Application Type	BLA
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Division / Office	OBRR/DH
Committee Chair	Stephanie Omokaro, MD
Clinical Reviewer(s)	Stephanie Omokaro, MD
Project Manager	Edward Thompson
Priority Review	No
Reviewer Name(s)	Jiang Hu, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Renée C. Rees, PhD., Team Leader, Therapeutics Evaluation Branch, (HFM-219)
	Boguang Zhen, PhD., Branch Chief, Therapeutics Evaluation Branch, (HFM-219)
Applicant	Baxter Healthcare Corporation
Established Name	Coagulation Factor IX (Recombinant)
(Proposed) Trade Name	–b(4)----(RIXUBIS)/ RIXUBIS
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	
Dosing Regimen	
Indication(s) and Intended Population(s)	This supplement seeks to extend the following indication for adult patients to include pediatric patients (<12 years of age): • Control and prevention of bleeding episodes in patients with hemophilia B

	• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia B • Perioperative management in patients with hemophilia B.

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GLOSSARY

ABR	Annualized bleeding rate
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
BE	Bleeding episode
BU	Bethesda Unit
CHO	Chinese hamster ovary
CL	Clearance
CPMP	Committee for Proprietary Medicinal Products
DIC	Disseminated intravascular coagulation

DMC	Data Monitoring Committee
ED	Exposure day
EDR	Electronic Document Room
FAS	Full analysis set
FFP	Fresh frozen plasma
FIX	Factor IX
HIV	Human immunodeficiency virus
HR QoL	Health-related quality of life
Ig	Immunoglobulin
INR	International normalized ratio
IP	Investigational product
IR	Incremental recovery
IU	International units
MRT	Magnetic resonance imaging
PCC	Prothrombin complex concentrate
PK	Pharmacokinetic
PKFAS	Pharmacokinetic full analysis set
SAE	Serious adverse event
T1/2	Elimination phase half-life
VSS	Volume of distribution at steady state

1. EXECUTIVE SUMMARY

This BLA supplement submission includes a final clinical study report for Baxter's clinical study that evaluated RIXUBIS BAX326 in pediatric subjects. It addresses the deferred pediatric study referenced in the Agency's June 26, 2013 approval letter for RIXUBIS (BLA 125446).

This statistical memo focuses on the study 251101. It was a Phase 2/3, prospective, uncontrolled, multicenter study investigating the hemostatic efficacy, safety, and immunogenicity of treatment with RIXUBIS over six months with twice-weekly prophylactic infusions for at least 50 EDs in 23 previously treated pediatric subjects.

The primary endpoint of this study is all adverse events (AE) possibly or probably related to the investigated product. A total of 48 AEs occurred in 17 (73.9%) subjects and none of the AEs were considered as treatment-related. Hemostatic efficacy was also examined. The mean annualized bleeding rate (ABR) of pediatric subjects was lower than that of the adult group and the historical on-demand cohort. Of the 26 bleeding episodes that occurred and were treated with RIXUBIS in this study, 25 were rated as excellent or good for bleeding resolution. Both safety analyses and hemostatic efficacy analyses were confirmed by this statistical reviewer. The statistical report supports the indication of RIXUBIS in pediatric subjects.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia B is an X-linked recessive, congenital bleeding disorder caused by deficient or defective coagulation factor IX (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. RIXUBIS temporarily replaces the missing clotting FIX that is needed for effective hemostasis.

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

RIXUBIS 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. RIXUBIS contains no preservatives.

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

The original BLA submission was submitted on August 30, 2012 and the approval letter from CBER was issued on June 26, 2013. In this approval letter, CBER deferred a possible pediatric indication until September 30, 2013 because the pediatric study (study

251101) was not completed at that time. The sponsor submitted the efficacy supplement 125446/31 to fulfill this required post-marketing study under 505B(a).

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

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

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

5.1 Review Strategy

This review memo focuses on both efficacy analyses and safety analyses of the pediatric study 251101.

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

The following documents of 125446/31 were reviewed:

- 2.5 Clinical Overview
- 2.7.2 Summary of Clinical Pharmacology Studies
- 2.7.3 Summary of Clinical Efficacy [Indication]
- 2.7.4 Summary of Clinical Safety
- 5.3.5.2 – Study 251101

This reviewer also used the original BLA 125446/0 as a reference.

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)----------

5.3 Table of Studies/Clinical Trials

The sponsor claimed that its clinical development program for RIXUBIS had been designed to comply with the Committee for Proprietary Medicinal Products (CPMP) Guideline on the Clinical Investigation of Recombinant FVIII and FIX products and the draft CPMP Guideline on the Clinical Investigation of Recombinant and Human Plasma-Derived Factor IX Products. The program includes 1 pivotal (250901), and 3 supportive clinical studies: a completed pediatric study (251101), an ongoing continuation study (251001), and an ongoing surgery study (251002). The design of each study is summarized in Table 1 below.

Table 1
Listing of studies in the BAX326 clinical development program

Study number Type of study	Study status Report (if available)	Subjects treated[a]	Main criteria for inclusion	Dose range and frequency
250901 Pivotal Phase 1/3, safety, efficacy, PK	Complete CSR 250901	73	PTP[b] 12 to 65 y	Prophylactic treatment: 50 IU/kg (range: 40 to 60 IU/kg, max 75 IU/kg) twice weekly Acute bleeding episodes: to be treated with BAX326
251001 Continuation Phase 3, safety, efficacy	Ongoing	82	PTP[b] completed 250901 or 251101	Prophylactic treatment: 50 IU/kg (range: 40 to 60 IU/kg, max 75 IU/kg) twice weekly in subjects ≥ 12 y; (range: 40-80 IU/kg) twice weekly in subjects < 12 y) Modified prophylaxis: determined by the investigator On demand Acute bleeding episodes: to be treated with BAX326
251002 Surgery Phase 3, safety, efficacy, PK	Ongoing iCSR 251002	25	PTP[b] undergoing major and minor surgical, dental or other invasive procedures	Surgical prophylaxis: Dose tailored per subject to raise FIX concentration to 80%-100% of normal for major surgeries and to 30%-60% of normal for minor surgeries
251101 Pediatric Phase 2/3, safety, efficacy, PK	Complete CSR 251101	23	PTP[b] < 12 y	Prophylactic treatment: 50 IU/kg (range: 40 to 80 IU/kg) twice weekly Acute bleeding episodes: to be treated with BAX326

[a] Number of subjects who received at least one infusion of BAX326 (n = 99 unique subjects). Data cut-off was June 14, 2013 for ongoing studies 251001 and 251002.
[b] Previously-treated patient: subject has hemophilia B and has been treated with FIX product previously.

Source: Original BLA125446/31; Clinical Overview, section 1.5.1, p.10.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1 : Study 251101

This review memo focuses on the pediatric study 251101, entitled "*A Phase 2/3, Prospective, Uncontrolled, Multicenter Study Evaluating Pharmacokinetics, Efficacy, Safety, and Immunogenicity in Previously Treated Pediatric Patients with Severe (FIX level <1%) or Moderately Severe (FIX level 1-2%) Hemophilia B.*"

6.1.1 Objectives

The purpose of this study was to assess RIXUBIS PK parameters, and to evaluate its hemostatic efficacy, safety, immunogenicity, and changes in health-related quality of life (HRQoL) in pediatric patients.

The primary objective is to evaluate all AEs possibly or probably related to RIXUBIS.

Secondary objectives of this study include the following:

- To evaluate the PK parameters of RIXUBIS in pediatric PTPs <12 years of age
- To monitor incremental recovery (IR) of RIXUBIS over time

- To evaluate the hemostatic efficacy of RIXUBIS in the management and prevention of acute bleeding episodes for a period of 6 months
- To evaluate safety in terms of immunogenicity for a minimum of 50 EDs, the occurrence of thrombotic events, as well as clinically significant changes in routine laboratory parameters (hematology/clinical chemistry) and vital signs
- To evaluate changes in HRQoL and health resource use

6.1.2 Design Overview

This was a Phase 2/3, prospective, uncontrolled, open-label multicenter study investigating the safety, immunogenicity, PK, hemostatic efficacy and HR QoL of RIXUBIS over 6 months with twice weekly prophylactic infusions or at least 50 EDs, whichever occurred last. Before the start of the 6-month prophylactic treatment period, a PK evaluation was to be performed. Twenty-four (24) pediatric subjects were to be enrolled in order to have 20 evaluable subjects.

All subjects were to receive the same dosing schedule of RIXUBIS. There were a total of 7 post-infusion time points over 72 hours for taking blood samples for the PK evaluation. These were to be divided between two subjects, with the result that there were four post-infusion time points per subject.

There were to be 2 cohorts of 12 subjects each, based on the age of the subjects: <6 years and 6 to < 12 years. Within each cohort, subjects were to be randomized to one of two blood sampling sequences for the PK assessment (first RIXUBIS infusion) to reduce the burden of frequent blood sampling on the individual subject. The total subject participation period was estimated to be 8 months from enrollment to subject completion (i.e., last study visit), unless prematurely discontinued.

6.1.3 Population

The main criteria for inclusion were as follows:

- Diagnosis of severe (FIX level <1%) or moderately severe (FIX level 1-2%) hemophilia B based on the one-stage aPTT assay, as determined by the central laboratory
- Subject age at time of screening: <12 years
- For subjects 6 to <12 years of age:
  Previously treated with plasma-derived and/or recombinant FIX concentrate(s) for ≥150 EDs (based on the subject's medical records). If a subject did not have a verifiable, documented history of 150 EDs, s/he could be enrolled if the following critiera were met:
  1) there were an estimated (not fully documented) 100-150 EDs to any FIX product (plasma-derived or recombinant FIX concentrate(s), PCC or FFP) (assumption based on the severity of disease and treatment history), and
  2) the subject had participated in IMMUNINE Protocol 050901 and accumulated either ≥50 EDs to IMMUNINE or a total of ≥150 EDs to aplasma-derived and/or recombinant FIX concentrate prior to enrollment.
- For subjects < 6 years of age:

Previously treated with plasma-derived and/or recombinant FIX concentrate(s) for >50 EDs (based on the subject's medical records). If a subject did not have a verifiable, documented history of >50 EDs, s/he could be enrolled if the following criteria were met:

1) there were approximately (not fully documented) 20-50 EDs to any FIX product (plasma-derived or recombinant FIX concentrate(s), PCC or FFP), and
2) the subject had participated in IMMUNINE Study 050901 and accumulated ≥30 EDs to IMMUNINE or a total of >50 EDs to a plasmaderivedand/or recombinant FIX concentrate prior to enrollment

- No history of FIX inhibitors (based on the subject's medical records). If a verifiable, documented history was unavailable, the subject could be enrolled if s/he had participated in Study 050901 for ≥30 EDs (< 6 years of age) or ≥50 EDs (6 to <12 years of age) to IMMUNINE prior to enrollment.
- Willingness to have prophylactic treatment over a period of 6 months
- Immunocompetent as evidenced by a CD4 count ≥ 200 cells/mm3 Human immunodeficiency virus (HIV) negative or HIV+ with a viral load <200 particles/μL ~ <400,000 copies/mL

The main criteria for exclusion were as follows:

- History of FIX inhibitors with a titer ≥0.6 Bethesda Units (BU) (as determined by the –b(4)---------- of the Bethesda assay or the assay employed in the respective local laboratory with the corresponding detection limit) at any time prior to screening
- Detectable FIX inhibitor at screening, with a titer ≥0.6 BU as determined by the
- --b(4)---------- of the Bethesda assay in the central laboratory
- History of allergic reaction, e.g. anaphylaxis, following exposure to FIX concentrate(s)
- Known hypersensitivity to hamster proteins or rFurin
- Evidence of an ongoing or recent thrombotic disease, fibrinolysis or disseminated intravascular coagulation (DIC)
- Abnormal renal function (serum creatinine >1.5 times the upper limit of normal)
- International Normalized Ratio (INR) >1.4
- Active hepatic disease with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels >5 times the upper limit of normal
- Diagnosis of an inherited or acquired hemostatic defect other than hemophilia B
- Platelet count <100,000/mL
- Clinically significant medical, psychiatric, or cognitive illness, that, in the opinion of the investigator, would affect subject's safety or compliance
- Subject is currently receiving, or is scheduled to receive during the course of the study, an immunomodulating drug (e.g. corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day, or α-interferon) other than antiretroviral chemotherapy

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were to receive an initial infusion with RIXUBIS at a dose of 75 ± 5 IU/kg for PK assessment. A minimum wash-out period of 5 days, preferably 7 days, had to be observed prior to the PK infusion and the subject had to be in a non-bleeding stage.

For the prophylactic regimen, subjects were to be treated with a recommended dose of 50 IU/kg RIXUBIS twice every week ranging from 40-80 IU/kg for a period of 6 months or for at least 50 EDs to RIXUBIS, whichever occurred last. The mean compliance in dose was 97.45 (± 8.848)% (median: 100%; range: 62.0-100%), and mean compliance in treatment frequency was 90.83(± 7.216)% (median: 92.45%; range: 74.5-100%). The infusion rate was not to exceed 10 mL/minute.

The first two prophylactic RIXUBIS infusions following the PK assessment were to be administered at the study site (Exposure Day ED 2 and ED 3) and the subject was to be monitored for vital signs and the occurrence of AEs over a period of 2 hours. The first prophylactic infusion (ED 2) was to coincide with the last post-infusion blood sampling time point of the PK study.

6.1.6 Sites and Centers

There were 15 study sites which participated but only 11 sites enrolled subjects. The remaining four sites were initiated but were inactive. No adjustment was made for center effect.

6.1.7 Surveillance/Monitoring

The safety of RIXUBIS in this study was monitored by an independent Data Monitoring Committee (DMC). The DMC was composed of five recognized experts in the field of hemophilia clinical care and research who are not actively recruiting subjects, and one independent statistician.

6.1.8 Endpoints and Criteria for Study Success

<u>Primary</u>
The primary outcome of this study is all AEs possibly or probably related to RIXUBIS. No criteria were given for study success.

<u>Secondary</u>
Secondary outcome measures include PK study endpoints, hemostatic efficacy endpoints, safety and immunogenicity endpoints, and changes in HR QoL parameters and health resource use.

The PK endpoints include the area under the plasma concentration versus time curve from 0 to 72 hours post-infusion (AUC0-72 h/dose), total AUC/dose, mean residence time (MRT), clearance (CL), incremental recovery (IR), elimination phase half-life (T1/2), volume of distribution at steady state (VSS), and IR over time

The hemostatic efficacy endpoints include:

- Treatment of bleeding episodes: number of infusions per bleeding episode, overall hemostatic efficacy rating at resolution of bleed
- Prophylaxis: annualized bleeding rate (ABR)
- Prophylaxis: number of bleeding episodes beginning within 24 and 48 hours of an infusion as exploratory outcome measures
- Consumption of RIXUBIS: number of infusions and weight-adjusted consumption per month and per year; weight-adjusted consumption per event

Safety and immunogenicity endpoints include:

- Development of inhibitory and total binding antibodies to FIX
- Occurrence of severe allergic reactions, e.g. anaphylaxis
- Occurrence of thrombotic events
- Clinically significant changes in routine laboratory parameters (hematology and clinical chemistry) and vital signs
- Development of antibodies to Chinese hamster ovary proteins and recombinant furin (rFurin)

The HR QoL parameters and health resource use endpoints include:

For subjects who are between 2 to 7 years of age:

- Generic: PedsQL™ (Parent-proxy versions: age group 2-4 years and age group 5-7 years)
- Health resource use (hospitalizations, emergency room visits, doctor office visits, etc.)

For subjects who are between 8 to 11 years of age:

- Disease-specific: Haemo-QoL, short version
- Generic: PedsQL™ Child version
- Health resource use (hospitalizations, emergency room visits, doctor office visits, etc.)

6.1.9 Statistical Considerations & Statistical Analysis Plan

For all outcome measures descriptive statistics were presented by age stratum. Point estimates (mean or median) and 95% CIs were also computed, if applicable.

There were no formal sample size considerations in this study. The sample size was based on the requirements in the EMA Guideline on the “Clinical investigation of recombinant and human plasma-derived FIX products”. According to the guideline, at least 10 subjects aged 6 to 12 years and 10 subjects aged < 6 years were required. To account for a potential drop out, a total of 24 subjects consisting of 12 subjects per age cohort were planned to be enrolled.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The Full Analysis Set (FAS) was defined to comprise all subjects who received at least one infusion during the study.

The Pharmacokinetic Full Analysis Set (PKFAS) was defined to comprise all subjects who have at least one plasma FIX activity level available during post-infusion time points.

A total of 23 subjects were enrolled in the study. All 23 subjects were treated with IP and completed the PK assessment and were therefore included in both the FAS and the PKFAS.

6.1.10.1.1 Demographics

The demographic and clinical characteristics are summarized by age cohort (<6 years, 6 - <12 years). Summaries of gender, race, age, weight, height and ABR prior to enrollment are provided in Table 3. Summaries of gene mutation, FIX activity, FIX antigen level, arthropathy at screening, number of target joints at screening and prior treatment (on-demand or prophylaxis) are provided in Table 4.

Table 3: Demographic Characteristics of Study Population

	< 6 years (N=11)	6 < 12 years (N=12)	All (N=23)
Gender			
male	11	12	23
female	0	0	0
Race			
White	10	12	22
Indian	1	0	1
Age (years)			
mean	3.83	9.80	6.94
median	3.35	10.39	7.10
standard deviation	1.541	1.510	3.394
Weight (kg)			
mean	16.3	30.7	23.8
median	16.8	32.5	21.2
standard deviation	3.29	6.19	8.83
Height (cm)			
mean	100.9	134.8	118.6
median	105.0	135.5	122.0
standard deviation	14.53	7.69	20.60
ABR prior to enrollment			

mean	6.7	6.9	6.8
median	2.0	2.5	2.0
standard deviation	9.84	9.13	9.26

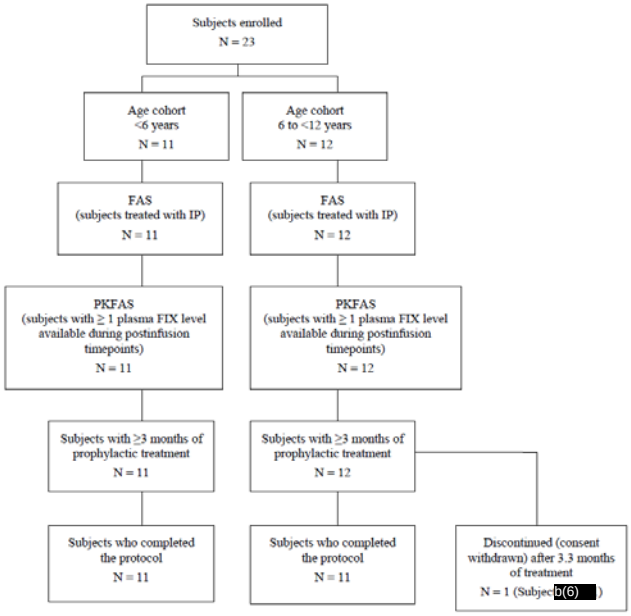
Table 4: Clinical Characteristics of Study Population

	< 6 years (N=11)	6 < 12 years (N=12)	All (N=23)
Gene Mutation			
missense	4	7	11
nonsense	2	0	2
splice site	1	0	1
deletion	1	1	2
frameshift	0	1	1
promoter	1	0	1
Not reported	2	3	5
FIX Activity Level			
<1%	9	8	17
1% - 2%	2	4	6
FIX Antigen Level			
<1%	6	2	8
1% - 2%	2	1	3
2% - 5%	0	0	0
5% - 40%	1	3	4
≥40%	2	6	8
Arthropathy at screening			
yes	0	4	4
no	11	8	19
Number of target joints at screening			
0	11	7	18
1-2	0	2	2
3-4	0	2	2
>4	0	1	1
Prior treatment			
on-demand	1	0	1
prophylaxis	8	8	16
both	2	4	6

6.1.10.1.3 Subject Disposition

Of the 23 subjects enrolled, 22 subjects completed the protocol; one subject (-b(6)---), who was 7 years old at the time of consent, discontinued the study (withdrawal by subject) after 35 EDs to RIXUBIS and a study duration of 4.34 months. Although the subject did not have ≥50 EDs to RIXUBIS, he did complete >3 months (i.e., 3.32 months) of prophylactic treatment. See Figure 1.

Figure 1: Subject Disposition for Study 251101



Source: Original BLS 125446/31; Clinical Study Report V503, p.41.

A total of 81 deviations were reported in 20 subjects during the study. Seven deviations in seven subjects were major and mostly concerned IP administration (see Table 5).

Table 5: Major Protocol Deviations

Subjects	Major protocol deviations
--b(6)--	IP administration: Wrong dose administered due to use of nominal potency instead of actual potency
-b(6)-----	IP administration: Incorrect potency of drug was infused during PK visit – 1000 IU vials were used instead of 500 IU vials
--b(6)----	IP administration: Wrong drug potency was used during PK – 1000 IU vials instead of 500 IU vials

--b(6)----	Protocol schedule: The washout period was not 5 days or more on the date of visit Week 5
--b(6)---	IP administration: On 01Feb2013 and 05Feb2013 expired drug was used – 1 vial of 500 IU, lot TNA11001A-15
--b(6)---	Other: safety reporting: SAE report re central venous catheter related infection was sent on 21Feb2013, SAE occurred on 27Nov2012
--b(6)----	Expired drug lot # TNA11001A was used for prophylactic infusion on 03Feb3013

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

A total of 48 AEs occurred in 17 (73.9%) subjects; 30 AEs occurred in 10 (83.3%) subjects in the 6-to-<12-year age cohort and 18 AEs occurred in 7 (63.6%) subjects in the <6-year age cohort. None of the AEs were considered treatment-related.

No deaths, no serious adverse reactions or severe allergic reactions and no thrombotic events occurred during or after treatment.

6.1.11.2 Analyses of Secondary Endpoints

Hemostatic efficacy -- Prophylactic treatment

All 23 subjects had >3 months of prophylactic treatment (mean: 5.98 [± 0.712] months; median: 5.95 months; range: 3.3-7.7 months). A mean of 1.97 (± 0.082) infusions (median: 1.97; range: 1.8-2.2) were administered in the subject population per week, at a mean dose of 56.25 (± 8.341) IU/kg per prophylactic infusion (median: 55.63 IU/kg; range: 43.0-75.5 IU/kg). Treatment duration, average number of infusions per week and average dose per infusion were comparable between the <6-year and the 6-to <12-year age cohorts (i.e., mean dose of 56.35 IU/kg [median: 55.63 IU/kg] per infusion in the younger and mean dose of 56.16 IU/kg [median: 55.51 IU/kg] per infusion in the older age cohort).

Hemostatic efficacy -- Annualized Bleeding Rate (ABR)

The ABR was calculated as (number of BEs/observed treatment period in days) *365.25.

The mean ABR for all 23 subjects with ≥3 months of prophylactic treatment was 2.7 (± 3.14) (median: 2.0; range: 0.0-10.8).

The mean ABR was higher in subjects 6 to <12 years of age than in subjects <6 years of age: mean ABR of 3.4 (± 3.93) (range: 0.0-10.8) in the older age cohort compared with 1.9 (± 1.89) (range: 0.0-5.4) in the younger age cohort. The median ABRs were

comparable between the cohorts: median ABR of 2.0 in subjects <6 years of age compared with median ABR of 1.8 in subjects 6 to <12 years of age. The highest bleed rates were recorded for three subjects in the older age cohort: Subjects –b(6)-- (ABR: 10.85), --b(6)-- (ABR: 8.16) and –b(6)--- (ABR: 7.81).

Reviewer comments: In study 250901 (the pivotal study in adult patients for the original BLA), the mean and median ABR in the prophylactic cohort (n=56) was 4.26 (± 5.80) and 1.99, respectively. Thus, the mean ABRs in study 251101 were lower than in study 250901, and the median ABRs were comparable in both studies. The mean and median ABR in the historical on-demand cohort (n=53) were higher than in both studies: 16.92 (± 16.72) and 13, respectively.

Hemostatic efficacy -- Analysis of Bleeding Episodes (BEs)

For bleeding episodes, 14 subjects had a total of 26 BEs after exposure with RIXUBIS. Nine (39.1%) subjects had no BEs: 4 were in the <6 years of age group and 5 were in the 6 to 12 years of age group. Twenty subjects did not experience any spontaneous bleeds or bleeds of unknown cause. The cause of BEs was mostly due to injury.

The hemostatic efficacy at resolution of bleed (using ratings of 'excellent', 'good', 'fair' and 'none') were evaluated for all BEs treated and were analyzed by bleeding site and cause. Table 6 summarizes the rating scale of hemostatic efficacy.

Table 6: Rating Scale for Treatment of Bleeding Episodes

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

The hemostatic efficacy of BEs treated with RIXUBIS was mostly rated "excellent" or "good", with only one rating of "fair" and no ratings of "none". Of 13 BEs with a rating of "excellent", 2 were spontaneous BEs, 10 were caused by injury and 1 had an unknown cause; the 13 BEs comprised one joint BE (14.3% of a total of 7 joint BEs) and 12 non-joint BEs (63.2% of a total of 19 non-joint BEs). All 12 BEs with a rating of "good" were injury-related; these comprised 5 joint bleeds with 1 target joint bleed, and 7 non-joint bleeds. Only one BE (non-target joint bleed caused by injury, treated with 2 infusions at a dose of 77.09 IU/kg each) had a rating of "fair".

6.1.12 Safety Analyses

6.1.12.1 Methods
Descriptive statistics were computed for the safety analyses.

6.1.12.3 Deaths
See Section 6.1.11.1.

6.1.12.4 Nonfatal Serious Adverse Events
See Section 6.1.11.1.

6.1.12.5 Adverse Events of Special Interest
None of the subjects developed FIX inhibitors ≥0.6 BU.

Total binding antibodies of indeterminate specificity to FIX were determined in 6 subjects (2 subjects in <6-year age cohort, 4 subjects in 6-to-<12-year age cohort). Antibodies of indeterminate specificity to rFurin were determined in 2 subjects (in the 6-to-<12-year age cohort). All post-treatment antibody titer increases were <2-dilution steps and therefore considered unrelated to treatment. Antibodies to CHO were not detected in any subject.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Study 251101 was the first pediatric study of RIXUBIS. There were 23 pediatric subjects enrolled in this study, with 12 subjects aged 6 to 12 years and 11 subjects aged < 6 years. Forty-eight AEs occurred in 17 subjects and none of the AEs were considered as treatment-related.

For hemostatic efficacy, pediatric subjects achieved a mean ABR of 3.4 in the 6 to 12 years of age cohort and 1.9 in the <6 years of age cohort. Both cohorts achieved a mean ABR lower than the mean ABR in the adult cohort in study 250901 for the original BLA. There were 26 BEs in this study; 25 BEs treated with RIXUBIS were rated as excellent or good, with only one rating of fair and no ratings of none in hemostatic efficacy.

10.2 Conclusions and Recommendations

Both the safety and hemostatic efficacy analyses in this supplemental biologics license application appear to support the claim for the use of RIXUBIS in the prophylactic treatment of pediatric patients with severe (FIX level <1%) or moderately severe (FIX level 1-2%) hemophilia B. There were no statistical issues in this submission due to the descriptive nature of the analyses.