



STATISTICAL REVIEW AND EVALUATION BLA (FINAL)

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Indication(s): Coagulation Factor IX (Recombinant)

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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)- years of age) with hemophilia B (congenital Factor IX [FIX] deficiency).

1.1 Conclusions and Recommendations

Statistical analyses of study results show that both the efficacy and the safety of the proposed product are acceptable. For the efficacy, the primary hemostatic endpoint of annualized bleeding rate (ABR) for the prophylactic group is significantly lower than that for the historical control meta-analysis group (4.26 vs. 20.0; $p < 0.0001$). No serious safety concerns were detected.

1.2 Brief Overview of Clinical Studies

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 the three ongoing clinical studies are Pediatric Study 251101, Continuation Study 251001 and Surgery Study 251002.

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

1.3 Major Statistical Issues and Findings

The hemostatic efficacy analyses are discussed in this memo. The data show that the ABR of the prophylactic group is significantly lower than the ABR of the historical control group. However, the ABR of the on-demand group is higher than the ABR of the historical control meta-analysis, even higher than the subjects' own historical data. However, this on-demand group was added after the study started as a reference. Therefore no superiority/equivalence/non-inferiority hypotheses testing procedures were designed for the on-demand group in this study. As a consequence, no statistical conclusion can be drawn based on the on-demand group. The sponsor also performed statistical analyses on treatment of bleeding episode and consumption of BAX326 through descriptive statistics. Safety endpoints are also examined in this memo.

2. INTRODUCTION

2.1 Overview

BAX326 is a purified protein produced by recombinant DNA technology (a genetically engineered Chinese hamster ovary (CHO) cell line). It is not derived from human blood or plasma products, and its manufacture does not include animal or human components. BAX326 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. BAX326 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 PTPs with severe or moderately severe hemophilia B. Pivotal Study 250901 was ongoing at the time of analysis but is now operationally complete, and the three ongoing clinical studies are Pediatric Study 251101, Continuation Study 251001 and Surgery Study 251002. The four studies are summarized below.

- 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 subjects 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.

The sponsor presents the hemostatic efficacy data of Pivotal Study 250901 in this submission to support the licensure of BAX326. The sponsor submitted the interim efficacy analysis of Study 250901 (dated June 8, 2012) in the original submission after 56 subjects had completed at least three months of prophylactic treatment during the study. On December 14, 2012 the sponsor submitted the final study report for Study 250901 (dated September 11, 2012). This statistical memo is based on the final study report as well as the datasets.

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:

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3. STATISTICAL EVALUATION

The 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 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 (a U.S. licensed product). Thrombotic markers were also to be determined at specified time points.

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 two infusions each, one infusion with BAX326 and one 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 subject body weight (kg).

In Part 2, all subjects were to receive exclusively BAX326. Subjects received either 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 subject randomization via the Interactive Voice Response System for those subjects participating in Part 1. The subject randomization number was assigned based on the master randomization list. 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 five days, preferably seven 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 both 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 (AUC_{0-72 h}/dose). Secondary PK endpoints include: total AUC/dose, mean residence time (MRT), clearance (CL), IR, elimination phase half-life ($T_{1/2}$), and volume of distribution at steady state (V_{ss}). IR over time will also be assessed.

The clinical efficacy of FIX treatment was defined as hemostatic efficacy. The primary hemostatic efficacy endpoint is annualized bleeding rate (ABR). The sponsor also analyzed the treatment of BEs and consumption of BAX326. The analysis of treatment of BEs included overall hemostatic efficacy rating at the resolution of bleed, and the number of infusions and total weight-adjusted dose per bleeding episode, by anatomical site (joint/non-joint), cause (spontaneous/injury), severity (minor, moderate, major, and life/limb-threatening), and treatment regimen (prophylaxis and on-demand treatment).

The number of BEs beginning within 24 and 48 hours of an infusion was also studied as an exploratory endpoint.

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

Analysis Populations

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

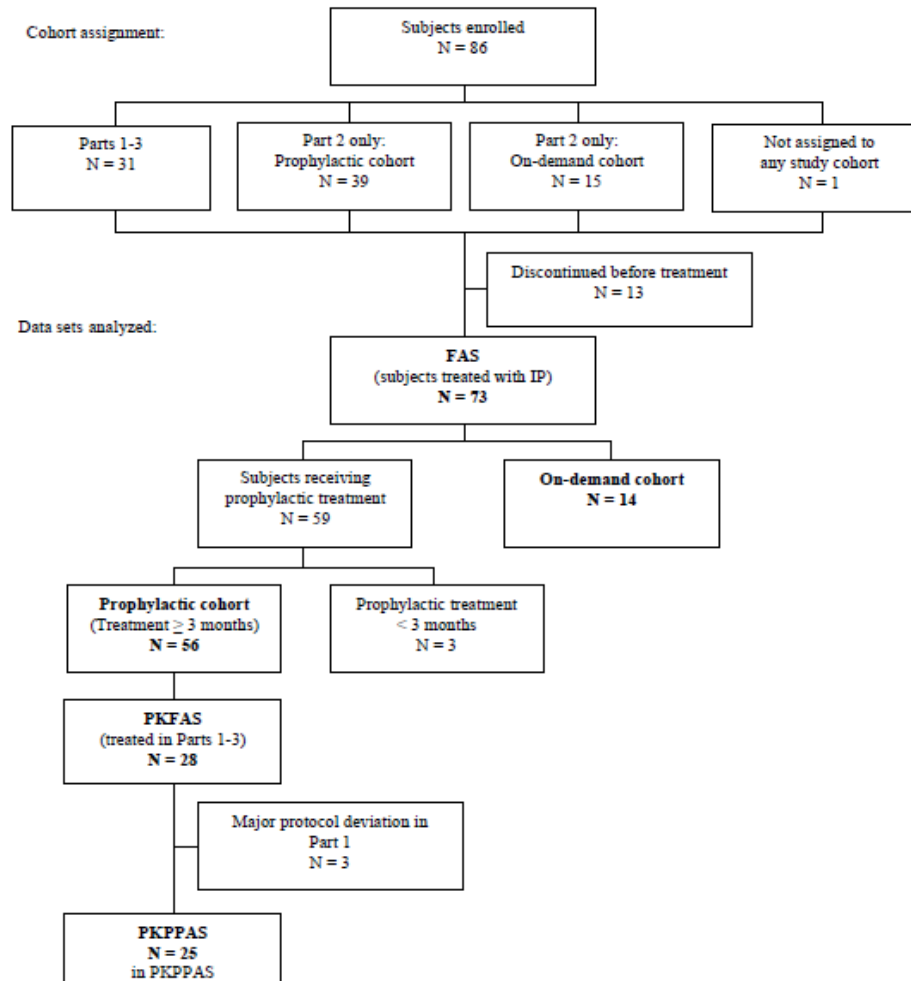
The Pharmacokinetic Per Protocol Analysis Set (PKPPAS) was comprised of all randomized and treated (received both of the assigned infusions) subjects who had no major violation affecting the PK period of the study. There were 25 subjects in the PKPPAS.

The historical control meta-analysis includes 12 studies published from 1976 to 2011 with a total of 276 hemophilia B subjects treated on-demand for an average of 19.6

months. Three studies were pediatric studies in subjects less than five years of age and nine studies included older subjects.

Figure 1 is the flow chart accounting for all the subjects in Study 250901.

Figure 1: Subject Disposition for Study 250901



Patient Disposition, Demographic and Baseline Characteristics

A total of 86 subjects were enrolled in this study as of the data cut-off on March 27, 2012. Among the 86 subjects, 31 subjects were enrolled for participation in Parts 1-3, 39 subjects in the prophylactic cohort of Part 2 only and 15 subjects 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 subjects were treated in Parts 1-3, and 31 subjects were treated in the prophylactic cohort and 14 subjects 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 two 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 the FAS

Parameter	Category	FAS				
		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 MRT and the $T_{1/2}$. To assess the PK equivalence of the BAX326 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. The ABR is calculated as (number of BEs/observed treatment period in days) *365.25. A meta-analytic approach was used in the historical control data to summarize the (annualized) bleed rates in hemophilia B subjects treated with on-demand infusions. The SAP (dated on April 9, 2012) submitted with the interim analyses specified that the ABR would be compared between the prophylactic cohort and the historical control meta-analysis with a one-sided z-test at a 2.5% significance level.

The same hypothesis testing procedure was also conducted between the on-demand cohort and the historical control meta-analysis as a supportive analysis. Descriptive statistics were applied on the remaining hemostatic efficacy endpoints, such as the overall hemostatic efficacy rating and consumption of BAX326. In the latest SAP dated as July 5, 2012, the sponsor removed the hypothesis testing procedure for ABR.

Results and Conclusions

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

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

The results reported in this memo are computed based on the final dataset submitted on December 14, 2012.

Analysis of Annualized Bleeding Rate (ABR)

The ABR was analyzed from data obtained during prophylaxis and on-demand treatment in Part 2.

A total of 59 subjects received prophylactic treatment. The prophylactic cohort comprised 56 subjects who had a minimum of three months of prophylactic treatment; 29 of these subjects received at least six months of prophylactic treatment (Listing 8 in the submission). The on-demand cohort comprised 14 subjects. The median treatment duration was 6.03 months (range: 5.36 to 9.13 months) in the prophylactic cohort with at least three months of prophylaxis (n=56), 5.98 months (range: 1.22 to 9.13 months) in all prophylactic subjects (n=59), and 3.4 months (range: 1.18 to 5.09 months) in the on-demand cohort (n=14).

Of 59 subjects who received prophylactic treatment (including three subjects who received prophylactic treatment for less than three 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 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 three months of prophylactic treatment (n=56).

Fifty-six (76.7%) of 73 subjects had 50 or more EDs to BAX326 during the study. Of all 59 subjects who received prophylactic treatment, 26 (44.1%) subjects experienced no bleeds. In the prophylactic cohort who had a minimum of three months of prophylactic treatment (n=56), 24 (42.9%) subjects experienced no bleeds. All 24 subjects had at least 50 EDs to BAX326.

The mean and median ABR in the prophylactic cohort (n=56) were 4.26 (\pm 5.80) and 1.99. The mean and median historical on-demand bleed rates given by 53 of these subjects were 16.92 (\pm 16.72) and 13. The mean rate of joint bleeds was 2.85 (\pm 4.25) compared with 1.41 (\pm 2.87) non-joint bleeds. The rate of spontaneous bleeds (mean: 1.72 \pm 3.26) was comparable to the rate of bleeds caused by injury (mean: 1.70 \pm 2.80).

All 14 of the subjects in the on-demand cohort of the FAS had bleeds. The mean ABR was 33.87 (\pm 17.37) and the median was 26.98, as compared to their own historical on-demand bleed rates with mean 24.50 (\pm 13.65) and median 17. The mean rate of joint bleeds was 29.88 (\pm 16.05) versus 3.99 (\pm 5.26) non-joint bleeds. The rate of spontaneous bleeds was higher (mean: 19.85 \pm 12.90) than the rate of bleeds caused by injury (mean: 10.58 \pm 13.58).

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. In the Efficacy Information Amendment dated on February 26, 2013, the sponsor further explained that subjects in the on-demand cohort had to have at least 12 bleeds requiring treatment in the 12 months prior to the study enrollment. This difference in inclusion criteria largely explains the differences observed in the mean ABR between the prophylactic cohort and the on-demand cohort.

For the historical control meta-analysis, ABR varied from 7.2 to 33.4 bleeds per subject-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 subject-year with a two-sided 95% confidence interval of 15.3 to 24.6 bleeds per subject-year.

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

	Sample size	Mean	Standard deviation	95% CI
Prophylactic	56	4.26	5.80	2.71, 5.81
On-demand	14	33.87	17.37	23.84, 43.89
Historical control meta-analysis	276	20.0	39.4	15.3, 24.6

The sponsor submitted two-sided z-test p-values in the interim report for comparisons to the historical control meta-analysis for both the prophylactic group and on-demand groups, but did not submit p-values in the final report as a consequence of a SAP revision dated July 5, 2012. However, this reviewer conducted both the two-sided and one-sided z-test based on the final datasets. Table 3 reports this reviewer's p-value calculations. According to the p-value of the two-sided z-test, both the ABR of the prophylactic cohort

and the ABR of the on-demand cohort are significantly different from the ABR of the historical control meta-analysis. The ABR of the prophylactic group is significantly lower than the ABR of the historical control meta-analysis ($p < 0.0001$). However, the ABR of the on-demand group is significantly higher than the ABR of the historical control meta-analysis ($p = 0.0039$) when compared to the pre-specified one-sided Type I error rate of 0.025.

Table 3: P-values of the z-test for Prophylactic/On-Demand vs. Historical Control Groups

	z-value	2-sided p-value	1-sided p-value (left)	1-sided p-value (right)
Prophylactic vs. Historical Control	-6.3085	<0.0001	<0.0001	>0.9999
On-demand vs. Historical Control	2.6606	0.0078	0.9961	0.0039

This sponsor further conducted the two-sided z-test between the on-demand group and this group's own historical data. The p-value is 0.1125, which means one cannot reject the hypothesis that the ABR from their BAX326 experience compared to their historical data are equal.

Analysis of Treatment of Bleeding Episodes

The sponsor provided descriptive statistics for BEs. There are 249 BEs in the FAS; 115 BEs occurred during prophylactic treatment and 134 BEs occurred in the on-demand cohort. By bleeding site, 197 were joint bleeds (of which 107 were bleeds into a target joint and 90 non-target joint BEs) and 52 were non-joint bleeds. While 130 bleeds were spontaneous bleeds, 90 were caused by injury; 29 were of unknown cause.

Of 249 BEs, the majority (153; 61.4%) were treated with one infusion. Fifty-eight (58; 23.3%) BEs were treated with two infusions, and 38 (15.3%) BEs were treated with three or more than three infusions. Of 197 joint bleeds, 122 (61.9%) were treated with one infusion and 47 (23.9%) were treated with two infusions.

Hemostatic efficacy at resolution of bleed was rated 'excellent' in 41.0% and 'good' in 55.0% of all treated BEs (total of 96.0%). Only 2.0% of bleed treatments were rated as 'fair', and zero had a rating of 'none'. The sponsor defined the "excellent", "good", "fair", and "none" for treatment of bleeding episode in the final study report, Table 9.5-1. This table was also defined in the latest protocol (amendment 7) as Table 11.5-1.

Analysis of BAX326 Consumption

An overview of BAX326 consumption by type of treatment was provided by the sponsor as in Table 4.

Table 4: Consumption of BAX326 per Subject per Event

Group	Sample Size	Mean	Std Dev	Median
Prophylactic	59	49.5	4.8	50.5
Bleeding	47	93.2	41.3	87.1

Table 5: Consumption of BAX326 per Subject per Month

Group	Sample Size	Mean	Std Dev	Median
Prophylaxis (Part 1 &3, Part 2 prophylaxis group only)	59	356.1	61.3	347.8
On-demand in Part 2	14	166.6	64.2	167.3

Hemostatic Efficacy Conclusions

The sponsor analyzed the ABR, the treatment of bleeding episode, as well as consumption of BAX326. The ABR of the prophylactic group is significantly lower than the ABR of the historical control meta-analysis group, but the ABR of the on-demand group is higher than the ABR of the historical control, even higher than the subjects' own historical data. However, this on-demand group was added after the study started as a reference. Therefore no superiority/equivalence/non-inferiority hypotheses testing procedures were designed for the on-demand group in this study. As a consequence, no statistical conclusion can be drawn based on the on-demand group. The descriptive statistics of BE and BAX326 consumption are acceptable.

3.2 Evaluation of Safety

The safety analysis of Pivotal Study 250901 was performed on the 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 the efficacy analysis, the safety analyses are based on a data cut-off of March 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. The database snapshot occurred on May 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 the database snapshot date. 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

Table 6 summarizes the subgroup analysis by gender, age and race for the Prophylactic group.

Table 6: Demographic Subgroup Analyses for the Prophylactic Group

	Subjects with bleeds (N=32)	Subjects without bleeds (N=24)
Gender		
Male	32	24
Female	0	0
Age		
12-16 years	2	0
>16 years	30	24
Race		
White	25	22
Black or African	1	0
Japanese	4	0
Native Latin	2	1
Mestizo	0	1

This reviewer conducted the subgroup analysis of ABR by age and race for the prophylactic group. Because all subjects are male, no subgroup analysis by gender is needed. No statistical comparisons were made due to small sample sizes in some of the subgroups.

Table 7: ABR subgroup analyses by age and race for Prophylactic Group

	Sample Size	Mean (sd)
Age		
12-16 years	2	13.28 (4.70)
> 16 years	54	3.93 (5.60)
Race		
White	47	3.35 (4.62)
Black or African	1	5.35
Japanese	4	15.72 (8.76)

Others	4	3.27 (4.70)
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The sponsor provided subgroup analysis of ABR by bleeding site and cause (Table 8).

Table 8: ABR by bleeding sites and cause on FAS

		Prophylactic (N=56)	On Demand (N=14)
Site	Joint	2.85 (4.25)	29.88 (16.05)
	Non-Joint	1.41 (2.87)	3.99 (5.26)
Cause	Spontaneous	1.72 (3.26)	19.85 (12.90)
	Injury	1.70 (2.80)	10.58 (13.58)
	Unknown	0.84 (2.64)	3.44 (8.13)
All		4.26 (5.80)	33.87 (17.37)

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 a historical control meta-analysis. The sponsor submitted two-sided z-test p-values in the interim report, but no p-values in the final report as a consequence of a SAP revision dated July 5, 2012. This statistical reviewer conducted both two-sided and one-sided z-tests. It is confirmed by this reviewer that the ABR of the prophylactic group is significantly lower than the ABR of the historical control meta-analysis (4.26 vs. 20.0; $p < 0.0001$). The ABR of the on-demand group (33.87) was compared with their own historical data (24.50) and the historical control meta-analysis (20.0). Because the study was not designed to test the superiority/equivalency/non-inferiority for the on-demand group, no valid statistical conclusion can be drawn for the ABR of the on-demand group.

Descriptive statistics were also provided by the sponsor for pre-specified hemostatic efficacy endpoints, including the analysis of treatment of bleeding episodes and BAX326 consumption.

For safety, no thrombotic events, deaths, serious adverse reactions or severe allergic reactions occurred during or after treatment as of the database snapshot date. No race and age statistical comparisons were made due to small sample sizes.

4.2 Conclusions and Recommendations

This statistical reviewer confirmed the z-tests from the interim report for Pivotal Study 250901. Although the sponsor did not conduct statistical tests in the final report, this

reviewer did conduct the appropriate statistical tests. The results support the efficacy of proposed product in the prophylactic group. No statistical conclusion of the primary hemostatic endpoint in the on-demand group can be drawn with current available data. The safety data were also examined and no serious concerns were detected. Subgroup analyses by age and race were also investigated in this memo.

This statistical review serves as the final assessment of the biological license application under STN 125446.

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