Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION
BLA (MID CYCLE)

BLA Supplement Number: STN 125446

Product Name: —b(4)-------

Indication(s):   Coagulation Factor IX (Recombinant)

Applicant: Baxter

Date(s):   August 30, 2012

Review Priority: Standard

Statistical Branch: Therapeutics Evaluation Branch (TEB)

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1.   EXECUTIVE SUMMARY

This submission supports the initial Biologics License Application of –b(4)---- (BAX326), which is a coagulation factor IX (recombinant) drug product (rFIX) intended for use in the control and prevention of bleeding episodes; as routine prophylaxis; and for perioperative management in patients –b(4)----- of age) with hemophilia B (congenital factor IX [FIX] deficiency).

1.1 Conclusions and Recommendations

-b(4)--- is a purified protein produced by a genetically engineered Chinese hamster ovary (CHO) cell line that is extensively characterized.

1.2 Brief Overview of Clinical Studies

This submission includes both the efficacy analyses and the safety analyses of study 250901.

The clinical development program for BAX326 comprises four studies designed to investigate the hemostatic efficacy in previously treated patients (PTPs) with severe (FIX level <1%) or moderately severe (FIX level 1-2%) hemophilia B. Pivotal Study 250901 was ongoing at the time of analysis but is now operationally complete, and three ongoing clinical studies: Pediatric Study 251101, Continuation Study 251001 and Surgery Study 251002.

1.3 Major Statistical Issues and Findings

The hemostatic efficacy analyses are discussed in this memo. The data shows that the annualized bleeding rate (ABR) of prophylactic group is significantly lower than ABR of historical control group, but the ABR of on-demand group is significantly higher than the ABR of historical control group. Note that the historical control group consists of only on-demand subjects. Statistical analyses can not support the efficacy of the proposed product completely. The sponsor is expected to justify the hemostatic efficacy analysis in the on-demand cohort, comparing with the historical control group.

2.   INTRODUCTION

2.1 Overview

-b(4)--- is a purified protein produced by recombinant DNA technology. It is not derived from human blood or plasma products, and its manufacture does not include animal or human components. –b(4)------ contains no preservatives.

Hemophilia B is an X-linked recessive, congenital bleeding disorder caused by deficient or defective coagulation FIX, a vitamin-K-dependent coagulation factor that belongs to the class of serine proteases. The plasma levels of FIX determine the severity of the disease; severe hemophilia B is associated with lower levels of FIX than mild or moderate hemophilia B. –b(4)--- temporarily replaces the missing clotting FIX that is needed for effective hemostasis.

The clinical development program for BAX326 comprises four studies designed to investigate the hemostatic efficacy in previously treated patients (PTPs) with severe (FIX level <1%) or moderately severe (FIX level 1-2%) hemophilia B. Pivotal Study 250901 was ongoing at the time of analysis but is now operationally complete, and three ongoing clinical studies: Pediatric Study 251101, Continuation Study 251001 and Surgery Study 251002. The sponsor presents the hemostatic efficacy data of pivotal study 250901 in this submission to support the licensure. The sponsor submitted the interim efficacy analysis of Study 250901 (dated 6/8/2012) in the original submission, after 56 subjects had completed at least 3 months of prophylactic treatment during the study. In December 2012 the sponsor submitted the complete study report of Study 250901 (dated 9/11/2012). This statistical memo covers both the interim study report and the complete study report.

2.2 Data Sources

The sponsor submitted its batch-analyses in pdf files as an eCTD submission located in the FDA's Electronic Document Room (EDR) at the following link:
----b(4)--

3.   STATISTICAL EVALUATION

The clinical development program for BAX326 comprises four studies designed to investigate the hemostatic efficacy in previously treated patients (PTPs) with severe (FIX level <1%) or moderately severe (FIX level 1-2%) hemophilia B:
- Pivotal phase 1/3 study 250901 (operationally complete)
- Phase 2/3 pediatric study 251101 (ongoing)
- Phase 3 continuation study 251001 (ongoing)
- Phase 3 surgery study 251002 (ongoing)

The safety of BAX326 is also under evaluation in the above four clinical studies.

Pivotal Study 250901 was a phase 1/3 prospective, controlled and uncontrolled, multicenter study evaluating pharmacokinetics (PK), efficacy, safety, and immunogenicity in PTPs with severe or moderately severe hemophilia B.

Pediatric Study 251101 is an ongoing phase 2/3 prospective, uncontrolled, multicenter study evaluating pharmacokinetics, efficacy, safety, and immunogenicity in previously treated pediatric patients with severe or moderately severe hemophilia B. The study population is divided into two age cohorts of 12 subjects each: < 6 years and 6 to < 12 years.

Continuation Study 251001 is an ongoing, prospective, open-label, multicenter, uncontrolled, phase 3 study to further investigate incremental recovery over time, hemostatic efficacy, safety, immunogenicity and health-related quality of life during BAX326 treatment in up to 100 PTPs with severe or moderately severe hemophilia B who completed pivotal study 250901 or pediatric study 251101.

Surgery Study 251002 is an ongoing, phase 3, prospective, open-label, uncontrolled, multicenter study designed to evaluate the hemostatic efficacy and safety of BAX326 in approximately 30 subjects with severe or moderately severe hemophilia B undergoing major and minor surgical, dental or other invasive procedures.

This initial licensing application is based primarily on the safety (N=73), PK (N=28) and efficacy (N=59 prophylaxis) data generated from pivotal study 250901.

3.1 Evaluation of Efficacy

Pivotal Study 250901 was conducted in Europe (Bulgaria, Czech Republic, Germany, Poland, Romania, Spain, Sweden, UK, Ukraine), Russia, South America (Argentina, Brazil, Chile, Colombia) and Japan. The study protocol, informed consent form, and all amendments were reviewed and approved by the Independent Ethics Committee (IEC) of each participating institution prior to the initiation of the study at that institution. The study was conducted in accordance with the Study Protocol, the International Conference on Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements.

Study Design and Endpoints

Study Design

This phase 1/3 study was designed as a prospective, multicenter study in PTPs to evaluate the PK parameters, safety, immunogenicity, hemostatic efficacy, and changes in health-related quality of life (HR QoL) of BAX326 in a total of 75-80 PTPs with severe or moderately severe hemophilia B. The study is divided into three parts:

Part 1 was a randomized, blinded, controlled, crossover study to compare the PK parameters of BAX326 with BeneFIX. Thrombotic markers were also to be determined at specified time points. Part 1 has been completed.

Part 2 was an open-label, uncontrolled evaluation of the hemostatic efficacy, safety, and HR QoL of BAX326 in those subjects receiving BAX326 for prevention and treatment of bleeding episodes (BEs) as described in the following objectives:
• To monitor incremental recovery (IR) of BAX326 over time

- To evaluate the hemostatic efficacy of BAX326 in the management and prevention of acute BEs for a period of 6 months
- To evaluate safety in terms of BAX326-related AEs, as well as clinically significant changes in routine laboratory parameters (hematology/clinical chemistry) and vital signs
- To evaluate immunogenicity following a minimum of 50 exposure days (EDs) to BAX326
- To evaluate changes in HR QoL and health resource use

Part 3 was an open-label, uncontrolled repeat evaluation of the PK parameters of BAX326 after 26 ± 1 weeks of treatment in Part 2 in subjects who participated in Part 1. The objective of Part 3 was to re-evaluate the PK parameters for BAX326 after a period of 6 months of treatment. Thrombotic markers were also to be determined at specified time points.

In Part 1, randomized subjects received 2 infusions each, 1 infusion with BAX326 and 1 infusion with BeneFIX, at a dose of 75 ± 5 IU/kg, each in a randomized order. The dose to be administered was calculated as 75 (IU) multiplied by patient body weight (kg).

In Part 2, all subjects were to receive exclusively BAX326. Subjects received either a prophylactic or on-demand treatment as decided by the investigator and the subject. Subjects in the prophylactic cohort were to be treated with a prophylactic regimen of 50 IU/kg BAX326 twice weekly for a period of 6 months or for at least 50 EDs, whichever occurred last. Subjects in the on-demand cohort were to receive BAX326 for on-demand treatment until the last subject of the prophylactic cohort had completed the study.

Subjects and investigators were only blinded in the crossover PK assessment in Part 1 of the study; Parts 2 and 3 of the study were uncontrolled and open label. After the eligibility of the subject had been confirmed, the investigator requested patient randomization via the Interactive Voice Response System (IVRS) for those subjects participating in Part 1. The subject randomization number was assigned based on the master randomization list (MRL). In this study, all 27 subjects who had participated in Part 1 were planned to enter Part 3 after 26 ± 1 weeks of treatment in Part 2 with a minimum of 30 EDs to BAX326. Subjects participating in Part 3 were to be infused with a single dose of 75 ± 5 IU/kg of BAX326. A minimum wash-out period of 5 days, preferably 7 days, was required between the last infusion in Part 2 of the study and the infusion for the repeat PK study, and the subject had to be in a non-bleeding state.

Study Endpoints

The efficacy measurements in this study included the assessment of appropriate PK data and assessment of clinical efficacy of FIX treatment (prophylaxis and management of acute bleeds) by the subjects themselves and treating physicians.

The primary PK endpoint (used as the basis for the sample size calculation for Parts 1 and

3) is the area under the plasma concentration versus time curve from 0 to 72 hours (AUC0-72 h /dose). Secondary PK endpoints include: total AUC/dose, mean residence time (MRT), clearance (CL), IR, elimination phase half-life (T1/2), and volume of distribution at steady state (Vss). IR over time will also be assessed.

The clinical efficacy of FIX treatment was defined as hemostatic efficacy. Hemostatic endpoints for treatment of bleeding episodes include the number of infusions per bleeding episode and the overall hemostatic efficacy rating at resolution of bleed. The primary hemostatic efficacy endpoint is annualized bleeding rate (ABR). The number of bleeding episodes beginning within 24 and 48 hours of an infusion (as exploratory endpoint) was also studied.

Safety was mainly assessed in terms of adverse events (AEs), immunogenicity, viral safety and thrombotic markers.

Population Analysis

The Full Analysis Set (FAS) were comprised of all subjects who received at least 1 infusion during the study. There were 73 subjects in FAS, with 59 subjects in the prophylactic cohort and 14 subjects in the on-demand cohort. Three subjects in FAS received prophylactic treatment but not for 3 months (subjects –b(6)--------------).
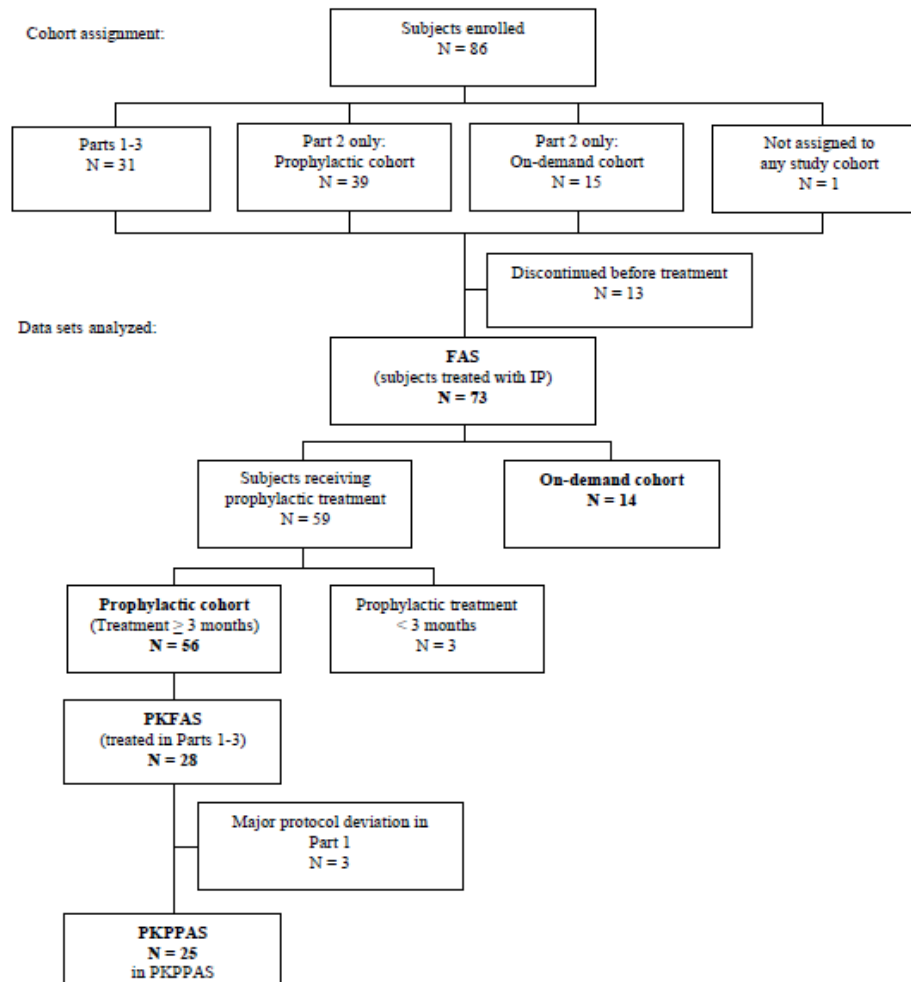
The Pharmacokinetic Full Analysis Set (PKFAS) were comprised of all subjects who were randomized and received at least 1 PK infusion and who provided acceptable data for PK analysis in Part 1. There were 28 subjects in PKFAS, with 3 subjects who had a major protocol deviation in Part 1 (subjects –b(6)----------------------------).

The Pharmacokinetic Per Protocol Analysis Set (PKPPAS) was comprised of all randomized and treated (received both of the assigned infusions) subjects who had no major violation affecting the PK period of the study. There are 25 subjects in PKPPAS.

The historical control group includes 12 studies published from 1976 to 2011 with a total of 276 hemophilia B patients treated on-demand for an average of 19.6 months in the meta-analysis. Three studies were pediatric studies in children less than 5 years of age and 9 studies included older patients.

Figure 1 is the flow chart accounting for all the subjects in this study.

Figure 1: Subject Disposition for Study 250901

Cohort assignment:

Subjects enrolled
N = 86

Parts 1-3
N = 31

Part 2 only:
Prophylactic cohort
N = 39

Part 2 only:
On-demand cohort
N = 15

Not assigned to
any study cohort
N = 1

Discontinued before treatment
N = 13

Data sets analyzed:

FAS
(subjects treated with IP)
N = 73

Subjects receiving
prophylactic treatment
N = 59

On-demand cohort
N = 14

Prophylactic cohort
(Treatment ≥ 3 months)
N = 56

Prophylactic treatment
< 3 months
N = 3

PKFAS
(treated in Parts 1-3)
N = 28

Major protocol deviation in
Part 1
N = 3

PKPPAS
N = 25
in PKPPAS

Patient Disposition, Demographic and Baseline Characteristics

A total of 86 subjects were enrolled in this study as of data cut-off on 3/27/2012. Among the 86 subjects, 31 were enrolled for participation in Parts 1-3, 39 in the prophylactic cohort of Part 2 only and 15 in the on-demand cohort of Part 2 only. There was one subject who was not assigned to any study cohort. Among 73 subjects who received BAX326, 28 were treated in Parts 1-3, and 31 were treated in the prophylactic cohort and 14 in the on-demand cohort of Part 2. Among the 31 subjects who were enrolled for Parts 1-3 and randomized to receive one of 2 PK infusion sequences in Part 1, 28 subjects completed Part 1 and 25 completed Part 1 without any major protocol deviation in Part 1.

All subjects were male (Table 1). The median age of all 73 subjects in the FAS was 33 years (range 12-59 years); there were three pediatric subjects aged 12, 13, and 15 years. Most subjects were white (83.6%); the rest were Asian (6.8%), Latin American/Mestizo (6.8%), Black or African American (1.4%) and Arabic (1.4%). The majority of subjects (87.7%) had arthropathy at screening; 1-2 target joints were present in 41.1% of subjects; 12.3% of subjects had 3-4 target joints and a further 12.3% of subjects had > 4 target

joints. Only 13 (17.8%) of subjects had received prophylactic treatment prior to enrollment, whereas 27 (37%) had received on-demand treatment only and the remainder (45.2%) both.

Table 1: Demographic and Baseline Characteristics for FAS

Parameter	Category	PKPPAS N = 25 n (%)	PKFAS N = 28 n (%)	All N = 73 n (%)	Prophylaxis[a] N = 56 n (%)	On-Demand N = 14 n (%)
Gender	Male	25 (100.0)	28 (100.0)	73 (100.0)	56 (100.0)	14 (100.0)
	Female	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age	12 - 16 yrs	1 (4.0)	1 (3.6)	3 (4.1)	2 (3.6)	1 (7.1)
	≥16 yrs	24 (96.0)	27 (96.4)	70 (95.9)	54 (96.4)	13 (92.9)
Race	White	19 (76.0)	21 (75.0)	61 (83.6)	47 (83.9)	14 (100.0)
	Black or African American	1 (4.0)	1 (3.6)	1 (1.4)	1 (1.8)	0 (0.0)
	Asian	1 (4.0)	2 (7.1)	5 (6.8)	4 (7.1)	0 (0.0)
	Native Latin American	3 (12.0)	3 (10.7)	3 (4.1)	3 (5.4)	0 (0.0)
	Mestizo	1 (4.0)	1 (3.6)	2 (2.7)	1 (1.8)	0 (0.0)
	Arabic	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)
Ethnicity	Not Reported	25 (100.0)	28 (100.0)	73 (100.0)	56 (100.0)	14 (100.0)
Gene Mutation	Missense	13 (52.0)	14 (50.0)	33 (45.2)	25 (44.6)	7 (50.0)
	Nonsense	5 (20.0)	5 (17.9)	14 (19.2)	11 (19.6)	2 (14.3)
	Splice Site	3 (12.0)	4 (14.3)	5 (6.8)	5 (8.9)	0 (0.0)
	Deletion	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (7.1)
	Frameshift	1 (4.0)	1 (3.6)	1 (1.4)	1 (1.8)	0 (0.0)
	No Mutation	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (7.1)
	Not Reported	3 (12.0)	4 (14.3)	18 (24.7)	14 (25.0)	3 (21.4)
FIX Activity Level [%]	<1%	12 (48.0)	14 (50.0)	39 (53.4)	29 (51.8)	10 (71.4)
	1% - 2%	13 (52.0)	14 (50.0)	34 (46.6)	27 (48.2)	4 (28.6)
FIX Antigen Level [%]	<1%	6 (24.0)	7 (25.0)	22 (30.1)	18 (32.1)	4 (28.6)
	≥1%	19 (76.0)	21 (75.0)	51 (69.9)	38 (67.9)	10 (71.4)
	1% - 2%	4 (16.0)	4 (14.3)	11 (15.1)	9 (16.1)	0 (0.0)
	<2% - 5%	3 (12.0)	3 (10.7)	4 (5.5)	4 (7.1)	0 (0.0)
	<5% - <40%	4 (16.0)	4 (14.3)	14 (19.2)	10 (17.9)	3 (21.4)
	≥40%	8 (32.0)	10 (35.7)	22 (30.1)	15 (26.8)	7 (50.0)
Arthropathy at Screening	Yes	25 (100.0)	27 (96.4)	64 (87.7)	48 (85.7)	14 (100.0)
	No	0 (0.0)	1 (3.6)	9 (12.3)	8 (14.3)	0 (0.0)
Prior Treatment	On-Demand	6 (24.0)	7 (25.0)	27 (37.0)	14 (25.0)	13 (92.9)
	Prophylaxis	3 (12.0)	3 (10.7)	13 (17.8)	11 (19.6)	0 (0.0)

	Both	16 (64.0)	18 (64.3)	33 (45.2)	31 (55.4)	1 (7.1)
Number of Target Joints at Screening	0	6 (24.0)	6 (21.4)	25 (34.2)	21 (37.5)	3 (21.4)
	1 - 2	9 (36.0)	11 (39.3)	30 (41.1)	23 (41.1)	6 (42.9)
	3 - 4	4 (16.0)	5 (17.9)	9 (12.3)	6 (10.7)	3 (21.4)
	>4	6 (24.0)	6 (21.4)	9 (12.3)	6 (10.7)	2 (14.3)
BAX326 Exposure Days ≥50[b]	Yes	NA	NA	52 (71.2)	52 (92.9)	0 (0.0)
	No	NA	NA	21 (28.8)	4 (7.1)	14 (100.0)

Statistical Methodologies

For PK endpoints, the area under the curves (AUC) were calculated and compared. Descriptive statistics were computed for most PK endpoints such as mean residence time and the elimination phase half-life. To assess the PK equivalence of the BAX 326 and BeneFix, the 90% confidence interval for the difference of the mean natural logarithms of AUC_{0-72h} /dose between the two groups was calculated. To establish the equivalence in AUC_{0-72h} / dose with a type I error of 5%, the calculated two-sided 90% confidence interval for the ratio has to be contained completely in the margins of equivalence defined as 80% to 125%. Least squares geometric means, ratio of geometric means, and its 90% confidence interval was reported.

For the hemostatic efficacy endpoints, the ABR during prophylaxis and on-demand treatment in Part 2 were computed. A meta-analytic approach was used in the historical control to summarize the (annualized) bleed rates in hemophilia B subjects treated with on-demand infusions. The SAP specified that the ABR would be compared between the prophylactic cohort and the historical control with a one-sided z-test at 2.5% significance level. The same hypothesis testing procedure was also conducted between the on-demand cohort and the historical control as a supportive analysis. Descriptive statistics were applied on the remaining hemostatic efficacy endpoints, such as the number of bleeding episodes beginning within 24 and 48 hours of prophylactic infusion.

Results and Conclusions

The analysis of PK endpoints will be covered in the PK review memo. In this statistical memo the hemostatic efficacy analysis is discussed.

The analysis for the hemostatic efficacy endpoints is based on data cut-off on 3/27/2012, after 56 subjects had completed this study with ≥ 50 EDs.

The ABR was analyzed during prophylaxis and on-demand treatment in Part 2. Of 59 subjects who received prophylactic treatment (including 3 subjects who received prophylactic treatment for less than 3 months), 96.73% (± 11.19) of subjects were in compliance with the determined dose (prophylactic infusion dose is 40 – 75 IU/kg), and 89.12% (± 9.74) were compliant with the planned frequency of dosing (i.e., any prior infusion is within 3.5 ± 1 days of the prophylactic infusion). The median treatment

duration was 5.995 months (range: 4.73 to 9.13 months) in the prophylactic cohort with > 3 months of treatment (n=56) and 3.35 months (range: 1.18 to 4.86 months) in the on-demand cohort (n=14). The median dose per prophylactic infusion was 50.49 IU/kg in all 59 subjects on prophylaxis, and was 50.475 IU/kg in the prophylactic cohort with at least 3 months of prophylactic treatment (n=56). Fifty two of the 56 (92.9%) subjects had 50 or more EDs to BAX326 during the study.

Twenty-six of 59 (44.1%) subjects experienced no bleeds. In the prophylactic cohort (n=56), 24 (42.9%) subjects experienced no bleeds. Twenty-two of these (91.7%) had at least 50 EDs to BAX326.

The mean ABR in the prophylactic cohort (n=56) was 4.20 (± 5.75) (median: 1.99). The mean rate of joint bleeds was 2.79 (± 4.16) compared with 1.41 (± 2.87) non-joint bleeds. The rate of spontaneous bleeds (mean: 1.70 ± 3.22) was comparable to the rate of bleeds caused by injury (mean: 1.70 ± 2.80).

Among the 14 subjects in the on-demand cohort of the FAS, all of whom had bleeds, the mean ABR was 35.19 (± 19.22) (median: 26.77). The mean rate of joint bleeds was 31.04 (± 17.52) versus 4.14 (± 5.38) non-joint bleeds. The rate of spontaneous bleeds was higher (mean: 20.72 ± 14.38) than the rate of bleeds caused by injury (mean: 10.92 ± 14.06).

These results show that ABRs were lower in subjects who received prophylactic treatment than in subjects who received on-demand treatment (Table 2). However, a statistical comparison between the prophylactic and the on-demand cohort was not performed due to the substantial baseline differences between the two study populations.

For the historical control group, ABR varied from 7.2 to 33.4 bleeds per patient-year with significant heterogeneity (I_2=91.8%, p <0.001, according to the historical record). Therefore the individual study bleeding rates were combined under a random effects model. The pooled mean ABR was 20.0 bleeds per patient-year with a two-sided 95% confidence interval of 15.3 to 24.6 bleeds per patient-year.

Table 2: Comparison of ABR for Prophylactic, On-Demand, and Historical Control Groups

	Mean	Standard deviation	95% CI
Prophylactic (n=56)	4.20	5.75	2.66, 5.74
On-Demand (n=14)	35.19	19.22	24.09, 46.28
Historical control (n=276)	20.0	39.4	15.3, 24.6

Table 3 reports this reviewer's p-value calculations. The p-values of the two-sided z-tests are the same as that provided by the sponsor in the interim analysis report dated 6/8/2012. According to the p-value of the two-sided z-test, both ABR of prophylactic cohort and ABR of on-demand cohort are significantly different from ABR of the historical control

group. It is confirmed by this reviewer that the ABR of prophylactic group is significantly lower than ABR of historical control group (p < 0.0001). However, the ABR of on-demand group is significantly higher than the ABR of historical control group (p = 0.0036) when compared to the pre-specified one-sided Type I error rate of 0.025.

Table 3: P-values of the z-test

	z-value	2-sided p-value	1-sided p-value (left)	1-sided p-value (right)
Prophylactic vs. Historical Control	-6.3378	<0.0001	<0.0001	>0.9999
On-demand vs. Historical Control	2.6848	0.0073	0.9964	0.0036

3.2 Evaluation of Safety

The safety analysis of Pivotal Study 250901 was performed on FAS. Descriptive statistics were provided for the following safety endpoints: occurrence of inhibitory and (treatment related) total binding antibodies to FIX, occurrence of (treatment related) antibodies to CHO proteins and rFurin, occurrence of severe allergic reactions (e.g. anaphylaxis), and occurrence of thrombotic events.

Similar to that of efficacy analysis, the safety analyses are based on data cut-off on 3/27/2012, after 50 subjects had completed Part 2 and had been evaluated for hemostatic efficacy, safety, and immunogenicity for a period of at least 50 EDs to BAX326. Database snapshot occurred on 5/11/2012, after cleaning of the data up to the data cut-off.

No thrombotic events occurred. No deaths and no serious adverse reactions or severe allergic reactions occurred during or after treatment as of snapshot date 5/11/2012. A total of 87 AEs occurred in 36 of the 73 (49.3%) subjects throughout the study (Parts 1-3). There were no treatment-related AEs within 24 hours after infusion with BAX326 or BeneFIX during Part 1 (n=28); non-serious related AEs (mild) were reported for 2 out of 73 (2.7%) subjects after infusion with BAX326 across all study parts.

The sponsor claimed that BAX326 is safe and well tolerated in the FAS.

3.3 Gender, Race, Age and Other Special/Subgroup Populations

The sponsor provided subgroup analysis of ABR by bleeding site and cause (Table 4).

Table 4: ABR by bleeding sites and cause on FAS

| | | Site | | Cause | | | All |
Treatment	Statistic	Joint[a]	Non-Joint[b]	Spontaneous	Injury	Unknown	
Prophylaxis[c]	N	56	56	56	56	56	56
	Mean (Std)	2.79 (4.16)	1.41 (2.87)	1.70 (3.22)	1.70 (2.80)	0.80 (2.63)	4.20 (5.75)
	Median	0.00	0.00	0.00	0.00	0.00	1.99
	Q25 ; Q75	0.0 ; 4.5	0.0 ; 2.0	0.0 ; 2.0	0.0 ; 2.1	0.0 ; 0.0	0.0 ; 6.5
	Min ; Max	0.0 ; 21.5	0.0 ; 10.7	0.0 ; 15.6	0.0 ; 10.7	0.0 ; 12.7	0.0 ; 23.4
On-Demand	N	14	14	14	14	14	14
	Mean (Std)	31.04 (17.52)	4.14 (5.38)	20.72 (14.38)	10.92 (14.06)	3.55 (8.19)	35.19 (19.22)
	Median	26.77	1.24	17.53	6.59	0.00	26.77
	Q25 ; Q75	18.1 ; 39.0	0.0 ; 7.2	13.2 ; 25.4	0.0 ; 10.6	0.0 ; 3.6	25.3 ; 44.6
	Min ; Max	8.6 ; 67.6	0.0 ; 14.8	0.0 ; 54.1	0.0 ; 40.6	0.0 ; 30.4	12.9 ; 81.2

a Major joints: wrist, elbow, shoulder, hip, knee, ankle
b Soft tissue, muscle, body cavity, intracranial and other
c Subjects received a minimum of 3 months of prophylactic treatment with BAX326.

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Table 5 summarizes the ABR subgroup analysis with or without anthropathy at screening.

Table 5: ABR by bleeding sites in subjects with/without anthropathy at screening

Treatment	Arthropathy at Screening	Statistic	Site		All
			Joint[a]	Non-Joint[b]	
Prophylaxis[c]	Yes	N	48	48	48
		Mean (Std)	3.09 (4.35)	1.39 (2.77)	4.48 (5.76)
		Median	1.77	0.00	2.10
		Q25 ; Q75	0.0 ; 5.1	0.0 ; 2.0	0.0 ; 7.1
		Min ; Max	0.0 ; 21.5	0.0 ; 10.7	0.0 ; 23.4
	No	N	8	8	8
		Mean (Std)	1.02 (2.21)	1.55 (3.64)	2.57 (5.74)
		Median	0.00	0.00	0.00
		Q25 ; Q75	0.0 ; 1.0	0.0 ; 1.0	0.0 ; 2.0
		Min ; Max	0.0 ; 6.2	0.0 ; 10.4	0.0 ; 16.6
On-Demand	Yes	N	14	14	14
		Mean (Std)	31.04 (17.52)	4.14 (5.38)	35.19 (19.22)
		Median	26.77	1.24	26.77
		Q25 ; Q75	18.1 ; 39.0	0.0 ; 7.2	25.3 ; 44.6
		Min ; Max	8.6 ; 67.6	0.0 ; 14.8	12.9 ; 81.2

a Major joints: wrist, elbow, shoulder, hip, knee, ankle
b Soft tissue, muscle, body cavity, intracranial and other
c Subjects received a minimum of 3 months of prophylactic treatment with BAX326.

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The subgroup analysis of ABR by bleeding age and race is on-going. All patients were male therefore there is no subgroup analysis for gender.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

This BLA submission includes the interim and final analysis of Pivotal Study 250901. This is a prospective, controlled and uncontrolled, multicenter, phase 1/3 study. Efficacy endpoints include PK endpoints and hemostatic efficacy endpoints. The sponsor submitted the comparison of the ABR as the hemostatic efficacy endpoint between the prophylaxis cohort and the historical control group. The sponsor submitted two-sided z-test p-values in the interim report, but no p-values in the final report. This statistical reviewer conducted both two-sided and one-sided z-tests. It is confirmed by this reviewer that the ABR of prophylactic group is significantly lower than ABR of historical control group ($p < 0.0001$). However, the ABR of on-demand group is significantly higher than the ABR of historical control group ($p = 0.0036$).

Descriptive statistics were also provided by the sponsor for pre-specified efficacy endpoints.

4.2 Conclusions and Recommendations

This statistical reviewer repeated the z-tests for Pivotal Study 250901. The results can NOT support the efficacy of proposed product completely. The ABR of the on-demand cohort is significantly higher than the ABR of the historical control group. The sponsor is expected to address this difference.

The following are comments from this statistical reviewer to the sponsor:
1. In the interim analysis report, the ABR of on-demand cohort was stated as "35.19 ($\pm$ 19.22)" (page 76, the last paragraph). However, in the final study report, the ABR of on-demand cohort was stated as "33.87 ($\pm$ 17.37)" (Page 75, the last paragraph). Please explain why the ABR of on-demand cohort changed in the final study report.
2. We recommend you conduct the baseline comparison between the prophylactic cohort, the on-demand cohort, as well as the historical control group to demonstrate the "substantial baseline differences" between the prophylactic cohort and the on-demand cohort as well as show comparability to the historical control group.
3. Please explain why in Section 11.4.1.4.1, the ABR of on-demand cohort was compared with these subjects' own historical bleed rates.
4. Please include the z-test result, as well as the corresponding confidence interval, in the final study report. The conduct of the z-test should follow the pre-specified statistical analysis plan.

This statistical review serves as the mid-cycle assessment of the biological license application under STN 125446.