charcot-Marie-Tooth disease. There was one case of spontaneous abortion in a 33-year-old female with history of diabetes and HTN. For the other 2 cases, there was report of live birth without any complications.

Drug Eruption:

One subject (b) (6) , reported a single mild AE of drug eruption that occurred 1 day after BAX 855 infusion which occurred after 196 exposure days manifested as itching and skin rash. This subject also participated in Phase 1 and Phase 3 study. This events was considered related to BAX 855 both by the investigator and applicant. This subject was able to tolerate subsequent BAX 855 infusions without any symptoms of rechallenge. The drug eruption resolved 3-4 weeks after study completion.

Reviewer's comment: These results from Study 302 are consistent with known safety profile of BAX 855. Section 6 of the PI will be updated to include the safety findings from this study.

6.2.13 Key Study Summary and Conclusions:

Study 302 confirmed the hemostatic efficacy of BAX 855 for prophylaxis using the twice weekly dosing regimen and for treatment of bleeding episodes. No new safety signals were identified. (b) (4)

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We agree that this subset analysis is hypothesis generating. If the applicant wishes to pursue an (b) (4)

and it was primarily designed to confirm the efficacy of an already approved prophylaxis regimen. No thromboembolic events were reported in the study. One subject developed an unconfirmed low titer FVIII inhibitor. Additionally, AEs of dizziness, increased eosinophil count, urticaria, drug eruption and ocular hyperemia are considered possibly related to BAX 855 and will be included in the label.

6.3 Study 3: 261204

A Phase 3, multicenter, open-label study of efficacy and safety of PEGylated r FVIII in previously treated patients with severe Hemophilia A undergoing surgical or other invasive procedures.

Background:

On December 25, 2016, BAX 855 was granted the indication for perioperative management based on interim efficacy data from 11 major and 4 minor surgeries in 15 subjects submitted in an interim study report. For details, please refer to the Clinical Review Memo by Dr Megha Kaushal under STN 125566/51 dated December 19, 2016. The primary outcome measure was the Global Hemostatic Efficacy Assessment (GHEA) which was composed of the three individual ratings:

1) Assessment of intraoperative hemostatic efficacy of BAX 855 performed by the operating surgeon.
2) Assessment of postoperative hemostatic efficacy of BAX 855 performed on postoperative Day 1 (i.e., the day following the day of surgery) by the operating surgeon.
3) Assessment of perioperative hemostatic efficacy of BAX 855 performed by the investigator at discharge or on postoperative Day 14 (whichever is first).

The hemostatic efficacy scales are included in Appendix A. In summary, excellent rating requires blood loss less than or equal to that expected for the type of procedure performed in a non-hemophilic population, good rating requires blood loss up to 50% more than expected for the type of procedure in a non-hemophilic population and fair rating requires that the blood loss be more than 50% of that expected for the type of procedure performed in a non-hemophilic population. Uncontrolled bleeding due to inadequate therapeutic response despite proper dosing necessitating rescue therapy resulted in “none” rating. For perioperative efficacy assessment of good or excellent, the required blood components for transfusions had to be less than or similar to that expected in a non-hemophilic population in addition to the requirement noted above for blood loss.

The scores of each of the three individual ratings described above are added together to form a GHEA score outlined in Table 27:

Table 27: GHEA Scores

Table 1.
Global Hemostatic Efficacy Assessment (GHEA)

Assessment	GHEA Score
Excellent	7[a] to 9 (with no category scored < 2)
Good	5 to 7[a] (with no category scored < 1)
Fair	3 to 4 (with no category scored < 1)
None	0 to 2 (or at least one category scored 0)

[a] For a GHEA score of 7 to be rated "excellent" (with no individual assessment scores less than 2), at least 1 individual assessment score must be 3 and the other 2 individual assessment scores must be at least 2; otherwise a score of 7 is rated "good".

Source: Study 261204:Protocol amendment 6; 2015

Secondary outcome measures for efficacy included intra- and post-operative blood loss at the end of surgery, at post-operative Day 1 and until discharge or Day 14 (whichever is first) compared to the estimated volume of expected average and maximum blood loss in a comparable healthy individual as predicted preoperatively by the investigator/ surgeon. Other measures included volume of blood products that were transfused, occurrence of bleeding requiring surgical intervention and daily and total weight adjusted consumption of BAX 855.

Efficacy Results reviewed by Dr. Kaushal at the time perioperative indication was granted is summarized below:
The intraoperative and perioperative efficacy of BAX 855 to provide hemostatic control was rated as "excellent" for all 11 major and 4 minor surgeries (15 in total). The postoperative efficacy as assessed by the operating surgeon on postoperative Day 1 was rated as "excellent" for 13 procedures. One minor surgery was rated as "good". The overall GHEA score was excellent for this minor surgery. For another minor surgery, postoperative hemostatic efficacy was not rated at the time of data cut-off for this report. Postoperative blood loss was observed in 5 major surgeries, but the maximum postoperative blood loss was not exceeded. There were three subjects with perioperative bleeding of over a liter but did not exceed the predicted perioperative blood loss of 1500 ml.

Safety Results:
No deaths and no related SAEs occurred. There were no AEs considered thrombotic events or related AEs considered allergic reactions by the investigator. None of the subjects developed inhibitory antibodies to FVIII. None of the subjects developed IgM binding antibodies, and there were no persistent IgG binding antibodies to FVIII, PEG-FVIII, and PEG. None of the subjects developed binding antibodies to CHO proteins. Overall, the clinical reviewer concluded that BAX 855 was efficacious and well tolerated for perioperative use.

In the final study report, which was provided in this current BLA submission, the Applicant has included additional efficacy data from 10 major surgical procedures and one minor surgical procedure. This is summarized below in Table 28:

Table 28. Perioperative Hemostatic Efficacy

Subject ID	Surgery	Type	Hemostatic Efficacy				Additional information
			Intraoperative	Postoperative	Perioperative	GHEA	
(b) (6)	Two third molar extraction	Major	Excellent	Excellent	Excellent	Excellent	
	Removing needle	Major	Excellent	Excellent	Excellent	Excellent	
	Elbow arthroscopy with synovectomy	Major	Excellent	Excellent	Excellent	Excellent	
	Revision of left total hip arthroplasty	Major	Excellent	Excellent	Excellent	Excellent	
	Alloplastic left knee	Major	Excellent	Excellent	Excellent	Excellent	Postoperative and perioperative blood loss > predicted blood loss. 293 ml of PRBC post-operative transfusion.
	Alloplastic left knee	Major	Excellent	Excellent	Excellent	Excellent	Postoperative and perioperative blood loss > predicted blood loss.
	Alloplastic right knee procedure	Major	Excellent	Excellent	Excellent	Excellent	536 ml of PRBC post-operative transfusion.
	Reconstruction of right Achilles tendon	Major	Excellent	Excellent	Excellent	Excellent	Postoperative and perioperative blood loss > predicted blood loss.
	Teeth extraction , cystectomy	Major	Excellent	Excellent	Excellent	Excellent	
	Hip replacement	Major	Excellent	Excellent	Excellent	Excellent	
	Incision and drainage of pilonidal sinus	Minor	Not known	Excellent	Excellent	Not known	

Reviewer's Comment: Three subjects who underwent major surgeries had post-operative and perioperative blood loss that was higher than predicted average blood loss. This included one subject who underwent alloplastic left knee procedure with higher actual postoperative (100 ml vs. 700ml) and perioperative (1450 ml vs.1000ml) blood loss

compared to the predicted average blood loss. However, in all three cases the blood loss was still lower than predicted maximum blood loss. None of these surgeries required additional surgical intervention or rescue therapy for hemostasis. No bleeding events were described from the start of surgery until the last treatment after hospital discharge.

In summary, a total of 21 major surgeries and 5 minor surgeries have been performed in the study to evaluate the perioperative hemostatic efficacy of BAX 855. All 21 major surgeries (14 orthopedic and 7 non-orthopedic) have overall global hemostatic efficacy assessment (GHEA) of excellent. Of the 5 minor surgeries, 3 have GHEA of excellent. For remaining two minor surgeries, GHEA is not available as assessments were missing for intraoperative assessment for one patient and postoperative assessment in another patient.

The following analysis are provided for all 26 surgical procedures that are included in the final submission:

Intraoperative blood loss:

The actual intraoperative blood loss was overall lower than the predicted average blood loss (median) of 150 ml (Range:0, 500 ml) for major orthopedic and 10 ml (Range:2, 150ml) for major non-orthopedic surgeries.

Post-operative blood loss: The median actual blood loss was 750 ml (Range 0,1200ml) for the orthopedic major surgeries and was higher than predicted average median of 213.5 ml (Range 0, 700 ml). However, the actual blood loss was a median of 100ml lower than maximum blood loss predicted pre-operatively for the specific procedures.

Blood transfusions:

No transfusions were required intraoperatively. Overall, five transfusions were administered for four surgeries. This includes three major orthopedics and one major non-orthopedic surgery. Two surgeries are included in current review (Table 28) and two surgeries (major orthopedic replacement and gastric band insertion) were included in the previous review by Dr. Kaushal. All transfusions were indicated for anemia.

Consumption of BAX 855 during surgery:

The preoperative loading dose ranged from 36 to 99 IU/kg with a median of 60 IU/kg. The total postoperative dose ranged from 23- 769 IU/kg with a median of 183IU/kg. The median total dose (including all administrations from pre-surgical PK and loading doses to post-hospital follow up) was 629 IU/kg (range: 464 – 1,457 IU/kg) for major orthopedic surgeries, 489 IU/kg (range: 296 – 738 IU/kg) for major non-orthopedic surgeries.

Safety Assessment:

No deaths or thrombotic events were reported in the study. None of the subjects developed antibodies to CHO proteins or inhibitory antibodies to FVIII. None of the subjects developed persistent IgG or IgM binding antibodies to FVIII, PEG-FVIII, and PEG. No allergic reactions were reported by investigator. One subject (b) (6) had positive IgG binding antibody to FVIII (1:80) at the termination visit, which was negative at screening. The same subject had a preexisting IgG binding antibody to BAX 855 at screening and at the completion/termination visit which did not increase during the study. This subject was enrolled for a second surgery as Subject (b) (6) and during screening was again positive at 1:80 for IgG binding antibody to BAX 855 but was negative for IgG binding antibody to FVIII.

Four treatment emergent SAEs in two subjects were considered unrelated to BAX 855 and include two events of diabetic gastroparesis, one esophageal ulcers and one device related infection. None of the AEs that were reported in the current submission are considered related to BAX 855.

Summary:
This final study report confirms the efficacy of BAX 855 in the perioperative management of 21 major and 5 minor surgeries. No deaths and no related SAEs occurred. There were no AEs considered thrombotic events or related AEs considered allergic reactions by the investigator

7. INTEGRATED OVERVIEW OF EFFICACY

Integrated Evaluation of Efficacy was not done given that the studies confirmed benefit of approved dosing regimens and the dosing regimens were not identical in the studies in all subjects, making integration challenging.

7.1 Indication #1

N/A

7.1.1 Methods of Integration

N/A

7.1.2 Demographics and Baseline Characteristics

N/A

7.1.3 Subject Disposition

N/A

7.1.4 Analysis of Primary Endpoint(s)

N/A

7.1.6 Other Endpoints

N/A

7.1.7 Subpopulations

N/A

7.1.8 Persistence of Efficacy

N/A

7.1.9 Product-Product Interactions

N/A

7.1.10 Additional Efficacy Issues/Analyses

N/A

7.1.11 Efficacy Conclusions

N/A

8. INTEGRATED OVERVIEW OF SAFETY

Integrated evaluation of safety was not conducted. Please refer to individual study results discussed above.

8.1 Safety Assessment Methods

N/A

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Studies 204, 302 and 303. (Please refer to Section 6)

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

N/A

8.2.3 Categorization of Adverse Events

N/A

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

N/A

8.4 Safety Results

8.4.1 Deaths

No deaths were reported due to suspected toxicity.

8.4.2 Nonfatal Serious Adverse Events

N/A

8.4.3 Study Dropouts/Discontinuations

N/A

8.4.5 Clinical Test Results

N/A

8.4.6 Systemic Adverse Events

N/A

8.4.7 Local Reactogenicity

N/A

8.4.8 Adverse Events of Special Interest

N/A

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

N/A

8.5.2 Time Dependency for Adverse Events

N/A

8.5.3 Product-Demographic Interactions

N/A

8.5.4 Product-Disease Interactions

N/A

8.5.5 Product-Product Interactions

N/A

8.5.6 Human Carcinogenicity

N/A

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

N/A

8.5.8 Immunogenicity (Safety)

Two subjects developed transient and low titer FVIII inhibitors without any clinically significant bleeding and were able to continue the BAX 855 regimen without need for dose modification.

8.6 Safety Conclusions

No new significant safety signals were detected as a part of this review.

9. Additional Clinical Issues

9.1 Special Populations

N/A

9.1.1 Human Reproduction and Pregnancy Data

N/A

9.1.2 Use During Lactation

N/A

9.1.3 Pediatric Use and PREA Considerations

The adolescent (Age 12 to <17 years) portion of Study 303 was a PREA PMR study. Given that the study was completed and submitted, this PREA PMR is considered fulfilled.

Reviewer's comment: Given that BAX 855 is approved for all three indications of routine prophylaxis, on-demand treatment and perioperative management in the pediatric population, it remains unclear why Study 303 was deemed a PREA PMR. The reviewer could not clearly identify the rationale from review of the prior documents. The most plausible reason may be that this study was (b) (4) for BAX 855.

9.1.4 Immunocompromised Patients

N/A

9.1.5 Geriatric Use

N/A

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

N/A

10. CONCLUSIONS

Overall, the completed surgical study continued to show efficacy and safety of BAX 855 in the perioperative management of hemophilia A. The extension study continued to show ABRs that were in line with the parent licensing studies without any new safety signals. The randomized controlled trial 303 (b) (4) .

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

There is no change to risk and benefit determination for BAX 855.

11.2 Risk-Benefit Summary and Assessment

N/A

11.3 Discussion of Regulatory Options

(b) (4)

11.4 Recommendations on Regulatory Actions

(b) (4) , I recommend approval of this BLA supplement. Completion of the immunogenicity PMC study (Study 203) is recommended.This submission fulfills the PREA PMR and PMC related to Study 303.

11.5 Labeling Review and Recommendations

Labeling negotiations are ongoing at the time of completion of this clinical review memo. In addition to the AE data from Studies 302, 303 and completed Study 204, the Applicant has updated Table 3 in Section 6 of the label to include additional AEs from studies 101, 201, 202 and 203 that were part of previous regulatory submissions. The reviewer analyzed the ISS study report and ISS dataset that was submitted under amendment 51/6 dated January 2016 to evaluate these adverse events. Overall, the updated Table 3 in the PI includes additional low-grade events of headache, diarrhea, nausea, rash, and dizziness from these previously reviewed studies. If an AE was found to be related in one subject, then the Applicant included all reported events of that type in frequency of the adverse drug reactions in Table 3 (Section 6). The plan to update the label to include these additional AEs in the label is reasonable as these AEs are considered as possibly related to the product based on clinical reviewer's assessment.

Additional changes being made to the label include the recommendation to adjust the *dosing interval* (to allow for dosing based on response) in addition to the dose of BAX 855 based on patient's clinical response in Section 2.1 and to update Section 6.2, Immunogenicity to include the two cases of Factor VIII inhibitor reported from Studies 302 and 303 respectively in addition to updated information related to binding antibodies against FVIII, pegylated FVIII, PEG and CHO from the safety database.

As a part of the labeling negotiations with the Applicant, the following statement was added to Section 14 to inform prescribers regarding extension Study 302:
An extension study in adult and pediatric patients evaluated the safety and efficacy of prophylactic treatment regimen in 216 previously treated patients with severe hemophilia A. Majority had completed the adult and adolescent study or the pediatric study. Similar efficacy was noted in this extension study.

11.6 Recommendations on Post-marketing Actions

With this submission, Applicant has a single PMC that is outstanding. This is Study 203, which is a Phase 3, multicenter, open label study to investigate safety, immunogenicity and efficacy of BAX 855 in PUPs.

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APPENDICES

Appendix A:

Table 2a: Treated Subjects who were unable to Complete the OPE and for whom "Post-Propel" Bleed Data was not Available Requiring Imputation (Study 261303)
Low Level

		Number of days for which imputation was performed		Average number of all bleeds that were imputed	
Subject ID	Last day on PROPEL	First 6-month period	Second 6-month period	First 6-month period	Second 6-month period
(b) (6)	2018-06-04	0	4	N/A	0.056
	2017-11-15	0	82	N/A	10.468
	2018-06-15	0	4	N/A	0.014
	2017-08-01	0	1	N/A	0.002
	2018-04-16	0	3	N/A	0.004

First 6-month period is defined as the period from subject´s observation day 1 until observation day 182.
Second 6-month period is defined as the period from subject´s observation day 183 until observation day 364.
OPE = Observation Period of Efficacy.
Low level = Low FVIII trough level (1-3%).
High level = High FVIII trough level (8-12%).

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Table 2b: Treated Subjects who were unable to complete the OPE and for whom "Post-Propel" Bleed Data was not Available Requiring Imputation (Study 261303)
High Level

		Number of days for which imputation was performed		Average number of all bleeds that were imputed	
Subject ID	Last day on PROPEL	First 6-month period	Second 6-month period	First 6-month period	Second 6-month period
(b) (6)	2017-03-06	160	182	1.922	2.186
	2018-01-25	0	2	N/A	0.083
	2017-08-17	7	182	0.040	1.053
	2017-06-19	100	182	0.038	0.069
	2018-02-06	0	57	N/A	0.129
	2018-01-16	0	17	N/A	0.015
	2017-04-05	125	182	0.289	0.420
	2017-06-07	0	174	N/A	1.194
	2018-07-26	0	1	N/A	0.002
	2017-09-18	58	182	0.147	0.461

First 6-month period is defined as the period from subject´s observation day 1 until observation day 182.
Second 6-month period is defined as the period from subject´s observation day 183 until observation day 364.
OPE = Observation Period of Efficacy.
Low level = Low FVIII trough level (1-3%).
High level = High FVIII trough level (8-12%).

Hemostatic Efficacy Scales:

Table 1.
Global Hemostatic Efficacy Assessment (GHEA)

Assessment	GHEA Score
Excellent	7[a] to 9 (with no category scored < 2)
Good	5 to 7[a] (with no category scored < 1)
Fair	3 to 4 (with no category scored < 1)
None	0 to 2 (or at least one category scored 0)

[a.] For a GHEA score of 7 to be rated "excellent" (with no individual assessment scores less than 2), at least 1 individual assessment score must be 3 and the other 2 individual assessment scores must be at least 2; otherwise a score of 7 is rated "good".

Table 2. **Intraoperative Efficacy Assessment Scale**		
A	*At the time of discharge from the OR, the operating surgeon will assess the intraoperative hemostatic efficacy*	
Rating	**Criteria**	**Score**
Excellent	Intraoperative blood loss was less than or equal to that expected for the type of procedure performed in a non-hemophilic population (≤100%)	3
Good	Intraoperative blood loss was up to 50% more than expected for the type of procedure performed in a non-hemophilic population (101-150%)	2
Fair	Intraoperative blood loss was more than 50% of that expected for the type of procedure performed in a non-hemophilic population (>150%)	1
None	Uncontrolled hemorrhage that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy	0

Table 3. **Postoperative Efficacy Assessment Scale (Postoperative Day 1)**		
B	*On postoperative Day 1, the operating surgeon will assess the postoperative hemostatic efficacy by the operating surgeon*	
Rating	**Criteria**	**Score**
Excellent	Postoperative blood loss was less than or equal to (≤100%) that expected for the type of procedure performed in a non-hemophilic population	3
Good	Postoperative blood loss was up to 50% more (101-150%) than expected for the type of procedure performed in a non-hemophilic population	2
Fair	Postoperative blood loss was more than 50% (>150%) of that expected for the type of procedure performed in a non-hemophilic population	1
None	Significant postoperative bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating rescue therapy	0

Table 4. **Perioperative Efficacy Assessment Scale (Discharge Visit or Day 14, whichever is first)**		
C	*At the discharge Visit or Day 14, whichever is first, a hematologist will assess the perioperative efficacy*	
Rating	**Criteria**	**Score**
Excellent	Perioperative blood loss was less than or equal to (≤100%) that expected for the type of procedure performed in a non-hemophilic population, Required blood components for transfusions were less than or similar to that expected in non-hemophilic population	3
Good	Perioperative blood loss was up to 50% more (101-150%) than expected for the type of procedure performed in a non-hemophilic population Required blood components for transfusions were less than or similar to that expected in non-hemophilic population	2
Fair	Perioperative blood loss was more than 50% of that expected for the type of procedure performed in a non-hemophilic population (>150%) Required blood components transfusions were greater than that expected in non-hemophilic population	1
None	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-hemophilic population	0

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