Application Type	BLA
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Division / Office	DB/OBE
Committee Chair	Ze Peng, PhD
Clinical Reviewer(s)	Stephanie Omokaro, MD
Project Manager	Edward Thompson
Priority Review	N/A
Reviewer Name(s)	Judy Li, PhD
Review Completion Date / Stamped Date	October 1, 2015
Supervisory Concurrence	Renee Rees, PhD
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Applicant	Baxter
Established Name	PEGylated rFVIII
(Proposed) Trade Name	BAX 855
Dosage Form(s) and Route(s) of Administration	intravenous infusions
Dosing Regimen	*Routine Prophylaxis*: 40-50 IU per kg 2 times per week. *Individualized Dosing:* (b) (4)
Indication(s) and Intended Population(s)	For adolescent (12 to less than18 years) and adult patients with hemophilia A (congenital factor VIII deficiency): On-demand treatment and control of bleeding episodes; Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

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GLOSSARY OF ACRONYMS

ABR	annualized bleeding rate
AE	adverse event
BLA	biologics license application
BW	body weight
CHO	Chinese hamster ovary
CI	confidence interval
CSR	clinical study report
ED	exposure day
FAS	full analysis set
FVIII	factor VIII
HRQoL	health-related quality of life
IR	information request
IU	international unit
OPE	observation period for efficacy
PEG	polyethylene glycol
PK	pharmacokinetics
PPAS	per protocol analysis set
PRO	patient reported outcome
PTP	previously treated patient
PUP	previously untreated patient
rAHF-PFM	recombinant anti-hemophilic factor, plasma/albumin-free method
rFVIII	recombinant factor VIII
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set

1. EXECUTIVE SUMMARY

The applicant submitted a biologics license application (BLA) for the use of BAX 855 (Antihemophilic Factor [Recombinant] PEGylated, rurioctocog alfa pegol) for the proposed indication of on-demand treatment and control of bleeding episodes in adolescent (12 to < 18 years) and adult (> 18 years) patients with hemophilia A (congenital factor VIII [FVIII] deficiency), as well as routine prophylaxis to prevent or reduce the frequency of bleeding episodes. The ratio of the mean ABR for the prophylaxis group versus the on-demand group is 0.1 (95% CI: 0.06, 0.19). The estimated success rate for the treatment of bleeding episodes is 0.96 (95% CI: 0.91, 0.98). The study efficacy success criteria for both indications were met. There was no death considered to be related to BAX 855. None of the subjects developed anti-FVIII inhibitory antibodies. The statistical results from this BLA appear to support the claim for use of BAX 855 in the treatment of Hemophilia A patients for routine prophylaxis to prevent or

reduce the frequency of bleeding episodes, and on-demand treatment and control of bleeding episodes.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A is an X-linked bleeding disorder that occurs predominantly in males and is characterized by deficiency of functional factor VIII (FVIII). The worldwide incidence of hemophilia A is approximately 1 case per 5000 male births. Numerous mutations that cause hemophilia have been identified. The F8 gene is one of the most complex genes in the genome. Individuals with severe hemophilia experience frequent and recurrent spontaneous or traumatic bleeding into the soft tissue and joints, leading to arthropathy, muscle contractures, and severe disability. Signs and symptoms include joint swelling, joint and muscle pain, as well as mucosal and gastrointestinal tract bleeding.

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

BAX 855 is an extended half-life (T1/2) recombinant human coagulation factor VIII (rFVIII) modified with polyethylene glycol (PEG). rFVIII is expressed in Chinese Hamster Ovary (CHO) cells and manufactured using Baxter's Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method (rAHF-PFM); it is also the active substance in Baxter's licensed product ADVATE. The investigational product, BAX 855, is manufactured by covalently binding a branched PEG reagent with a molecular weight of 20 kDa to Baxter’s rFVIII.

The original protocol for the pivotal study 261201 was submitted on November 23, 2012 to IND 15299. On February 7, 2014, the applicant submitted the latest version of the protocol in amendment #4, which also includes several changes from protocol amendment #1 (dated July 8, 2013). The changes in the SAP are acceptable.

On January 31, 2014, the applicant requested a pre-BLA meeting. FDA sent a pre-BLA correspondence instead of a face to face meeting (refer to CRMTS #9324, IND 15299, March 25, 2014, with clarification to the applicant on March 28, 2014). One of the questions inquired about the overall Statistical Analyses Plan (SAP) for study 261201. FDA responded by suggesting the applicant include subgroup analyses, revise the null hypothesis, specify the analysis set for the primary efficacy endpoint, as well as provide justifications for comparing the Haemo-SYM pain score to 11.

Two Information Requests (IR) for analysis program codes were made for the verification of the study results. The applicant provided the information in Amendments #15 and #18 of the BLA application.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a statistical review without unreasonable difficulty.

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

5.1 Review Strategy

Per discussion with the clinical reviewer, this review mainly focuses on the review of the pivotal study 261201. Specifically, the efficacy analyses will focus on the primary efficacy outcome measure, the key secondary efficacy outcome measure, other secondary efficacy outcome measures including the number of BAX 855 infusions needed for the treatment of bleeding episodes and time intervals between bleeding episodes.

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

This review memo was based on the data files (module 5.3.5.1), draft labeling (module 1.14.1), protocol and its amendment (module 5.3.5.1), and study report body (module 5.3.5.1) submitted in the original submission, and the SAS program codes submitted in amendments #15 and #18.

5.3 Table of Studies/Clinical Trials

A 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 was conducted in adult previously-treated patients (PTPs) with severe hemophilia A (FVIII <1%). This phase 1 study (261101) included a total of 19 evaluable adult PTPs.

Based on the results of the phase 1 study, a phase 2/3, multicenter, non-randomized open label study in adult and adolescent male PTPs with severe hemophilia A was performed to evaluate efficacy, safety, and PK parameters of BAX 855 and to assess health-related quality of life (HRQoL) in subjects using a prophylactic dosing regimen or an on-demand treatment regimen (261201). The study included 138 evaluable subjects.

Three studies are currently ongoing: a study in pediatric PTPs (261202), a study in subjects undergoing surgery or other invasive procedures (261204), and a continuation study for subjects who have completed previous BAX 855 studies (261302). After closure of enrollment for pediatric study 261202 and pivotal study 261201, the continuation study will also be open to BAX 855 naïve pediatric and adolescent/adult patients.

Two studies are planned: A study to evaluate safety and immunogenicity in previously untreated patients (PUPs) < 6 years of age (261203) and a study to compare the safety and efficacy of PK guided BAX 855 treatment targeting two different FVIII trough levels (261303). The latter will be open to subjects who previously completed another BAX 855 study as well as to subjects naïve to BAX 855. Table 1 summarizes the studies for the development of BAX855.

Table 1. Listing of Studies in the Development of BAX 855 (Source: module 5 section 5.2)

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 Acutebleedingepisodes: treated with BAX 855 PKevaluation: 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	Ongoing	60 2 age cohorts (<6 years and 6 to <12 years) of 30 subjects each	PTPs[b] <12 years FVIII <1%	Prophylaxis: 50 ±10 IU/kg BW over a period of 6 months, or at least 50 EDs[c] Acutebleedingepisodes: treated with BAX 855 PKevaluation: ADVATE and BAX 855 at prophylactic dose level

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	Ongoing	~50 major and minor surgeries or other invasive procedures in ~40 subjects to evaluate ≥ 10 major surgical/ invasive procedures in ≥5 subjects	PTPs[b] 2 to 75 years FVIII <1%	Surgicalprophylaxis: 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	Ongoing	250	PTPs[b] who completed another BAX 855 study or BAX 855 naïve ≤75 years FVIII <1%	Prophylaxis: dose and frequency based on previous treatment regimen or PK guided to maintain FVIII trough levels of at least 3%; subject exposure for a minimum of 100 EDs[c] (as accumulated across all BAX 855 studies)
261203	**BAX 855 PUPs** Phase 3, multi-center, open-label study to investigate safety and immunogenicity of BAX 855 in PUPs	Planned	110 (100 evaluable)	PUPs <6 years, FVIII <1%, who have undergone <3 EDs[c] with previous FVIII products	Prophylaxis: 30±5 to 45±5 IU/kg once or twice weekly

Study Number	**Short Study Title and Description**	**Study Status Report (if available)**	**Sample Size[a]**	**Main Criteria for Inclusion**	**Dose Range and Frequency**
261303	**BAX 855 PK-guided Prophylaxis** Phase 3, prospective, randomized, open-label multi-center clinical study to compare the safety and efficacy of PK guided BAX 855 treatment regimen targeting 2 different FVIII trough levels	Planned	116 to have 96 evaluable patients (48 per treatment arm)	PTPs[b] who completed another BAX 855 study or BAX 855 naïve 12 - 65 years FVIII <1%	BAX 855 dose will be PK-guided to maintain FVIII target trough levels of 1 - 3% or approx. 10% (8 - 12%) FVIII trough level 1 - 3%: at least twice weekly FVIII trough level approx. 10% (8% - 12%): every other day

[a]Actual sample size for completed studies, planned sample size for ongoing and projected studies
[b] Previously-treated patient (PTP): subject has hemophilia A and has been treated with FVIII product previously.
[c] An exposure day (ED) is defined as any calendar day on which at least one infusion of BAX 855 was administered.
Abbreviations: BW = body weight; CSR = clinical study report; ED = exposure day; FVIII = factor VIII; HRQoL = health-related quality of life;
IU = International Unit; PK = pharmacokinetics; PTP = previously treated patient; PUP = previously untreated patient

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #261201

6.1.1 Objectives (Primary, Secondary, etc)

Primary
The primary objective was to compare the annualized rates of bleeding episodes (ABR) between subjects who received a prophylactic dosing regimen of BAX 855 with those who received an on-demand treatment regimen.

Secondary
The key secondary objective was to estimate the rate of success of BAX 855 for treatment of bleeding episodes.

Other secondary efficacy objectives included:
Efficacy:

1. To characterize BAX 855 for treatment of bleeding episodes through the number of BAX 855 infusions needed for the treatment of a bleeding episode and through the length of intervals between bleeding episodes
2. To compare the total weight-adjusted consumption of BAX 855 for each regimen

Safety:

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

Patient Reported Outcomes (PROs):

1. To assess Health-Related Quality of Life (HRQoL) over time for subjects receiving BAX 855, using the Haemo-SYM and the short form-36 (SF-36) questionnaires

Other
The pharmacokinetic and exploratory objectives are not reviewed in this memo.

6.1.2 Design Overview

This was a phase 2/3, multicenter, open-label, non-randomized two-arm study to be conducted in a total of approximately 119 evaluable adult and adolescent male PTPs with severe hemophilia A. Approximately 104 evaluable (115 planned) subjects were to receive prophylactic treatment (Arm A) compared to approximately 15 evaluable (17 planned) subjects receiving on-demand treatment (Arm B) with BAX 855. Subjects were assigned to a treatment arm based upon their pre-study FVIII treatment regimen; however, once 17 subjects were assigned to the on-demand arm, subsequent subjects who had previously received on-demand treatment were assigned to prophylaxis.

6.1.3 Population

Approximately 132 male Previous Treated Patients (PTPs) with severe hemophilia A (FVIII < 1%) were planned to be enrolled in the study.

Inclusion Criteria
The main criteria for inclusion were a diagnosis of severe hemophilia A, previous treatment with FVIII concentrates for ≥150 EDs, and that the subject be male and aged 12-65 years at screening.

Exclusion Criteria
The main criteria for exclusion were the presence of detectable FVIII inhibitory antibodies (≥ 0.4 BU using the (b) (4) Bethesda assay), history of FVIII inhibitory antibodies, diagnosis of an inherited or acquired defect other than hemophilia A, or that the subject had recently used another pegylated product.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The treatments were administered as intravenous infusions. In Arm A, prophylaxis with BAX 855 were to be treated twice weekly at a dose of 45 ± 5 IU/kg for ≥50 EDs, or six months ±2 weeks, whichever occurred last. In Arm B, on-demand therapy with BAX 855 at a dose of 10 to 60 ± 5 IU/kg was administered until the bleeding episode/threat was resolved during the study period.

The prophylactic dose of BAX 855 was selected based on phase 1 clinical study data, to ensure that the majority of subjects maintained a trough level above 1%. Based on the investigator's clinical evaluation, the dose for prophylactic treatment may have been increased for subjects receiving prophylactic treatment at any time to ensure subject safety was adequately managed, following approval by the Medical Director. Subjects meeting any of the following criteria during prophylaxis may have had their BAX 855 dose increased from 45 ± 5 IU/kg to 60 IU/kg:

- Two or more spontaneous (not related to trauma) bleeding episodes in the same target joint within any 2-month period, or
- One or more spontaneous (not related to trauma) bleeding episodes in a non-target joint within any 2-month period or
- FVIII trough level < 1% and the investigator assessed the subject was at increased risk of bleeding.

6.1.6 Sites and Centers

Eighty-six study sites participated in this study; 72 study sites enrolled subjects and 14 sites were initiated but were inactive.

6.1.8 Endpoints and Criteria for Study Success

Primary Outcome Measure

The primary efficacy outcome measure of the study was ABR. ABR is calculated as the number of bleeding episodes divided by the observation period (in days) and multiplied by 365.2425. Prophylactic treatment was considered successful if the upper limit of the 95% CI for the ratio of the prophylaxis to on-demand treatment regimens did not exceed 0.5 (corresponding to a 50% reduction of the mean prophylaxis ABR compared to the on-demand treatment).

Secondary Outcome Measures

Efficacy

1. Rate of success of BAX 855 for treatment of bleeding episodes. Efficacy was evaluated for each bleeding episode and was assessed by the subject 24 h (± 2 h) after initiating treatment using the Efficacy Rating Scale for Treatment of Bleeding Episodes shown below. Success is defined as a response of Excellent or Good at the 24-h post-infusion time point. The lower limit of the 95% CI for the proportion of success was compared to the threshold of 70%.

Efficacy Rating Scale for Treatment of Bleeding Episodes	
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	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.

2. Number of BAX 855 infusions used for the treatment of bleeding episodes
3. Time intervals between bleeding episodes
4. Weight-adjusted consumption of BAX 855

Safety

1. Occurrence of AEs and serious adverse events (SAEs)
2. Changes in vital signs and clinical laboratory parameters (hematology, clinical chemistry, and lipids)
3. Immunogenicity
    - Inhibitory antibodies to FVIII
    - Binding antibodies (IgG and IgM) to FVIII, PEG-FVIII, and PEG
    - Anti-CHO antibodies

For the safety success criterion, the upper limit of the 95% CI for the proportion of subjects who developed inhibitors was compared to the threshold of 6.8%.

PROs

Changes from baseline in the following PROs:

1. Bleed and pain severity as measured using the Haemo-SYM questionnaire
2. HRQoL as assessed using the SF-36 questionnaire

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis populations
The following analysis populations were utilized in the analyses.

- *Full Analysis Set (FAS)*
  FAS comprised all subjects who were assigned to the prophylactic arm or the on-demand treatment regimen. This is the population pre-specified for the primary efficacy analysis.

- *Per Protocol Analysis Set (PPAS)*
  PPAS comprised all subjects who were assigned to the prophylactic or the on-demand treatment regimen, treated with their originally assigned dose for the entire duration of study participation and who fulfilled the compliance requirements defined as follows:

  1. Prophylaxis:
  a. Infusion interval of 5 or more days did not occur more than 3 times in the OPE
  b. The daily dose was below 35 IU/kg in no more than 10% of the infusions in the OPE.
  c. The daily dose was above 55 IU/kg in no more than 10% of the infusions in the OPE.

  2. Treatment of bleeding episodes (prophylaxis and on-demand)
  Dose to treat the bleeding episode was below 5 IU/kg for minor bleed, below 10 IU/kg for moderate bleeding episode, or below 25 IU/kg for a major bleeding episode for no more than 5 bleeding episodes (minor/moderate/major taken together).

- *Safety Analysis Set (SAS)*
  SAS comprised all subjects treated with at least one BAX 855 dose. All safety analyses for BAX 855 were to be performed on the SAS.

Primary efficacy endpoint
Comparisons between prophylactic and on-demand treatment were based on ABR estimates from a negative binomial regression model, taking into account the fixed effect of regimen (prophylaxis vs on-demand), stratum (presence or absence of target joints at screening), age at screening as a continuous covariate, and the duration of the observation period for efficacy (OPE) as an offset. Ratios of treatment means (point estimates and their 95% CIs) were estimated within this model. Subgroup analyses for ABR were also performed by age (12 to <18 years, 18 to 65 years) and race.

Key secondary efficacy endpoint
Success proportion was analyzed using a general estimating equation (GEE) model with a logit link function and an independent variance covariance working correlation structure. Treatment arm, bleed type (joint vs non-joint bleed) and severity were included in the analysis as fixed effects.

Other secondary efficacy endpoints
Frequency tables were to be prepared for the number of infusions required for the treatment of a bleeding episode (ADVATE and BAX 855). The median number of infusions (and nonparametric 95% CI), the number of infusions per bleeding episode summarized by bleed type (joint versus non-joint), by severity (mild versus moderate versus severe) and by cause of the bleeding episode (spontaneous versus injury) were tabulated.

Safety endpoints
Summary tables and descriptive statistics including the number and percentage of subjects reporting non-serious AEs and SAEs that occurred after treatment with BAX 855 were provided. AEs were described by severity (mild, moderate, severe) and relatedness. AEs that occurred prior to receiving ADVATE/BAX 855 or during PK-1(ADVATE) or PK-2 (BAX 855) were listed separately. Descriptive statistics were prepared for the number of AEs associated with BAX 855 infusions. The Clopper-Pearson exact 95% confidence interval was computed for the proportion of subjects who developed inhibitory antibodies during the study, including all subjects who developed inhibitory antibodies and all subjects who did not develop inhibitory antibodies and had $\geq$ 50 EDs.

Missing data
Missing data were not imputed for the primary efficacy endpoint since the duration of the OPE is included in the model as an offset. However, if body weight was missing for a subject then the last value of available body weight measurement was carried forward in order to compute weight-adjusted BAX 855 consumption.

Regarding missing data in AE records:

- If the date of onset for an AE is missing completely then it was imputed with the date of the first study drug application.
- If a subject experienced an AE with a missing causality assessment, the relationship of the AE was to be counted as “related”.
- If a subject experienced more than one AE categorized under the same preferred term, one of them was categorized as “mild” or “moderate” and one of them was categorized as “unknown”, the severity of this AE was to be counted as “unknown”.
- If a subject experienced more than 1 AE categorized under the same preferred term, e.g., one of them was categorized as “severe” and one of them was categorized as “unknown”, the severity of this AE was to be counted as “severe”.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 159 subjects were enrolled in the study, of whom 137 subjects were treated with BAX 855 during the treatment period, and 1 subject was assigned to receive BAX 855 but did not receive any BAX 855 during the treatment period.

The numbers of subjects in each analysis set were:

- FAS: 138 subjects (121 subjects prophylactic arm; 17 subjects on-demand arm)
- PPAS: 118 subjects (101 subjects prophylactic arm; 17 subjects on-demand arm)
- SAS: 137 subjects (120 subjects prophylactic arm; 17 subjects on-demand arm)

None of the subjects assigned to the on-demand arm (in the FAS) were excluded from the PPAS. Twenty (20) subjects assigned to the prophylactic arm (in the FAS) were excluded from the PPAS. There were 25 adolescents (aged 12 to < 18 years) and 113 adults (aged 18 to 65 years) in the FAS, and 19 adolescents and 99 adults in the PPAS.

There were no subjects were included in the SAS but excluded from the FAS. One subject (483001) was assigned to prophylactic treatment with BAX 855 (in the FAS), but was treated with ADVATE only, and thus was not in the SAS.

6.1.10.1.1 Demographics

Tables 2 and 3 provide summary statistics for the demographics of the FAS population.

Table 2. Mean (SD) and Median (Min; Max) Age in Years of Subjects by Treatment Arm in FAS (Source: full clinical study report 261201 Table 3)

Subgroup	Total		Prophylaxis		On-Demand	
All	30.0 (12.34) 29.0 (12 ; 58)	N=138	29.8 (12.53) 28.0 (12 ; 58)	N=121	31.5 (11.05) 32.0 (13 ; 56)	N=17
12 to < 18 years	14.5 (1.58) 15.0 (12 ; 17)	N=25	14.5 (1.53) 15.0 (12 ; 17)	N=23	15.0 (NA) NA (13 ; 17)	N=2
18 to 65 years	33.4 (10.96) 31.0 (18 ; 58)	N=113	33.4 (11.18) 30.0 (18 ; 58)	N=98	33.7 (9.7) 32.0 (19 ; 56)	N=15

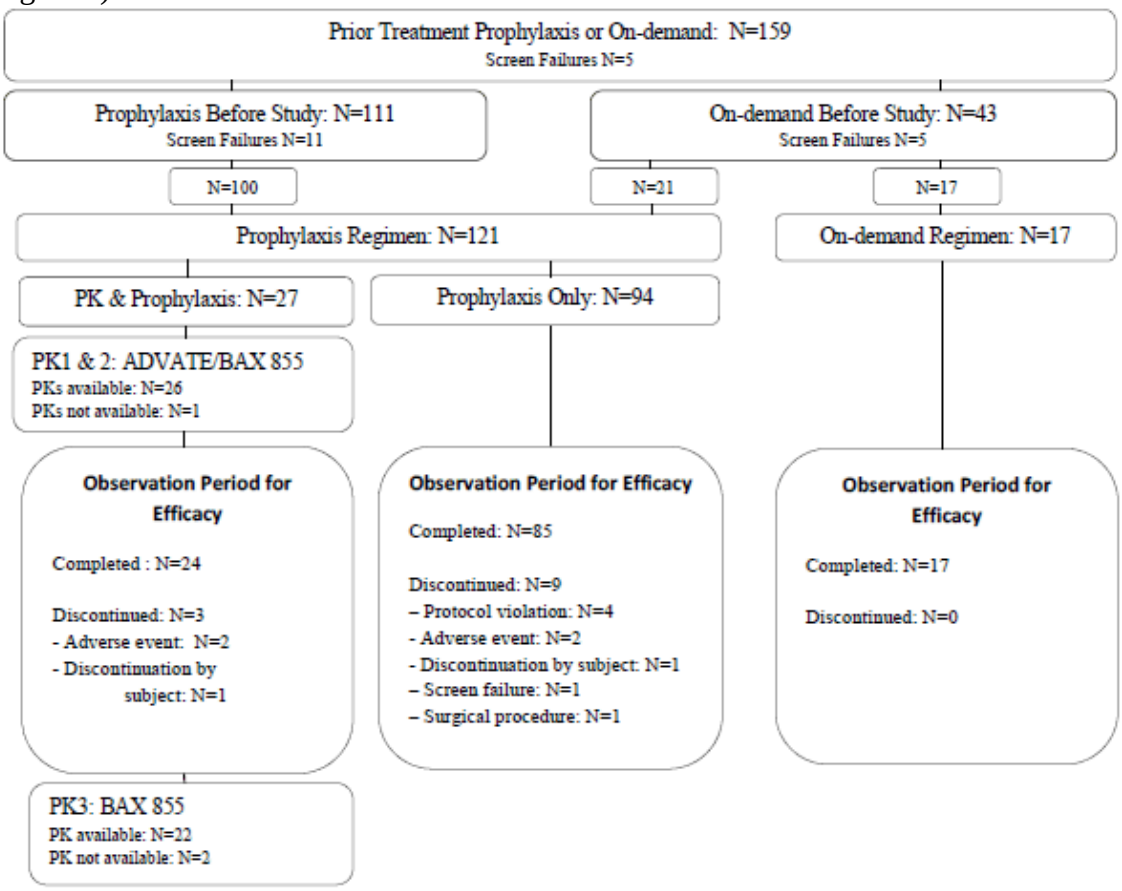
Table 3. Race and Ethnicity of Subjects by Treatment Arm in FAS (Source: full clinical study report 261201 Table 4)

Demographic	**Prophylaxis (N=121)** n(%)	**On-Demand (N=17)** n (%)
Race		
Asian	27(22.3%)	6(35.3%)
Black or African American	1 (0.8%)	0 (0%)
White	93 (76.9%)	11 (64.7%)
Other	0 (0.0%)	0 (0.0%)
Ethnicity		
Hispanic or Latino	6 (5.0%)	0 (0%)
Not Hispanic or Latino	115 (95.0%)	17 (100.0%)

6.1.10.1.3 Subject Disposition

Of the 159 enrolled subjects, 126 subjects completed the study (109 prophylaxis, 17 on-demand). See Figure 1.

Figure 1. Subject decomposition flowchart for FAS (Source: full clinical study report 261201 Figure 1)



6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The estimated ABR ratio of the prophylaxis group to the on-demand group is 0.1 (95% CI: 0.06, 0.19). The upper 95% CI limit is lower than 0.5, which meets the success criteria as it corresponds to a reduction of the mean ABR of at least 50% compared to the on-demand treatment regimen. The estimated mean ABR was 4.3 (95% CI: 3.4, 5.5) for prophylaxis and 43.4 (95% CI: 25.2, 74.8) for on-demand treatment. The estimated mean ABR was calculated based on the generalized linear model with the negative binomial link.

> ***Statistical Reviewer's Comment****: The applicant analyzed the efficacy endpoint based on the SAS population, but reported it as the FAS population analysis. Although the study was not a randomized study, it is pre-specified that the primary efficacy endpoint will be analyzed based on the FAS population. There is only one subject included in the FAS population and not in the SAS population: Subject 483001 was assigned to the prophylactic arm but received only ADVATE during the screening period and did not receive any BAX 855 during the treatment period. The rest of the review is based on the analysis results provided by the applicant based on the SAS population. From a statistical perspective, since the study is not a randomized study and there is only one*

subject excluded from the FAS population, the efficacy analyses based on the SAS population for this study is acceptable. This reviewer defers to the clinical reviewer to decide whether the analyses based on FAS or the SAS should be reported in the package insert.

While the primary analysis was performed with a pre-specified generalized linear model, the applicant also conducted pre-specified sensitivity analyses using alternative model equations which examined the effects of the presence or absence of target joints and age categories. The sensitivity analyses provided results consistent with the primary analysis.
Table 4 provides summary descriptive statistics of ABR by etiology based on the SAS population.

Table 4. Mean (Median) ABR by treatment (SAS) (Source: full clinical study report 261201 Table 23)

Bleeding Episode Etiology	On-Demand Treatment (Median) N=17	Routine Prophylaxis Treatment (Median) N=120
Overall	40.8 (41.5)	4.7 (1.9)
Joint	34.7 (38.1)	2.9 (0.0)
Non-Joint	6.1 (3.7)	1.8 (0.0)
Spontaneous	26.0 (21.6)	2.9 (0.0)
Traumatic	14.9 (9.3)	1.8 (0.0)

One factor that could potentially affect the ABR during the study is the pre-study treatment regimen. Summary statistics on ABRs by treatment regimen used during pre-study and the study period are provided in Table 5. For subjects enrolled in the prophylactic arm, mean ABRs during the study were moderately higher for those treated on-demand before the study than for those treated on prophylaxis before the study; however median ABRs were similar. As expected, ABRs for subjects treated on prophylaxis during the study who were treated on-demand before the study were much lower than ABRs for those treated on-demand during the study who were treated on-demand before the study.

One subject 252006 (an adult) was assigned to the prophylactic arm during the study and treated on-demand before the study; his ABR during the study was higher (52.2) than the reported pre-study value (9). Although this subject was assigned to the prophylactic arm, he used BAX 855 for on-demand treatment of bleeding episodes. However, he was included in the prophylactic arm in the FAS and SAS.

Table 5. Summary of Bleeding Rate by Pre-study Treatment Regimen (Source: full clinical study report 261201 Table 73)

Regimen before study	Regimen during study	Statistic	Units	Bleeding rate During the Study (OPE)
Prophylaxis	Prophylaxis	N	Subjects	99
		Mean (SD)	Bleeds/year	4.5 (7.4)
		Median	Bleeds/year	2.0
		Q1 ; Q3	Bleeds/year	0.0 ; 6.0
		Min ; Max	Bleeds/year	0.0 ; 59.6
On-Demand	Prophylaxis	N	Subjects	21
		Mean (SD)	Bleeds/year	5.7 (13.2)
		Median	Bleeds/year	1.9
		Q1 ; Q3	Bleeds/year	0.0 ; 2.2
		Min ; Max	Bleeds/year	0.0 ; 52.2
	On-Demand	N	Subjects	17
		Mean (SD)	Bleeds/year	40.8 (16.3)
		Median	Bleeds/year	41.5
		Q1 ; Q3	Bleeds/year	31.7 ; 51.1
		Min ; Max	Bleeds/year	12.9 ; 67.9

6.1.11.2 Analyses of Secondary Endpoints

Rate of Success of BAX 855 for the Treatment of Bleeding Episodes (SAS)

The estimated success rate for treatment of bleeding episodes for the 81 subjects in the SAS is 0.96 (95% CI: 0.91, 0.98). The lower limit of the 95% CI is 0.91, which is larger than 70% and therefore meets the success criteria for the key secondary endpoint. Table 6 provides a summary of treatment of bleeding episodes by site of the bleeding episode.

Table 6. Summary Statistics of Treatment of bleeding episodes by site of bleeding episode (Source: full clinical study report 261201 Table 26).

Bleeding Episode Etiology	All	Joint	Non-joint
Number of bleeds treated	591	455	136
Rate of success in treat bleeding episodes*	563(95.3%)	436(95.8%)	127(93.4%)

* One bleed on joint and two bleeds on non-joint were missing the treatment success outcome results. Those missing subjects were included in the calculation of the percentage as failures.

Number of Infusions Used for the Treatment of Bleeding Episodes (SAS)

From all treated subjects in the SAS, 591 bleeding episodes were reported during the OPE, of which 230 were in the prophylactic arm and 361 were in the on-demand arm. Of 120 subjects in the prophylactic arm, 45 (37.5%) reported no bleeding episodes during their treatment period. In contrast, all of the 17 subjects in the on-demand arm reported bleeding episodes during their treatment period. Of 591 bleeding episodes, 272 were minor, 282 were moderate, and 37 were severe. More infusions tended to be used as bleeding episode severity increased. Table 7 summarizes the characteristics of all bleeding episodes treated with BAX855. From the summary statistics, the number of infusions used seems to be comparable between the prophylactic and on-demand arms.

Table 7. Characteristics of All Bleeding Episodes Treated with BAX 855 (SAS) (Source: full clinical study report 261201 Table 28)

Parameter	Category/ Statistics	Units	Prophylaxis N=230 n (%)	On-Demand N=361 n (%)	All N=591 n (%)
	Age Group = All				
# of infusions per bleed	1		187 (81.3)	318 (88.1)	505 (85.4)
	2		31 (13.5)	33 (9.1)	64 (10.8)
	3		9 (3.9)	6 (1.7)	15 (2.5)
	≥4		3 (1.3)	4 (1.1)	7 (1.2)
	Mean (Std)		1.3 (0.7)	1.2 (0.6)	1.2 (0.7)
	Median		1.0	1.0	1.0
	Min ; Max		1 ; 6	1 ; 8	1 ; 8
Hemostatic Efficacy at 24h	Excellent		85 (37.0)	151 (41.8)	236 (39.9)
	Good		129 (56.1)	198 (54.8)	327 (55.3)
	Fair		8 (3.5)	10 (2.8)	18 (3.0)
	None		5 (2.2)	2 (0.6)	7 (1.2)
	Not Reported		3 (1.3)	0 (0.0)	3 (0.5)
Total dose per bleed [IU/kg]	N	Bleeds	230	361	591
	Mean (Std)	IU/kg	43.9 (29.4)	33.3 (26.5)	37.5 (28.1)
	Median	IU/kg	39.6	26.4	30.9
	Q1 ; Q3	IU/kg	24.2 ; 47.9	19.2 ; 40.8	21.2 ; 45.3
	Min ; Max	IU/kg	8.4 ; 257.1	6.8 ; 400.0	6.8 ; 400.0

Time Intervals between Bleeding Episodes (SAS)

In total, 45 of 120 (37.5%) subjects in the prophylactic arm did not report any bleeding episodes. In the on-demand treatment arm, all subjects experienced at least one joint bleeding episode of spontaneous or unknown cause. The interval between bleeding episodes was generally longer for subjects on prophylaxis compared to those treated on-demand (Table 8). All subjects treated on-demand had ≤ 1 month between bleeding episodes, whereas the 70% of subjects treated on prophylaxis had ≥2 months between bleeding episodes. Similar trends were observed for joint and spontaneous/unknown bleeding episodes.

Table 8. Interval Between Bleeding Episodes Episodes Occuring Within OPE By Age Group for SAS (Source: full clinical study report 261201 Table 30)

Bleed Interval[a] Category (Month)	# of prophylaxis subjects (%)	# of on-demand subjects (%)
No bleed	45 (37.5)	0 (0.0)
>6	5 (4.2)	0 (0.0)
6	20 (16.7)	0 (0.0)
5	3 (2.5)	0 (0.0)
4	0 (0.0)	0 (0.0)
3	11 (9.2)	0 (0.0)
2	16 (13.3)	0 (0.0)
≤1	20 (16.7)	17 (100.0)

[a] Interval between Bleeds[Month]= (OPE[days]/# of bleeds)*(12/365.2425)

6.1.11.3 Subgroup Analysis

Age subgroup analysis of ABR: For the adult subgroup, the upper limit of the 95% CI for the ratio of mean prophylaxis ABR to mean on-demand ABR was below 0.5. Therefore, the prophylaxis ABR success criterion was met even though the study was not powered for this subgroup analysis. For the adolescent subgroup, there were only two subjects in the on-demand arm, but the ABR results follow the same trend as for the adults and all subjects. Table 9 provides a summary of the ABR for each age subgroup.

Table 9. ABR by age for SAS (Source: full clinical study report 261201 Table 18, Table 20).

	Statistics[a]	Prophylaxis	On-Demand	Ratio Prophylaxis/On-Demand	One-sided p-value
All Ages	N	120	17	NA	
	Mean (95% CI)	4.3 (3.4 ; 5.5)	43.4 (25.2 ; 74.8)	0.10 (0.06 ; 0.19)	p <0.0001
Subgroup: 12 to <18 Years	N	23	2	NA	
	Mean (95% CI)	5.0 (3.2 ; 7.7)	39.9 (11.5 ; 138.8)	0.17 (0.04 ; 0.68)	p =0.0630
Subgroup: 18 to 65 Years	N	97	15	NA	
	Mean (95% CI)	4.1 (3.1 ; 5.5)	43.9 (23.9 ; 80.8)	0.10 (0.05 ; 0.19)	p <0.0001

[a] Point estimates for the mean with 95% CI from negative binomial regression model
Source: Table 18, Table 20.

Race subgroup analysis of ABR: For the White subgroup, the ratio of prophylaxis to on-demand treatment ABR indicates a reduction in ABR, given a point estimate of 0.07 (95% CI: 0.04; 0.15). For the Asian subgroup, the point estimate of the ratio is 0.22 (95% CI: 0.08; 0.62), indicating a reduction in ABR, although the small sample size in the on-demand arm limits any interpretations. Table 10 provides a summary of the ABR for each race subgroup.

Table 10. ABR by race in SAS (Source: full clinical study report 261201 Table 20).

Subgroup	Statistics[a]	Prophylaxis	On-Demand	Ratio Prophylaxis/On-Demand
Asian	N	27	6	NA
	Mean (95% CI)	6.9 (4.3 ; 11.0)	41.9 (17.6 ; 99.8)	0.22 (0.08 ; 0.62)
White	N	92	11	NA
	Mean (95% CI)	3.4 (2.6 ; 4.5)	44.4 (23.5 ; 83.9)	0.07 (0.04 ; 0.15)

[a] Point estimates for the mean with 95% CI from negative binomial regression model.
Source: Table 20.

Age subgroup analysis of rate of success of BAX855 treatment of bleeding: The point estimates for proportion of bleeding episodes with BAX 855 treatment rated excellent or good for adolescents and adults were:

- 12 to < 18 years subgroup (n = 17): Point estimate 0.97 (95% CI: 0.89; 0.99)
- 18 to 65 years subgroup (n = 64): Point estimate 0.96 (95% CI: 0.90; 0.99)

These proportions compare favorably to the overall success rate of 96%.

Race subgroup analysis of rate of success of BAX855 treatment of bleeding: The summary statistics for proportion of bleeding episodes with BAX855 treatment rated excellent or good were:

- Asian (n=199): Point estimate 0.96 (95% CI: 93.2, 98.7)
- White (n=388): Point estimate 0.96 (95% CI: 93.6, 97.7)
- Black or African American (N=1): Point estimate 1.0

There were three bleeds missing the treatment success outcomes results; those missing bleeds were not included in the calculations.

6.1.11.4 Dropouts and/or Discontinuations

Out of the 121 subjects who were assigned to the prophylactic arm A, a total of 12 subjects discontinued from the prophylactic arm (during the OPE). None of the 17 subjects assigned to the on-demand arm discontinued from the on-demand arm.

Table 11. Reasons for Subjects Discontinued from Study 261201 (Source: full clinical study report 261201 Table 1)

Reasons for Discontinuation	**N**
Subject had adverse event(s)	4
Subject was non-compliant with the requirements of the protocol, in the opinion of the investigator	4
Other reason	2
Discontinuation by subject	1
Subject required a surgical or dental procedure but did not participate in the surgery study or did not resume participation in this study	1
Screen Failure	1[a]
[a]Subject 483001 was assigned to the prophylactic arm (thus was included in the FAS) and received only ADVATE during the screening period.	

Subjects who needed dose adjustment were recorded and the data following dose adjustment was censored for the main efficacy analysis as described in protocol amendment #4. Three subjects in the prophylactic arm reported a dose adjustment. Two subjects met the dose adjustment criterion of multiple spontaneous bleeds in target joints within the period of a month: both subjects (252003 and 422004) were adjusted from 45 IU/kg to 60 IU/kg. ABRs for these subjects before the dose adjustment were 59.6 and 35.7, respectively. ABRs after the dose adjustment were 22.3 and 32.3, respectively. For Subject 361001, the total IU was adjusted due to a weight change but his weight-adjusted dose remained at 45 IU/kg. The censoring of the observations after the dose adjustment provides a more conservative estimate of the ratio of mean ABRs,

6.1.12 Safety Analyses

6.1.12.3 Deaths

There was no death considered to be related to BAX 855. One subject (521001) died of neuroendocrine carcinoma after 22 EDs to BAX 855, approximately 3 weeks after the last dose.

6.1.12.4 Nonfatal Serious Adverse Events (SAEs)

There were a total of 5 SAEs that occurred in 5 of 137 (3.6%) subjects treated with BAX 855, none of which were considered related to IP as assessed by the investigator and the sponsor. Four SAEs were considered severe (osteoarthritis, herpes zoster infection neurological, humerus fracture, and neuroendocrine carcinoma) and one SAE was considered moderate (muscle haemorrhage).

6.1.12.5 Adverse Events of Special Interest (AESI)

None of the subjects developed anti-FVIII inhibitory antibodies; the 95% CI for the proportion of subjects developing inhibitors is (0, 0.038). Nine subjects showed pre-existing antibodies against FVIII (IgG: Subject 511006), against PEG- FVIII (IgG: Subjects 115001, 203001, 251002,

501002, 524003, and 527001 or IgM: Subjects 107001 and 122001) or PEG (IgM: 107001 and 122001) prior to first exposure with BAX 855. Seven subjects who tested as negative at screening developed transient IgG antibodies against FVIII (Subjects 117001, 272003, 421002, and 522001) or PEG-FVIII (Subjects 203003, 300001, and 483003) at one or two consecutive study visits after exposure to BAX 855. Antibodies were transient and not detectable at subsequent visits or at completion of the study.

6.1.12.7 Dropouts and/or Discontinuations

Four subjects discontinued due to an AE; no discontinuations were considered related to BAX 855 treatment by the sponsor.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

No major statistical issues were identified during the review of this BLA. The primary efficacy endpoint was analyzed based on the SAS population instead of the pre-specified FAS population. These populations differed by one subject who was randomized to the prophylaxis arm but did not receive BAX855 (received only ADVATE during the screening period and discontinued the study). Based on the SAS population, the ratio of the mean ABR for the prophylaxis group versus the on-demand group is 0.1 (95% CI: 0.06, 0.19). The estimated success rate for the treatment of bleeding episodes is 0.96 (95% CI: 0.91, 0.98). The study efficacy success criteria for both indications were met. There was no death considered to be related to BAX 855. None of the subjects developed anti-FVIII inhibitory antibodies.

10.2 Conclusions and Recommendations

No major statistical issues were identified during the review of this BLA. Both the primary efficacy endpoint and the key secondary efficacy endpoint meet the efficacy success criteria of the pivotal study reviewed in this memo. None of the subjects developed anti-FVIII inhibitory antibodies. The statistical results from this BLA appear to support the claim for use of BAX 855 in the treatment of Hemophilia A patients for routine prophylaxis to prevent or reduce the frequency of bleeding episodes, and on-demand treatment and control of bleeding episodes.