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Division / Office	CBER/OBE
Committee Chair	Megha Kaushal, MD
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Priority Review	N/A
Reviewer Name(s)	Judy Li, PhD
Review Completion Date / Stamped Date	October 28, 2016
Supervisory Concurrence	Renee Rees, PhD, Team Leader, Therapeutics Evaluation Branch
	Boguang Zhen, PhD, Chief, Therapeutics Evaluation Branch
Applicant	Baxalta US Inc.
Established Name	PEGylated rFVIII
(Proposed) Trade Name	Bax855
Indication(s) and Intended Population(s)	In children, adolescents, and adults with hemophilia A (congenital factor VIII deficiency) for: • On-demand treatment and control of bleeding episodes • Perioperative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes

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GLOSSARY

ABR	Annualized bleeding rate
aPTT	Activated partial thromboplastin time
ASAS	ADVATE safety analysis set
BSAS	BAX 855 safety analysis set
EDs	Exposure Days
ENR	All Subjects Enrolled Set
FAS	Full analysis set
GHEA	Global Hemostatic Efficacy Assessment
HRQoL	Health Related Quality of Life
PPAS	Per Protocol Analysis Set
PTP	Previous Treated Patients
SAE	Serious adverse events

1. EXECUTIVE SUMMARY

BAX 855 (Antihemophilic Factor [Recombinant] Pegylated, rurioctocog alfa pegol) was approved for routine prophylaxis and on-demand treatment of bleeding events in adolescent and adult patients with hemophilia A (congenital factor VIII [FVIII] deficiency) in November 2015. The current submission is an efficacy supplement in support of proposed BAX 855 labeling changes based on the final efficacy, PK, and safety data from the completed pediatric study (261202), and interim efficacy and safety data from the ongoing perioperative study (261204).

The final study results from study 261202 are based on data from 66 pediatric subjects. The median [mean] overall annualized bleeding rate (ABR) was 2.0 [3.61] for the 66 subjects in the treated population and the median [mean] ABRs for spontaneous and joint bleeding episodes were both 0 [1.18 and 1.12, respectively]. Of the 70 bleeding episodes observed during the pediatric study, 82.9% were controlled with 1 infusion and 91.4% were controlled with 1 or 2 infusions. Control of bleeding was rated excellent or good in 63 out of 70 (90%) bleeding episodes. There were no deaths and no subjects developed an inhibitor during the study.

The interim analysis of the ongoing study 261204 is based on the data of 15 surgeries in 15 subjects. There were 11 major and 4 minor surgeries. The perioperative hemostatic efficacy was rated as excellent for all 15 procedures. No deaths and no related serious adverse events occurred.

There is no remaining statistical issue with the supplement and the study results support the proposed labeling changes.

2. CLINICAL AND REGULATORY BACKGROUND

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

BAX 855 (Antihemophilic Factor[Recombinant] Pegylated, rurioctocog alfa pegol) was approved for routine prophylaxis and on-demand treatment of bleeding events in adolescent and adult patients with hemophilia A (congenital factor VIII [FVIII] deficiency) in November 2015. In addition to the proposed labeling changes for BAX 855, the current submission also provides the study results for the deferred pediatric study requirement. The clinical studies for BAX 855 were conducted under IND 15299.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

This supplement application includes the study results for the completed pediatric study 261202, and the interim analysis of the ongoing extension study 261204. The labeling has been revised and updated based on the newly submitted study results in this application. This review will focus on reviewing the study results that have been included in the updated labeling.

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

The submission can be accessed in the CBER EDR (125566/51.0). The materials reviewed in this memo include:

- Module 1.14.1.3: PI20160212 ADYNOVATE Surgery and Pediatric Update Redline Word
- Module 2.5: Clinical Overview 2016Feb12.pdf
- Module 5.3.5.2: 261202-study-report-body-full-2015dec29.pdf
- Module 5.3.5.2: 261204-study-report-interim-2015mar27.pdf
- Module 5.3.5.2: Data files

5.3 Table of Studies/Clinical Trials

Table 1. Studies/Clinical Trials in the Clinical Development Program

Study Number	Short Study Title and Description	Study Status Report (if Available)	Sample Size[a]
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
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
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)
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 Interim CSR 261204	~50 major and minor surgeries or other invasive procedures in ~40 subjects to evaluate ≥ 10 major surgical/ invasive procedures in ≥5 subjects
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 (200 evaluable)

Source: BLA125566/51.0. Table 1 of iss-2016jan26.pdf p13 of 51

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Pediatric Study 261202

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective was to assess the incidence of FVIII inhibitory antibodies
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The secondary objectives were:
1. To evaluate the PK parameters of BAX 855 in pediatric PTPs <12 years of age
2. To monitor incremental recovery (IR) of BAX 855 over time
3. To evaluate hemostatic efficacy of BAX 855 in the management of acute bleeding episodes and for prophylaxis over a period of 6 months
4. To assess all AEs possibly or probably related to BAX 855
5. To evaluate immunogenicity (binding antibodies to FVIII, BAX 855, PEG and Chinese hamster ovary [CHO]) proteins and clinically significant changes in routine laboratory parameters (hematology, clinical chemistry and lipids) and vital signs.

6.1.2 Design Overview

This was a Phase 3, prospective, uncontrolled, multi-center, open-label study to investigate PK, hemostatic efficacy, safety, immunogenicity and Health Related Quality of Life (HRQoL) in pediatric previous treated patients (PTPs) with severe hemophilia A. There were to be 2 age cohorts with the following age ranges: <6 years and 6 to <12 years. Subjects were enrolled to receive twice weekly prophylactic treatment over a period of 6 months or at least 50 exposure days (EDs), whichever occurred last. A subset of subjects (12 evaluable) within each age cohort was to undergo a PK evaluation prior to the start of prophylactic treatment.

The overall duration of the study was approximately 22 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit). The subject participation period was approximately 8 to 10 months from enrolment to subject completion (i.e., last study visit), unless prematurely discontinued, depending on whether or not the subject participated in the PK portion of the study.

6.1.3 Population

The main criteria for inclusion were a diagnosis of severe hemophilia A (FVIII <1%) as determined by the central laboratory, or a historical FVIII level <1% as determined at any local laboratory and/or a FVIII gene mutation consistent with severe hemophilia A. Subjects had to be aged <12 years at the time of screening and, based on each subject's medical records, been previously treated with plasma-derived and/or rFVIII concentrate(s) for a minimum of 150 EDs (subjects aged 6 to 12 years) or a minimum of 50 EDs (subjects aged <6 years).

6.1.4 Study Treatments or Agents Mandated by the Protocol

Prophylaxis treatment: Subjects were to be treated with 50 ±10 IU/kg of BAX 855 administered twice weekly. Based on the Investigator's clinical evaluation, the dose could be increased up to a maximum of 80 IU/kg but not exceeding plasmatic FVIII peak levels of 200% for subjects receiving prophylactic treatment at any time to ensure subject safety was adequately managed.

Treatment of bleeding episodes: BAX 855 was to be used for the treatment of bleeding episodes (i.e., breakthrough bleeding episodes during prophylaxis) as soon as possible after occurrence of the bleeding episode, according to the guidelines specified in the protocol.

6.1.6 Sites and Centers

Fifty-two study sites (17 US, 13 Asian/Pacific, 22 Europe) participated in this study; 39 study sites enrolled subjects and 13 sites were initiated but inactive.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint: The primary outcome measure was the incidence of FVIII inhibitory antibodies (≥0.6 BU using the (b) (4) Bethesda assay).

Secondary endpoints (efficacy):
1. ABR: The ABR was calculated as (Number of bleeding episodes/observed treatment period in days) * 365.2425.
2. Number of infusions and weight-adjusted consumption per month and per year
3. Number of infusions per bleeding episode, overall hemostatic efficacy rating at resolution of bleed (recorded by the subjects or by authorized, qualified personnel at the participating site [Table 2])
4. Weight-adjusted consumption per bleeding episode

Table 2. 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 one 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 one infusion for complete resolution.
None	No improvement or condition worsens.

Source: BLA125566/51.0. Table 3 of 261202-protocol-amend-2-2015mar.pdf p47 of 95

Safety:
1. All AEs and serious adverse events (SAEs) possibly or probably related to BAX 855
2. Clinical significant changes in vital signs (pulse, respiration, supine blood pressure and temperature) and clinical laboratory parameters (hematology, clinical chemistry and lipids)
3. Assessment of binding antibodies to FVIII, BAX 855, PEG and CHO

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size:
There are no formal sample size considerations. The sample size is based on the requirements of the EMA "Guideline on clinical investigation of recombinant and human plasma-derived factor VIII products". A total of 50 subjects <12 years evenly distributed between two age cohorts of <6 years and ≥6 to <12 years are required. To account for a potential drop out, a total of 60 subjects consisting of 30 subjects per age cohort were planned to be enrolled.

Analysis Populations:
The full analysis set (FAS) contained all subjects in the all subjects enrolled (ENR) set who received at least one dose of BAX 855 in either the PK part of the study or prophylaxis part of the study.

The ADVATE safety analysis set (ASAS) contained all subjects in the ENR set who received at least one dose of ADVATE in the PK part of the study.

The BAX 855 safety analysis set (BSAS) contained all subjects in the ENR set who received at least one dose of BAX 855.

The Per Protocol Analysis Set (PPAS) contained all subjects in the FAS who fulfilled the following compliance criteria for prophylactic treatment.

- Infusion interval of 5 or more days did not occur more than 5 times in the Observation Period (refer to Section 13 of the Statistical Analysis Plan Version 1.2, 2015 OCT 15).
- The daily dose was below 40 IU/kg in no more than 10% of the infusions in the Observation Period.
- The daily dose was above 80 IU/kg in no more than 10% of the infusions in the Observation Period.

All efficacy analyses were performed on the FAS. The FAS was the primary analysis set. The supportive analysis was based on the PPAS. The analysis of safety outcome measures was performed on the BSAS. Adverse events were also presented on the ASAS.

Statistical Methods:
All outcome measures descriptive statistics were presented by age stratum. Point estimates (mean or median) and 95% confidence intervals (CIs) were computed. A Clopper-Pearson exact 95% CI was calculated for the number of subjects who developed inhibitory antibodies to FVIII. The ABR was analyzed in a generalized linear model

framework assuming a negative binomial distribution with a logarithmic link function and presence or absence of target joints and age at screening <6 years versus 6 to <12 years as covariates, and the duration of the observation period in years as an offset. Point estimates and 95% CIs were to be estimated based on the model.

Missing Data:
Missing data were in general not to be imputed. In the situation where the event date was partial or missing, the date appeared as partial or missing in the listings. Imputations on dates for AEs and medications were performed. In addition, the duration of observation period in years was included as an offset covariate in the analysis model, which will incorporate the subjects with different amount of follow up time.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The FAS comprised 66 subjects; of these, 65 were included in the PPAS. One subject aged 6 to <12 years (Subject (b) (6)) did not qualify for the PPAS because the subject infused doses below 40 IU/kg for more than 10% of infusions. The BSAS set comprised 66 subjects (32 subjects aged <6 years and 34 subjects aged 6 to <12 years).

6.1.10.1.1 Demographics
Among the 66 subjects in the FAS, one (1.5%) was female (Subject (b) (6)) and all other subjects (98.5%) were male.

The majority of subjects 43/66 (65.2%) were White, 18/32 (56.3%) in the <6 year and 25/34 (73.5%) in the 6 to <12 year age cohort. Seventeen of 66 (25.8%) subjects, 10/32 (31.3%) in the <6 year and 7/34 (20.6%) in the 6 to <12 year age cohort were Asian. Among the Asians, 1 was Japanese, 4 were Chinese, 2 were Indian, and 10 were reported as “other”. Four subjects (4/66; 6.1%) were Black or African American, 2/32 (6.3%) aged <6 years and 2/34 (5.9%) aged 6 to <12 years. In the <6 year age cohort, race was indicated as “other” for one subject and as “multiple” for another. Four of 66 (6.1%) of subjects, 1/32 (3.1%) in the <6 year age cohort and 3/34 (8.8%) in the 6 to <12 year age cohort were of Hispanic or Latino ethnicity.

The mean (SD) age of all subjects was 6.0 (2.70) years. In the <6 years age cohort, the mean (SD) age was 3.7 (1.17) years, in the 6 to <12 years age cohort, the mean (SD) age was 8.1 (1.92) years.

6.1.10.1.3 Subject Disposition
A total of 73 subjects were enrolled in the study, of whom 36 were <6 years and 37 were 6 to <12 years of age. A total of 31 subjects were dosed in the PK part of the study, 14 were <6 years and 17 were 6 to <12 years of age. Sixty-six subjects (32 aged <6 years, and 34 aged 6 to <12 years) were dosed in the prophylactic part of the study. Sixty-four subjects completed the study.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Please see Section 6.1.12.4 for the analysis of the primary endpoint.

6.1.11.2 Analyses of Secondary Endpoints

The mean (±SD) dose per prophylactic infusion was 51.13 (±5.460) IU/kg (median 51.26 IU/kg; range 39.9, 66.8 IU/kg). In subjects <6 years, the average mean (±SD) dose was 51.29 (±4.875) IU/kg (median 51.58 IU/kg; range 42.3, 61.3 IU/kg); in subjects aged 6 to <12 years, the average mean (±SD) dose was 50.99 (±6.029) IU/kg (median 50.42 IU/kg; range 39.9, 66.8 IU/kg). The average mean (±SD) frequency of infusions per week was 1.82 (±0.170) (median 1.87, range 1.0, 2.0).

The median [mean] overall ABR was 2.0 [3.61] for the 66 subjects in the treated population and the median [mean] ABRs for spontaneous and joint bleeding episodes were both 0 [1.18 and 1.12, respectively]. Of the 66 subjects treated prophylactically, 25 (38%) experienced no bleeding episodes, 44 (67%) experienced no spontaneous bleeding episodes, and 48 (73%) experienced no joint bleeding episodes. The point estimate from the model for the overall mean ABR was 3.04 (95% CI 2.208 – 4.186). Point estimates for the mean ABR were lower in the younger age cohort 2.37 (95% CI 1.486 – 3.778) compared to 3.75 (95% CI 2.429 - 5.781) in the older age cohort.

Reviewer Comment: I verified the analysis of the ABR using SAS. The point estimate for the overall mean ABR was 3.054 (95% CI 2.22, 4.28), which is slightly different from the number the applicant reported. Since the difference is minor and does not affect the inference, it is acceptable.

Of the 70 bleeding episodes observed during the pediatric study, 82.9% were controlled with 1 infusion and 91.4% were controlled with 1 or 2 infusions. Control of bleeding was rated excellent or good in 63 out of 70 (90%) bleeding episodes.

6.1.11.3 Subpopulation Analyses

A summary of ABR and interval between bleeding episode by age is provided in Table 3.

Table 3. ABR by age (FAS)

Parameter	Statistic	Statistic Unit	Age < 6 (N = 32)	Age 6 to <12 (N = 34)	Total (N = 66)
Annualized Bleeding Rate	Number of Subjects	n	32	34	66
	Bleeding Rate per Subject	Mean (SD)	2.40 (3.508)	4.76 (9.046)	3.61 (6.988)
		Median	1.95	2.00	2.00
		IQR (Q1, Q3)	3.850 (0.000, 3.850)	5.900 (0.000, 5.900)	3.900 (0.000, 3.900)
		Minimum, Maximum	0, 18.4	0, 49.8	0, 49.8
		Patients Included in Analysis	32	34	66
		Point Estimate for Mean	2.37	3.75	3.04
		95% Confidence Interval for the Mean	[1.486 - 3.778]	[2.429 - 5.781]	[2.208 - 4.186]

Source: BLA125566/51.0. In text Table 5 of 261202-study-report-body-full-2015dec29.pdf. p77 of 1240

Reviewer Comment: I verified the analysis of ABR by age group. The point estimate for mean ABR of age <6 was 2.37 (95% CI 2.22, 4.28), and for age 6 to <12 was 3.78 (95% CI 2.4, 5.95). Again, this is slightly different from the numbers the applicant reported in the table, but the differences are acceptable.

Point estimates for mean ARBs by geographical region were 3.881 (95% CI 2.369 - 6.359) in the US, 2.264 (95% CI 1.511 - 3.392) in Europe and 1.942 (95% CI 0.930 - 4.057) in the Asian/Pacific region. For all geographic regions, point estimates for mean ABR showed higher ABRs for the older than for the younger age cohort: 4.727 (95% CI 2.434 - 9.181) vs. 3.141 (95% CI 1.533 - 6.433) in the US, 2.441 (95% CI 1.378 - 4.325) vs. 2.095 (95% CI 1.164 - 3.774) in Europe, and 2.453 (95% CI 0.829 - 7.257) vs. 1.418 (95% CI 0.490 - 4.109) in the Asian/Pacific region

6.1.11.4 Dropouts and/or Discontinuations

No subject discontinued due to an AE. One subject (Subject (b) (6)) was withdrawn upon the physician's decision22 days after the first administration of BAX 855 due to the development of bleeding and insufficient response to BAX 855. Another subject (Subject (b) (6)) was withdrawn by the applicant 109 days after first administration of BAX 855 because of deviations from the inclusion/exclusioncriteria.

Reviewer Comment: The incomplete observation period for any subject in the study has been taken into consideration by including the duration of the observation period as an offset in the analysis model. There were no special handling of the withdrawn cases which is acceptable. The one subject who withdrew from the study due to insufficient response to BAX855 could potentially cause concerns on the efficacy of the product. However, since it is only one subject, this reviewer defers to the clinical reviewer as to whether it is acceptable.

6.1.12 Safety Analyses

Overall, the mean (SD) number of EDs to BAX 855 was 53.98 (±7.713) (median: 55.00; range: 9.0-65.0).

6.1.12.3 Deaths

There were no deaths.

6.1.12.4 Nonfatal Serious Adverse Events

One (3.1%) subject aged <6 years (Subject (b) (6) had inhibitory antibodies to FVIII with a titer of ≥0.6 BU at screening (-56 days prior to first infusion of BAX 855) which was not confirmed upon re-testing. For 7 subjects (2 subjects aged <6 years and 5 subjects aged 6 to <12 years), the inhibitor titer at screening could not be determined. In 7 of the 64 subjects who completed the study, the FVIII inhibitor titer also could not be determined (3 subjects aged <6 years and 4 subjects aged 6 to <12 years). Of the remaining 57 subjects who completed the study, the proportion of subjects with inhibitory antibody titer was 0 (95% CI: 0.0000 - 0.0627).

A total of 4 SAEs occurred in 3/66 (4.5%) of subjects after treatment with BAX 855, none of which were assessed by the investigator and applicant as related to IP. The SAEs include moderate acute gastritis, severe abdominal pain, moderate febrile neutropenia and moderate pancytopenia.

6.2 TRIAL #2

Study 161204 (reporting period: July 01, 2013 - Jun 30, 2014)

6.2.1 Objectives (Primary, Secondary, etc)

The primary objective is to evaluate the perioperative hemostatic efficacy of BAX 855 in male PTPs with severe hemophilia A (FVIII <1%) undergoing major or minor elective or minor emergency surgical, dental or other invasive procedures.

Secondary objectives include:

- Efficacy : To determine intra- and post-operative blood loss, volume of blood, red blood cells, platelets, and other blood products transfused, the occurrence of bleeding episodes and additional need for surgical intervention, and daily and total weight-adjusted consumption of BAX 855 per subject.

- Safety: To determine the safety of BAX 855 in subjects undergoing surgery, as assessed by occurrence of AEs and changes in vital signs and clinical laboratory parameters.

6.2.2 Design Overview

This is an ongoing Phase 3, prospective, open-label, single-arm, uncontrolled, multicenter study to evaluate the efficacy and safety of BAX 855 in PTPs with severe hemophilia A (FVIII level <1%) who are undergoing approximately major or minor elective or minor

emergency surgical, dental or other invasive procedures. The goal is to evaluate a minimum of 10 major surgical/invasive procedures in at least 5 subjects.

6.2.3 Population

Subjects are eligible if they are actively participating in or have completed participation in another BAX 855 study (pivotal study 261201 from the original BLA, pediatric study 261202 or continuation study 261302) but can also be newly recruited if they meet the entry criteria as outlined in the Study Protocol.

The main criteria for inclusion are a diagnosis of severe hemophilia A (FVIII <1%), previous treatment with FVIII concentrates for ≥150 EDs, male 2-75 years of age, and requires a minor or major elective, or minor emergency surgical, dental or other invasive procedure.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Within 60 minutes before initiating surgery, subjects will receive a loading dose of BAX 855 to raise the pre-infusion plasma level of FVIII to 80-100 % of normal for major and to 30-60 % of normal for minor procedures. The dose and frequency of BAX 855 administered will be individualized based on the subject's PK parameters for major surgeries and the most recent IR value for minor surgeries and the required FVIII target levels. Laboratory assessments of FVIII activity and activated partial thromboplastin time (aPTT) will be carried out following the loading dose. If the FVIII activity results are not available within a reasonable time period prior to the start of surgery, at least the post-infusion value of the aPTT must be obtained. The FVIII activity level following the loading dose must be obtained within 4 hours of infusion of BAX 855 and dose adjustments must be performed as needed. Surgery can only begin if aPTT has normalized. If the aPTT is not normalized or the desired FVIII activity is not attained, a supplemental loading dose(s) of BAX 855 can be given at the discretion of the investigator.

6.2.6 Sites and Centers

Eleven study sites (4 in the US, 6 in Europe and 1 in Asia) have enrolled subjects who are included in this interim analysis.

6.2.8 Endpoints and Criteria for Study Success

The primary outcome measure is the Global Hemostatic Efficacy Assessment (GHEA) score, which is composed of three individual ratings (Tables 4-6):

- Assessment of intraoperative hemostatic efficacy of BAX 855 performed by the operating surgeon (Table 4)

Table 4. Intraoperative Efficacy Assessment Scale

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

Source: BLA125566/51.0. Table 2 of 261204-protocol-amend-5-2014may 21.pdf p26 of 87

- 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 (Table 5)

Table 5. Postoperative Efficacy Assessment Scale (Postoperative Day 1)

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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

Source: BLA125566/51.0. Table 3 of 261204-protocol-amend-5-2014may 21.pdf p27 of 87

- Assessment of perioperative hemostatic efficacy of BAX 855 performed by the investigator at discharge or on postoperative Day 14 (whichever is first) (Table 6)

Table 6. Perioperative Efficacy Assessment Scale (Discharge Visit or Day 14, whichever is first)

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

Source: BLA125566/51.0. Table 4 of 261204-protocol-amend-5-2014may 21.pdf p27 of 87

The scores of each of the three individual ratings described above, are added together to form a GHEA score (Table 7). For a GHEA score of 7 to be rated "excellent" no individual assessment score is less than 2 (i.e., one individual assessment score must be 3 and the other two individual assessment scores must be 2). The only other option to achieve a GHEA score of 7 is for two individual assessment scores of 3 and one individual assessment score of 1. Although this GHEA score will not qualify for a rating of "excellent," the GHEA score will satisfy the definition of "good," (with no individual assessment score less than 1).

Table 7. Global Hemostatic Efficacy Assessment

Assessment	GHEA Score
Excellent	7 to 9 (with no category scored < 2)
Good	5 to 7 (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)

Source: BLA125566/51.0. Table 1 of 261204-protocol-amend-5-2014may 21.pdf p26 of 87

Secondary efficacy endpoints included:

- Intra- and postoperative blood loss

- Transfusion requirements
- Bleeding episodes
- Consumption of BAX 855

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample size:
The sample size determination is not based on statistical considerations. Approximately 50 major and minor surgeries or other invasive procedures in approximately 40 subjects are needed to meet the minimum of 10 evaluable major surgical/invasive procedures in at least 5 subjects.

Analyses populations:
The full analysis set (FAS) will comprise all subjects with at least one available hemostatic assessment.

The per-protocol analysis set (PP) will comprise all subjects with available perioperative hemostatic efficacy assessed by:

i) the operating surgeon within 60 minutes post-surgery,
ii) postoperative hemostatic control assessed by the operating surgeon postoperatively at 24 hours and
iii) perioperative hemostatic control assessed by the investigator at Day 14 or discharge, whichever is first.

Only subjects who met all study entry criteria and who had no major protocol violations that might impact hemostatic efficacy assessments will be included in the PP analysis set.

The safety analysis set (SAS) will comprise all subjects who received any amount of BAX 855.

The primary efficacy analysis and all secondary efficacy analyses are based on the FAS.

Statistical Analysis:
Descriptive statistics were provided.

6.2.10. Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Of the 21 subjects enrolled (19 unique subjects since two subjects were enrolled twice), 17 (16 unique) subjects were exposed to IP and 15 completed the protocol following treatment with BAX 855 for surgery. Each subject underwent one procedure. All 15 subjects who underwent surgery completed the protocol and are included in the FAS. Two subjects were withdrawn from the study due to AEs and did not undergo surgery; a total of 17 (16 unique) subjects are included in the SAS.

6.2.10.1.1 Demographics

All subjects were male and between 19 and 52 years of age (mean ± SD: 35.6 ±12.63 years) at the time of enrollment. All subjects except one had severe hemophilia A (FVIII <1%) as confirmed by the central laboratory at screening. The majority of subjects (16/17, 94.1%) were white, and one subject was Asian.

6.2.10.1.3 Subject Disposition

See Section 10.2.10.1

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

Eleven major surgical procedures (3 knee replacements, 2 arthroscopic synovectomies, 1 cyst extirpation, 1 port placement, 1 gastric band placement, and 3 multiple tooth extractions including 1 radicular cyst removal) and 4 additional minor surgeries (1 synoviorthesis, 1 radiosynovectomy, 1 tooth extraction, 1 dermatological surgery) were performed in 15 subjects. The pre-operative loading dose ranged from 36 IU/kg to 99 IU/kg (median: 65 IU/kg) and the total post-operative dose ranged from 177 IU/kg to 769 IU/kg (median: 305 IU/kg). The median total dose for major surgeries was 362 IU/kg (range: 237-863 IU/kg) and the median total dose for minor surgeries was 97 IU/kg (range: 73-119 IU/kg).

Perioperative hemostatic efficacy was rated as excellent for all 15 (11 major, 4 minor) procedures. The median (IQR) observed intra-operative blood loss (n=10) was 10.0 (Q1: 5.0, Q3: 50.0) mL compared to the predicted average blood loss (n=11) of 50.0 (Q1: 6.0, Q3: 150.0) mL for major surgeries.

6.2.11.4 Dropouts and/or Discontinuations

Two subjects (b) (6) , with unique subject ID (b) (6) were withdrawn from the study after the PK infusion due to AEs which were unrelated to the investigational product (diabetes-induced gastroparesis and worsening of gastroparesis). They did not undergo surgery.

6.2.12 Safety Analyses

Overall, there have been 192 EDs in the SAS.

6.2.12.3 Deaths

None of the subjects analyzed in this interim analysis died during the study.

6.2.12.4 Nonfatal Serious Adverse Events

Four severe SAEs that were considered unrelated to IP occurred in one unique subject (unique subject ID (b) (6) . This subject was enrolled twice (subject IDs (b) (6) and (b) (6) and did not undergo surgery but was withdrawn from the study after PK assessment; two SAEs were reported for Subject ID (b) (6)

(b) (6) (esophageal ulcer, diabetic gastroparesis) and two SAEs were reported for Subject ID (b) (6) (two diabetic gastroparesis).

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This efficacy supplement was submitted to support proposed labeling changes for BAX 855. The study results from study 261202 are based on data from 66 pediatric subjects. The median [mean] overall ABR was 2.0 [3.61] for the 66 subjects in the treated population and the median [mean] ABRs for spontaneous and joint bleeding episodes were both 0 [1.18 and 1.12, respectively]. Of the 70 bleeding episodes observed during the pediatric study, 82.9% were controlled with 1 infusion and 91.4% were controlled with 1 or 2 infusions. Control of bleeding was rated excellent or good in 63 out of 70 (90%) bleeding episodes. There were no deaths and no subjects developed an inhibitor during the study.

The interim analysis of the ongoing perioperative study 261204 is based on the data of 15 surgeries in 15 subjects. There were 11 major and 4 minor surgeries. The perioperative hemostatic efficacy was rated as excellent for all 15 procedures. No deaths and no related serious adverse events occurred.

10.2 Conclusions and Recommendations

The applicant submitted the final efficacy and safety results from the completed pediatric study 261202 and interim results from the ongoing surgical study 261204 for BAX 855. There is no statistical issue with the information submitted in the supplement, and the study results support the proposed pediatric labeling changes for routine prophylaxis for the control of bleeding episodes, as well as the perioperative management of bleeding labeling changes.