

Summary Basis for Regulatory Action

Date	June 26, 2013
From	Mikhail V. Ovanesov, PhD, Committee Chair
Subject	Summary Basis for Regulatory Action
BLA #	STN 125446/0
Applicant	Baxter Healthcare Corporation
Date of Submission	30 August 2012
PDUFA Goal Date	30 June 2013
Proprietary Name / Established Name	RIXUBIS™ / Coagulation Factor IX (Recombinant)
Dosage form	Lyophilized powder in 10-mL glass vials of five nominal dosage strengths: 250, 500, 1000, 2000, and 3000 IU per vial. Each vial is reconstituted with 5 mL of Sterile Water for Injection prior to intravenous injection.
Proposed Indications	<ul style="list-style-type: none"> • Control and prevention of bleeding episodes in adults with hemophilia B; • Peri-operative management in adults with hemophilia B; • Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults with hemophilia B.
Recommended Action	Approval
Signatory Authority Action	<p>Jay S. Epstein, MD, OMPT/CBER/OBRR</p> <hr/> <p><i>Offices Signatory Authority</i></p> <p><input type="checkbox"/> <i>I concur with the summary review</i></p> <p><input type="checkbox"/> <i>I concur with the summary review and include a separate review or addendum to add further analysis</i></p> <p><input type="checkbox"/> <i>I do not concur with the summary review and include a separate review or addendum</i></p>

Discipline**Reviewer**

Clinical	Stephanie O. Omokaro
Clinical Pharmacology	Iftekhhar Mahmood
Biostatistics	Jiang Hu
CMC / Product	Mikhail V. Ovanesov, Ze Peng & Yideng Liang
Pharmacology / Toxicology	M. Keith Wyatt & Anne M. Pilaro
Bioresearch Monitoring	Carla Jordan
Establishment Inspection Report	Pankaj Amin, Michael Vardon & Mikhail V. Ovanesov
Labeling	Loan Nyguen & Lisa Stockbridge
Conformance Lot Testing	Lokesh Bhattacharyya & Karen Campbell
Epidemiology	Bethany Baer
Administrative / Regulatory	Edward Thompson & Mark Shields
Administrative	Amy Malla
Advisory Committee	Not presented

1. Introduction

Baxter Healthcare Corporation (Baxter) submitted a biologics license application (BLA) for Coagulation FIX (Recombinant), under the proprietary name RIXUBIS™, for the following proposed indications in adults with hemophilia B: (1) control and prevention of bleeding episodes, (2) peri-operative management and (3) routine prophylaxis to prevent or reduce the frequency of bleeding episodes. The product is currently not licensed or authorized to be marketed in any country.

The recombinant Coagulation FIX (rFIX) is expressed in Chinese Hamster Ovary (CHO) cells, and purified using a process that includes two validated viral inactivation/reduction steps, namely solvent/detergent treatment and nanofiltration. Other than the cell substrate used to express the recombinant protein, no human or animal materials are employed in the manufacture of RIXUBIS™.

2. Background

RIXUBIS was developed for the U.S. market under IND 14488 for control and prevention of bleeding episodes, peri-operative management, and prophylaxis for adults with hemophilia B.

Currently, one rFIX product (BeneFIX®, Wyeth/Pfizer) and several plasma-derived (pd) FIX concentrates and FIX-containing prothrombin complex concentrates (PCC) are licensed in the U.S. and elsewhere for the treatment of patients with hemophilia B. The protein structure and function of RIXUBIS™ are similar, but not identical, to those of the Ala-148 allelic form of pd FIX. Although both RIXUBIS™ and licensed recombinant product are expressed in CHO cells, the manufacturing processes are different. RIXUBIS™ vials are labeled with the actual FIX potency as measured by a one-stage clotting assay in units traceable to the 4th World Health Organization (WHO) International Standard for FIX concentrate, which is a pd preparation.

3. Chemistry, Manufacturing and Controls (CMC)

a) Product Manufacture and Product Quality

The Bulk Drug Substance (BDS) is manufactured at Baxter's multi-product facility in --b(4)---
----- Other than the cell substrate used to express the recombinant protein, RIXUBIS™ is
manufactured without the use of any animal- or human-derived components. The purification
process includes two validated virus inactivation/removal steps, namely solvent/detergent
treatment with a -----b(4)-----
----- and nanofiltration through a 15-nm ---b(4)-----filter.

The rFIX is secreted by a CHO cell line ----b(4)-----

-----b(4)-----

The rFIX is purified by a process of chromatographic steps. ----b(4)-----

The RIXUBIS™ Final Drug Product (FDP) is a lyophilized powder manufactured at Baxter's multi-product facility in ----b(4)-----
to the appropriate strength, formulated, filled in vials, and lyophilized.

Quality by Design (QbD) elements were used in developing the manufacturing process. However, the CMC sections of the BLA are presented as a traditional process validation exercise, and Baxter has not proposed any QbD-associated regulatory approach. For example, the quality of the RIXUBIS™ is controlled with a comprehensive panel of lot release tests that is comparable to that of currently licensed recombinant coagulation factor products.

The manufacturing process is well developed and controlled as evidenced by:

- An established design space within which the manufacturing process is robust in delivering product of consistent yield, purity, and potency. This was demonstrated in a series of small-scale and commercial scale product runs utilizing the *Design of Experiments* concept.
- Identification, validation, and control of critical steps and intermediates throughout the manufacturing process.
- Consistency among over ----b(4)-----

- A subset of representative conformance batches that has been fully characterized by an extensive battery of tests described below.
- Appropriately chosen and validated in-process and lot release tests and their specifications.

Control of Starting Materials

All compendial chemicals used are of --b(4)----- grade, and are purchased from reliable sources. Quality control testing of raw materials not listed in pharmacopeia is performed either by the raw material manufacturer, Baxter or contractors except for identity testing. Identity testing is carried out in Baxter laboratories. USP-grade purified water is produced --b(4)-----
All materials used in the cell culture media are manufactured from raw materials that contain no animal parts, products, or by-products. The safety of the genetically-engineered CHO cell line used to develop the RIXUBIS™ --b(4)----- was extensively characterized ---b(4)-----

transmissible spongiform encephalopathy agents. The viral safety margins of the CHO cell line used for the production of RIXUBIS™ are supported by the virus safety risk assessment.

Viral tests on the –b(4)– for RIXUBIS™ are consistent with International Conference on Harmonisation (ICH) Q5A(R1) guideline. All results for viral testing were negative except for the –b(4)– particles found on –b(4)–. The –b(4)– particles are retrovirus-like particles, and are considered to be nonpathogenic. Moreover, the viral tests, including –b(4)–, for retro- and adventitious viruses were negative at the limit of *in vitro* cell age used for production (–b(4)–). In addition, cell cultures in the manufacturing process are routinely tested for adventitious viruses. These data demonstrate that the potential of contamination by infectious viruses is well controlled for up to –b(4)–.

Additionally, the potential of viral contamination of RIXUBIS™ is mitigated by two dedicated viral clearance steps: Solvent/Detergent (S/D) treatment (–b(4)–), and 15 nm nanofiltration. Baxter has evaluated these and other manufacturing steps in –b(4)– studies. The viruses selected in these studies include –b(4)–.

These model viruses resemble viruses which may have the potential to contaminate the RIXUBIS™ drug product, and represent a wide range of physico-chemical properties in evaluating the ability of the manufacturing process to inactivate or remove viruses. –b(4)–.

These results are sufficient to support the effectiveness of viral clearance in the commercial manufacturing process.

Impurities

The levels of impurities in the product are found to be acceptable and not likely to affect its safety and efficacy as demonstrated in clinical studies. A summary of product evaluation and process validation studies regarding impurity levels is provided in the table below:

[b(4)]
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[

b(4)

]

Specifications

[

b(4)

]

[b(4)]

Notes:

---b(4)-----

The methods and established specifications are acceptable and RIXUBIS FDP release methods and specifications are presented in the table below:

Test method	Specification
--b(4)-----	---b(4)-----
Appearance – Reconstituted Solution	Clear solution, practically free from foreign particles
Reconstitution Time	--b(4)-----
--b(4)-----	--b(4)-----
Endotoxin--b(4)-----	--b(4)-----

Sterility – ---b(4)-----	--b(4)-----
Total Protein	--b(4)----- -----
rFIX Activity – Clotting method [#]	--b(4)----- --b(4)----- --b(4)----- --b(4)----- --b(4)----- ---b(4)----- ----- ----- -----
Specific Clotting Activity of rFIX – Calculation ¹	≥ 200 IU/mg of protein
--b(4)-----	--b(4)-----
rFIX Pre-activation – Calculation ¹	≤ 0.03%
--b(4)----- -----	--b(4)----- --b(4)----- --b(4)-----
--b(4)-----	--b(4)-----
--b(4)-----	--b(4)-----
--b(4)----- -----	--b(4)----- --b(4)-----
--b(4)-----	--b(4)-----
--b(4)-----	--b(4)-----
Polysorbate-80 -----b(4)----- -----	--b(4)-----
--b(4)-----	--b(4)-----
--b(4)-----	--b(4)-----
--b(4)-----	--b(4)-----
Sucrose – --b(4)-----	--b(4)-----
Mannitol – --b(4)-----	--b(4)-----
----b(4)----- ----- ----- -----	

After discussions with FDA, Baxter agreed to tighten the specifications for rFIX pre-activation and rFIX potency based on the available manufacturing data. Furthermore, Baxter conducted additional evaluation of the rFIX pre-activation specification. Activated FIX (FIXa) is a potentially thrombogenic product-related impurity which is found in all FIX-containing products. The level of FIXa is usually controlled at release of FDP with a --b(4)----- test for activated coagulation factors, -b(4)---. For the release of RIXUBIS™, Baxter developed a ---b(4)-----.

Using this and other assays, including the --b(4)-----, lower levels of FIXa were found in RIXUBIS™ lots in comparison to licensed FIX-containing products.

The quality of RIXUBIS™ is further assured by the comprehensive testing panel of BDS release assays. Compared to the FDP, the BDS testing panel evaluates the following additional process-related impurities: --b(4)----- . Although process validation studies demonstrated consistent removal of --b(4)---, Baxter agreed to add -b(4)- as a BDS release test in response to the development of --b(4)-- antibodies in subjects in clinical trials. The --b(4)----- antibodies in subjects were low, and their presence was not associated with any adverse reactions. ---b(4)----- antibodies were observed in some patients before RIXUBIS™ administration as well as in a population of normal healthy individuals. Please refer to the clinical review section of this memorandum for further information on antibody development.

Stability

The available stability data indicate no critical trends during the observed long-term storage period. The data support the proposed shelf-life of RIXUBIS™ for 18 months at $5 \pm 3^\circ\text{C}$. The data also support storage at approximately room temperature (i.e., 25°C or 30°C) for 6 months. The reconstituted product is stable for 3 hours at controlled room temperature.

Stability studies are ongoing and Baxter has committed to placing one commercial lot on stability annually rotating among different dosage strengths.

During the BLA review Baxter reported multiple out-of-specification (OOS) results in potency in the ongoing stability studies. The root-cause for these OOS results was identified as poor robustness of the potency assay. Retesting using a revalidated potency assay showed that the OOS results were incorrect and that all product lots met the stability specifications during stability testing. Adequate performance of the revalidated potency assay has been demonstrated through a series of intra- and inter-laboratory studies.

To exclude uncertainties in potency assignment that might have originated from the lack of robustness of the potency assay, Baxter retested potencies of all available FDP batches used in the pre-clinical and clinical investigations and found that the assay deficiencies had no impact on the outcomes of the clinical investigations, stability studies and manufacturing validation studies. In addition, Baxter used the re-tested potency data for analyses of all the pharmacokinetic data.

b) Exemption from CBER Lot Release

Since RIXUBIS™ is a well-characterized recombinant DNA-derived product, alternatives to official lot release are allowed under the provision described in Federal Register 58:38771-38773. Furthermore, in the Federal Register Notice (60 FR 63048) published on 8 December 1995, the Director of CBER announced that routine lot-by-lot release by CBER is no longer required for licensure of this class of products. The exemption of RIXUBIS™ from lot-by-lot release by CBER is further supported by Baxter's ability to adequately control the manufacturing process and produce a product of established quality.

As part of the review of the BLA, conformance lots of RIXUBIS™ representing the --b(4)-----
----- nominal potencies (---b(4)----- approach) were assayed by CBER for the

There are no ongoing/pending investigations or compliance actions with respect to the Baxter, -b(4)- facility. Therefore, the Office of Compliance and Biologics Quality, Division of Case Management does not object to the approval of this submission.

The inspection of the FDP manufacturing facility at ---b(4)-----
-----was waived based on acceptable compliance records of recent inspections. The -b(4)----- was subject to an FDA CBER-led Level II GMP inspection that occurred on -b(4)----- The scope of the inspection included all licensed manufacturing operations within the facility including -b(4)--- Bulk Manufacturing suites, final product formulation, aseptic filling, finishing, packaging, quality control testing, and quality assurance release of intermediate and final products. The inspection of this site was waived for this BLA. The last inspection of this facility was performed within the two year required window and all significant GMP issues were resolved.

d) Environmental Assessment

Baxter submitted a request for a Categorical Exclusion to omit preparation of an environmental assessment pursuant to 21 CFR 25.31(c). Based on the submitted information and the nature of this product, the Division of Manufacturing and Product Quality concluded that Baxter's request for Categorical Exclusion from an Environmental Assessment under 21 CFR 25.31(c) is justified, as this product is composed of naturally occurring substances. Manufacturing of this product will not significantly alter the concentration and distribution of the natural substance, its metabolites, or degradation products in the environment and no extraordinary circumstances exist that might cause this action to have a significant effect on the quality of the human environment.

Recommendation

The reviewers from the Division of Hematology and the Division of Manufacturing and Product Quality find the information and data on chemistry, manufacturing, and controls for RIXUBIS™ provided by Baxter adequate to support product identity, quality, purity, potency, and safety.

4. Nonclinical Pharmacology/Toxicology

The data from the following nonclinical studies provide evidence for the safety and pharmacologic activity of RIXUBIS™, thereby supporting its approval. The pharmacology, pharmacokinetics and safety of RIXUBIS™ were assessed by conducting: (1) pro-coagulant studies in rats, monkeys, and in human plasma; (2) tail-bleed and carotid occlusion studies in FIX-deficient mice; (3) safety pharmacology in monkeys; (4) thrombogenicity (---b(4)-----) studies in rabbits; (5) pharmacokinetic studies in rats, monkeys, and FIX-deficient mice; (6) acute-dose toxicology studies in mice; (7) general toxicology studies in rats and monkeys; (8) local tolerance studies in rabbits and; (9) a comparative immunogenicity study in mice. A comprehensive safety assessment of excipients used in formulating the final RIXUBIS™ drug product was also performed. In accordance with guidance provided in the ICH S6(R1) *“Guidance to Industry: Preclinical Safety Evaluation of Biotechnology-derived*

Pharmaceuticals,” the carcinogenic, mutagenic, and developmental and reproductive toxic potential of RIXUBIS™ were not evaluated.

Pro-coagulant activity of RIXUBIS™ was demonstrated at clinically relevant doses in a series of nonclinical studies conducted in genetically-modified mice deficient for FIX, and in wild-type rats and monkeys. Results from *ex vivo* studies conducted by mixing RIXUBIS™ and FIX-deficient blood showed reduced clotting times and R values, measured using the --b(4)----- methodology. Similar results demonstrating pro-coagulant activity were generated *in vivo* in carotid occlusion and tail-bleed models conducted in mice deficient for FIX, using RIXUBIS™ doses of 10 -100 IU/kg. Overall, the results indicate the nonclinical blood clotting activity of RIXUBIS™ was comparable to that of other licensed plasma-derived and recombinant Coagulation FIX products.

Safety pharmacology studies conducted in monkeys did not detect any respiratory or other safety signals after a maximum, single RIXUBIS™ dose of 450 IU/kg, or approximately 9-fold greater than the weekly dose of 40 to 60 IU/kg indicated for prophylaxis of bleeding in patients with hemophilia B, when scaled on a body weight basis.

The thrombogenic potential of RIXUBIS™ and the potential effects of rFIXa (activated FIX) impurities in the final product were both evaluated in rabbits. Results from the thrombogenicity (--b(4)-----) assay indicate that RIXUBIS™ was not thrombogenic at a maximum dose of 750 IU/kg which is approximately 10-fold greater than the intended clinical dose. Moreover, results from spiking studies indicated that the levels of the activated rFIX impurity in RIXUBIS™ were acceptable, and present only a minimal risk to patients.

The potential acute toxicity of RIXUBIS™ was evaluated in mice at a maximum dose of 7500 IU/kg; this dose level is approximately 150-fold greater than the weekly dose of RIXUBIS™ indicated for prophylaxis of bleeding in patients with hemophilia B. The single dose toxicity study was followed by dose-escalation and repeat-dose toxicology studies in both rats and monkeys. These studies included an assessment of exposure (toxicokinetics), and evaluated doses of RIXUBIS™ ranging from 200-750 IU/kg, or approximately 4- to 15-fold greater than the intended clinical dose of 40 to 60 IU/kg when scaled on a body weight basis. Results from the dose-escalation and repeat-dose studies showed no remarkable toxicities following administration of either RIXUBIS™ or the comparator recombinant FIX, with the exception of transient clinical signs on study day 23 of hypoactivity, hypothermia and hunched posture in a single male monkey treated with 750 IU/kg BAX 326. Toxicokinetic evaluations confirmed that animals in both studies were continuously exposed to either RIXUBIS or comparator product during the treatment period, with no remarkable differences in the calculated AUC values at day 28 after the final dose, as compared to the AUC values obtained after dosing on study day 1. No binding or neutralizing (i.e. --b(4)-----) antibodies to FIX were detected in rats in the repeat-dose toxicity studies at scheduled necropsy on day 28 following dosing with either dose level of RIXUBIS or with 200 IU/kg/dose of the comparator product. However, positive anti-FIX binding antibody responses were detected in rats in the recovery groups at day 42, specifically in one rat dosed with 200 IU/kg/dose and two rats dosed with 750 IU/kg/dose RIXUBIS™ and in 0/10 rats dosed with comparator product, although the --b(4)----- were negative. By contrast, positive anti-FIX binding antibody responses were

observed in 3/10 and 1/4 comparator product-treated monkeys at days 28 and 42, respectively, and at study day 28 in 2/10 low dose (200 IU/kg/dose) and 1/10 high dose (750 IU/kg/dose) monkeys treated with RIXUBIS. At study day 42, positive binding antibodies were detected in 3/4 low dose and 4/4 high dose, RIXUBIS treated monkeys; however, none of the monkeys with positive anti-FIX binding antibody titers developed neutralizing anti-FIX activity, as measured by the –b(4)----- assay. Based on results from the dose-escalation and repeat-dose toxicity studies, a no observable adverse effect level (NOAEL) for RIXUBIS™ was identified at 750 IU/kg.

An 8-week, repeat-dose study was also conducted in mice to evaluate the immunogenicity of low levels of protein impurities attributable to the CHO cells used to manufacture RIXUBIS™. The results showed that the CHO protein impurity levels were acceptable; they did not induce an anti-CHO cell protein antibody response in mice administered RIXUBIS™ following 8 weekly injections. In a separate local tolerance study, edema and inflammation observed in rabbits administered RIXUBIS™ at a maximum dose of 3650 IU/animal by the intravenous route were also considered acceptable.

Pharmacokinetic (PK) studies were conducted in rats, FIX-deficient mice and wild-type monkeys comparing the exposure profiles of RIXUBIS™ and other previously licensed pd and recombinant FIX products at doses up to 1500 IU/kg. The studies yielded similar areas under the concentration-time curve (AUC), and confirmed that comparable exposures to licensed comparator product and RIXUBIS™ were achieved prior to day 14 during the repeat-dose toxicology studies in rats and monkeys. After study day 14, development of anti-FIX antibodies by either species limited the exposure to both RIXUBIS™ and the licensed comparator product. The comparability of exposures between RIXUBIS™ and licensed comparator product together with the absence of toxicity observed during the repeat-dose nonclinical toxicity studies support the safety of RIXUBIS™ in the on-demand treatment of bleeding episodes, and for perioperative management or prophylactic treatment of patients with hemophilia B.

Results from a comprehensive safety assessment of the excipients present in the RIXUBIS™ final formulation were provided in this submission (BLA 125446/0), and demonstrate that the levels of –b(4)----- and other excipients present in the final drug product impart an acceptable risk to patients.

Recommendation

The results from the nonclinical studies submitted by the Applicant establish the expected biologic activity and predict the safety of RIXUBIS™, thereby supporting its approval for the routine prophylaxis, perioperative management, and control and prevention of bleeding episodes in patients with hemophilia B who are b(4) years of age and older.

5. Clinical

Study Design

The data to support the indications were derived from a Phase 1/3 study that was designed as a prospective, multicenter study in previously treated patients (PTPs) to evaluate the PK parameters, safety, immunogenicity and efficacy.

The study was divided into three parts (see APPENDIX 1):

Part 1 was a randomized, blinded, controlled, crossover study to compare the pharmacokinetic (PK) parameters of RIXUBIS™ with those of a licensed rFIX as measured by the AUC 0-72h /dose with a single dose of 75 ± 5 IU/kg.

The sample size estimate was calculated for a Type-1 (α) error level of 0.05 and a Type-II (β) error level of 0.10 or 90% power, under the assumption that the true (population) means are equivalent. The within subject variability used (the square root of mean square error = 0.233) was estimated by increasing the variance observed in previous studies of FIX by 10%. The sample size was estimated to be 26 evaluable subjects.

Part 2 was an open-label, uncontrolled evaluation of the safety, and efficacy of RIXUBIS™. Subjects received treatment either on-demand or on a prophylactic regimen at 50 IU/kg twice weekly (range 40-60 IU/kg) which could be increased up to 75 IU/kg, if required. Allocation to the on-demand or prophylactic cohort was determined by the investigator and patient based on the patients' individual needs. Randomization was not considered as it is unethical to randomize subjects receiving prophylaxis to an on-demand cohort. The subjects entering both cohorts were required to have an annualized bleed rate of at least 12 bleeding episodes per year prior to enter the study. Subjects treated during Part 1 (PK study) continued treatment during Part 2, and additional subjects were enrolled only for participation in Part 2 (see APPENDIX 2).

The efficacy endpoints assessed during the open-label prophylactic or on-demand treatment with RIXUBIS™ included:

- Treatment of bleeding episodes (BEs):
 - Number of infusions per BE
 - Overall efficacy rating (excellent, good, fair, none) at resolution of bleed
-
- Consumption
 - Number of infusions and weight-adjusted consumption per month and per year.
 - Weight-adjusted consumption per event
- Prophylaxis only: annualized bleeding rate (ABR)

The following safety endpoints were assessed throughout the study:

- Development of inhibitory and total binding antibodies to FIX

- Development of antibodies to Chinese hamster ovary (CHO) proteins and recombinant Furin (rFurin)
- Occurrence of severe allergic reactions, e.g., anaphylaxis
- Occurrence of thrombotic events and changes in thrombogenic markers during the PK parts of the study: prothrombin fragment 1.2 (F 1.2), thrombin-antithrombin III (TAT) and D-dimers.

This study part was powered for evaluation of safety. In order to succeed, no more than one patient could develop inhibitor antibodies. With the sample size of 54 subjects, the upper limit of the 95% CI of the rate of subjects with an inhibitor would be less than 10% if no subject or 1 subject developed an inhibitor during the study.

Hemostatic efficacy was to be performed on a full analysis set. The efficacy of bleeding treatment was summarized on an efficacy rating scale using descriptive statistics.

The annualized rate of bleeding episodes was calculated as: Number of bleeding episodes/observed treatment period in days multiplied by 365. A 50% reduction in the ABR in the prophylactic cohort compared to on-demand cohort was considered as the study success criterion.

Part 3 was an open-label, uncontrolled repeat evaluation of the PK parameters of RIXUBIS™ after 26 ± 1 weeks of treatment in Part 2 in the subjects who participated in Part 1. Subjects had to have a minimum of 30 Exposure Days (ED) to RIXUBIS™ at the time of the PK assessment in Part 3. This study was conducted to show that multiple dosing is not associated with accumulation of product. Decreases in PK parameters would suggest the presence of antibodies that were causing an increase in FIX clearance.

Surgical study;

In addition to the above, a surgery study was performed as an open-label, uncontrolled, multicenter study designed to evaluate efficacy and safety in approximately 30 subjects with severe or moderately severe hemophilia B undergoing major and minor surgical, dental or other invasive procedures. The efficacy endpoint was assessed intra-operatively and post-operatively on a pre-specified hemostatic rating scale. In addition, RIXUBIS™ consumption (daily and total weight-adjusted dose per subject) and blood product use was also captured for efficacy assessment. For subjects undergoing major elective surgery who did not undergo a PK assessment in the pivotal study, PK parameters were assessed.

a) Results

Efficacy

Part 1 and 3

In the PK study, RIXUBIS™ was administered to 27 previously treated patients (15 to 55 years of age) with severe or moderately severe hemophilia B. The patients received 75 ± 5 IU/kg RIXUBIS™ by intravenous infusion. Blood samples for the estimation of PK parameters were collected at regular intervals up to 72 hours, and FIX activity was measured by a one-stage aPTT based clotting assay. The half-life, clearance, and volume of distribution

at steady state were 27 ± 10 hours, 0.06 ± 0.01 dL/kg/hour, and 2.02 ± 0.8 dL/kg, respectively. *In vivo* recovery at 30 minutes was 0.87 ± 0.22 IU/dL:IU/kg.

RIXUBIS™ PK were compared with the PK of a licensed rFIX. The PK of both products were comparable and the 90% confidence interval for $AUC_{(0-\infty)}$ was within the acceptable range of bioequivalence (0.8-1.25).

After 26 weeks of treatment with a minimum of 30 exposure days to RIXUBIS™, the patients who took part in the previous PK study received another infusion of 75 ± 5 IU/kg of RIXUBIS™. Within a 26-week period, these patients had received prophylactic treatment of RIXUBIS™ twice weekly. The dose range was 40-60 IU/kg and was increased up to 75 IU/kg, if required. The PK parameters were comparable between the first dose and multiple dosing (after 26 weeks of dosing) indicating that multiple dosing did not lead to accumulation of RIXUBIS™ in the tissues and that the clearance after a minimum of 30 exposure days was similar to clearance after a single dose. This implied that antibodies that could increase FIX clearance did not develop after multiple dosing.

Part 2

The median age of all 90 subjects in the full analysis set was 33 years (range 12-59 years) and included 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. Only 13 (14.4%) subjects had received prophylactic treatment prior to enrollment, whereas 27 (30%) had received on-demand treatment only and the remainder (55.5%) both. The patient characteristics in the two cohorts were similar for age, race and ethnicity and pre-existing arthropathy.

Prophylaxis

The ABR was analyzed during prophylaxis (n=56) and on-demand treatment (n=14) in a total of 70 subjects. The median treatment duration was 6 months (range: 4.73 to 9.13 months) in the prophylactic cohort (n=56) and 3.3 months (range: 1.18 to 4.86 months) in the on-demand cohort (n=14). In the prophylactic cohort, the mean number of exposure days was 55.8 ± 7.6 and the median was 54. Fifty-two (92.9%) of 56 subjects had 50 or more exposure days.

The median dose per prophylactic infusion was 50.5 IU/kg. The ABR resulting from twice-weekly prophylactic treatment with RIXUBIS™ was calculated and compared to the ABR of patients from a historical control treated on-demand instead of the subjects enrolled in the on-demand arm of the study. The mean ABR during prophylaxis was 4.20. This was a 75% reduction compared to the mean ABR of 20 for on-demand treatment in the historical control group. Patients with arthropathy at study entry was associated with a higher ABR. Forty eight subjects had arthropathy at screening and a mean ABR of 3.2 compared to an ABR of 1 in the remaining subjects who had no arthropathy.

In the on-demand arm of the study the mean annual bleed rate was 35.19 ± 19.22 , i.e. 38% greater than the mean historical on-demand rate of 20. This difference between the mean

historical on-demand bleeding rate and the mean annual on-demand bleed rate observed during the study may be attributed to differences in the characteristics of the subjects within the study.

Annualized Bleeding Rate Comparison (Full Analysis Set)			
	Parameter	Prophylaxis	Historical Control
Annualized Bleed Rate	N	56	276
	Mean	4.20	20.0
	95% C.I.	2.66, 5.74	5.3, 24.6

On-Demand Treatment of Bleeding Episodes

Patients in the prophylaxis cohort with breakthrough bleeds were treated with the same dosing regimen as subjects in the on-demand cohort. In subjects who received prophylactic treatment (n=56), 113 BEs were reported in 32 subjects. In subjects who received on-demand treatment (n=14), 124 BEs occurred. By site and causality for all bleeds, 79% were joint bleeds, 21% were non-joint, 52% were spontaneous, 36% traumatic, and 12% were of unknown cause. Sixty-one percent of all bleeds required one infusion, 23% were treated with 2 infusions and 16% required more than 3 infusions.

For each bleeding episode, subjects were trained to record the efficacy of RIXUBIS™ on a pre-specified four point scale of excellent to poor, in subject diaries provided by Baxter. These diaries were reviewed by the investigator at each study visit. Two percent of the bleeding episodes were reported as not rated for efficacy due to subject non-reporting. Of those that were reported, 41% were rated as excellent, 55% as good, and 2% as fair and 2% were not rated. The mean total dose per bleed was 83.83 ± 58.82 IU/kg (median: 62.29 IU/kg). Three subjects were treated with more than 300 IU/kg for a gastroduodenal ulcer bleed; a knee bleed secondary to injuries; as well as an elbow bleed of unknown cause. Review of the case reports showed that the dose corresponded to the type of bleed and severity and did not reveal any lack of effect. The subject with the elbow bleed had an indeterminately positive antibody to Furin 2 months prior to the bleed but was negative when assessed 1 month after the bleed. No inhibitors or other antibodies were observed in these 3 subjects.

Peri-operative prophylaxis during surgery

The efficacy of RIXUBIS™ to control bleeding during surgery was evaluated according to the surgeon's assessment of: a) estimated blood loss intra-operatively, b) post-operative blood loss, c) hemostatic efficacy intra-operatively and d) hemostatic efficacy post-operatively. Data from 14 surgeries conducted in 14 subjects were submitted in the BLA. The surgical procedures included 11 major surgeries and 3 minor procedures. Perioperative FIX replacement was by bolus infusion. Continuous infusion was not evaluated in the study.

Subjects who had major surgery including joint replacement, open synovectomy, excision of neurofibroma, and hernioplasty received bolus infusions at an initial pre-surgery dose of 134-296 IU/kg with subsequent dosing from 20-237 IU/kg. The mean incremental recovery at 30 minutes was 1.06 IU/dL.

The efficacy was assessed on a pre-specified four point rating scale in the peri-operative period. In addition, actual intra-operative blood loss was compared to average and maximum blood loss predicted preoperatively by the operating surgeon. Hemostasis control and blood loss were rated as excellent or good in all procedures and acceptable FIX levels were achieved in the peri-operative periods. Transfusion support was required in 4 subjects who underwent orthopedic surgery and had a mean post-operative blood loss of 704 mL which is expected for this type of surgery in individuals with normal clotting factor levels.

Efficacy of RIXUBIS™ for Surgical Procedures

Procedure (category, number of subjects)	Assessment of Response		
	Intra-operative	At time of drain removal or on post-operative day 3	At time of discharge
Removal of intramedullary nail (Major, n=1)	Excellent	Good	Excellent
Joint replacement (Major, n=5)	Excellent	Good (3) Excellent (2)	Excellent (3) Good (2)
Open synovectomy (Major, n=1)	Excellent	Excellent	Excellent
Neurofibroma excision (Major, n=1)	Excellent	Excellent	Excellent
Hernioplasty (Major, n=2)	Excellent	Excellent	Good (1) Excellent (1)
Tooth extraction (Major, n=1)	Excellent	Excellent	Excellent
Tooth extraction (Minor, n=2)	Excellent	Excellent	Excellent
Intra-articular injection (Minor, n=1)	Excellent	Not applicable	Excellent

Efficacy conclusions:

The outcomes from the study support efficacy of RIXUBIS™ in adult hemophilia B for control and prevention of bleeding, peri-operative management and routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

6. Safety

During the clinical development (including the ongoing continuation and pediatric study, data lock date of September 2012) 91 PTPs had received at least one infusion of RIXUBIS™ as part of either on-demand treatment of bleeding episodes, peri-operative management, routine prophylaxis, or PK evaluation of RIXUBIS™. Six subjects (6.6%) were <6 years of age, 10 (11%) were 6 to <12 years of age, 3 (3.3%) were adolescents (12 to <16 years of age), and 72 (79%) were adults (16 years of age and older). The subjects received a total of 7,353 infusions with a median of 85 infusions of RIXUBIS™ (range 3 to 212 infusions), for a median of 83 exposure days per subject.

There were no deaths reported during the study. A total of 161 adverse events (AE) were reported in 48 (52.7%) of the 91 subjects. Of these AEs, 6 AEs in 5 patients were considered serious. All 6 of the serious adverse events (SAEs) were considered by the investigator and the clinical reviewer to be unrelated to RIXUBIS™.

Serious Adverse Events from RIXUBIS™ Clinical Trials¹

Preferred Term	Study	Severity	Relatedness to RIXUBIS™
Duodenal ulcer hemorrhage	251001	Severe	Not related
Intestinal obstruction	250901	Severe	Not related
Cervical vertebral fracture	250901	Severe	Same patient for both AEs. Not related – motor vehicle accident
Traumatic hematoma	250901	Severe	
Convulsion	250901	Moderate	Not related
Hepatitis B core antibody positive	250901	Mild	Not related

¹

The patient with the duodenal ulcer had a gastrointestinal bleed 1 day after treatment with RIXUBIS™. He was treated with an additional dose of RIXUBIS™ and the bleeding was controlled. He continued on prophylactic RIXUBIS™.

The patient with the intestinal obstruction was found on laparotomy to have a foreign body (impacted vegetable fibers). Thus, this AE was determined to be unrelated to RIXUBIS™.

The subject with the cervical vertebral fracture and the traumatic hematoma sustained the injuries as a pedestrian hit by a motor vehicle. He received emergency treatment with a comparator product and was thus withdrawn from the study due to receipt of a non-investigational product.

The patient with the convulsion had a history of seizures diagnosed 4 years prior to study participation. The patient typically had 1-2 seizures per year. He had a seizure several hours following RIXUBIS™ administration. The study investigator considered that his seizure was due to his pre-existing seizure disorder.

The patient who tested positive for Hepatitis B core antibodies had a history of chronic persistent hepatitis B.

There were 155 non-serious AEs in the clinical program. Adverse reactions that occurred in >1% of subjects are shown in Table below.

Summary of Adverse Reactions

System Organ Class	Adverse Reactions (AR)	Number of ARs (N)	Number of Subjects (N=91) n (%)	Percent per Infusion (N=7353)
Nervous System Disorders	Dysgeusia	2	1 (1.1%)	0.03%

Summary of Adverse Reactions

System Organ Class	Adverse Reactions (AR)	Number of ARs (N)	Number of Subjects (N=91) n (%)	Percent per Infusion (N=7353)
Musculoskeletal and Connective Tissue Disorders	Pain in extremity	1	1 (1.1%)	0.01%
Investigations	Furin antibody test positive ^a	1	1 (1.1%)	0.01%
	FIX or Furin antibodies of indeterminate specificity ^a	9	7 (7.7%)	0.12%

^a See Immunogenicity.

Immunogenicity

All 91 subjects were monitored for inhibitory and binding antibodies to FIX, and binding antibodies to CHO impurities and Furin, at the following time points: at screening, at 72 hours following the first infusion of RIXUBIS™ and the commercial recombinant FIX product in the cross-over portion of the pharmacokinetic study, after 5 and 13 weeks following first exposure to RIXUBIS™, and thereafter every 3 months. Antibodies against Furin were tested by an in-house enzyme-linked immunosorbent assay (ELISA). A titer of 1:20 or 1:40 was considered to be indeterminate for the above validated assay, as these titers were too low to be verified by the confirmatory assay.

No subjects developed neutralizing antibodies to FIX. Thirteen subjects (14.3%) developed low-titer, non-neutralizing antibodies against FIX at one or more time points. Two of these 13 subjects were found to have these antibodies at screening, prior to receiving RIXUBIS™. No clinical adverse findings were observed in any of these 13 patients.

Thirteen subjects (14.3%) had signals for antibodies against Furin of indeterminate specificity. Four of these 13 subjects expressed signals for antibodies at screening, prior to RIXUBIS™ treatment. An additional subject had an antibody signal after treatment with the comparator product and prior to RIXUBIS™ treatment. Another additional subject had a positive titer of 1:80 that was not present when checked at a later time-point and therefore considered transient. A second subject had a positive antibody signal after the data cutoff date that also was transient. No clinical adverse findings were observed in any of these 15 patients.

In order to assess the significance of the development of antibodies against Furin, Baxter conducted a study on prevalence of Furin antibodies in healthy individuals. In this study, 500 normal volunteers were tested using the same anti-Furin assay as was used in the clinical studies. Seven per cent had titers of 1:20 or 1:40 and 1.2% had higher titers ranging from 1:80 to 1:320. These are thought to be naturally occurring antibodies. To date, these antibodies have not been associated with any clinical adverse findings.

Thrombogenicity

There was no clinical evidence of thromboembolic complications in any of the subjects. Out-of-range values for thrombogenicity markers (thrombin-antithrombin III, prothrombin fragment 1.2, and D-dimer), determined during the PK portion of the combined study, did not reveal any pattern indicative of thrombogenicity with either RIXUBIS™ or a comparator FIX-containing product.

Hypersensitivity (Including Anti-CHO Antibodies)

There were no severe allergic reactions and no antibodies to CHO detected in any clinical study subject before or after treatment.

Viral Transmission: RIXUBIS™ is synthesized in a genetically engineered CHO cell line which reduces the risk of transmission of infective agents such as viruses. The manufacture of RIXUBIS™ also includes two viral inactivation/reduction steps (solvent/detergent treatment and nanofiltration). One patient in the clinical studies was reported to have an AE involving a positive hepatitis B core antibody test. However, this subject was known to have a history of chronic persistent hepatitis that preceded his enrollment in the study.

Safety Conclusions:

The safety profile of RIXUBIS™ is acceptable.

b) Pediatrics

Safety and efficacy in children has not been established. A pediatric study is ongoing with 16 subjects <12 years currently enrolled. A Pediatric Research Equity Act (PREA) deferral was requested and granted for all pediatric ages. The Pediatric Review Committee (PeRC) agreed with the deferral request.

c) Other Special Populations

Not studied

Bioresearch Monitoring Summary

CBER Bioresearch Monitoring (BIMO) issued high-priority inspection assignments at four different clinical sites in Europe. There were no domestic sites enrolled for this study. Four clinical investigator inspections were performed. Study subject enrollment and previous inspection history were among the factors used to select the inspected sites. The inspections focused on specific questions concerning the study protocol and the comparison of data submitted in the BLA to source documents. The BIMO inspections did not reveal any problems that would impact the data submitted in the BLA.

6. Advisory Committee Meeting

There were no issues related to this product that prompted the need for discussion by the Blood Products Advisory Committee (BPAC). FDA has determined that referral of this application to the BPAC prior to approval (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]) was not needed for the following reasons:

- The mechanism of action and function of FIX (FIX) in the blood coagulation cascade are well studied and understood. RIXUBIS™ is identical in amino acid sequence and structurally similar to plasma-derived (pd) human FIX. *In vitro* and *in vivo* biochemical and functional characterization of RIXUBIS™ demonstrated that its hemostatic activities are comparable to those of human pd and recombinant FIX. Currently, one recombinant FIX and several pd FIX-containing products are licensed in the U.S.
- Evaluation of the safety data in RIXUBIS™ clinical studies did not reveal unexpected safety issues. The study design to evaluate efficacy of RIXUBIS™ was adequate, and the results of the study did not raise any concerns related to its safety and efficacy.
- Products manufactured by recombinant DNA technology may provide additional safety assurance regarding adventitious agents. Manufacture of RIXUBIS™ includes solvent/detergent treatment and nanofiltration steps for viral clearance.
- Review of the information submitted in the BLA for RIXUBIS™ did not raise any controversial issues or pose unanswered scientific questions which would have benefited from advisory committee discussion and recommendations.

7. Other Relevant Regulatory Issues

There were no other regulatory issues observed during the review of this BLA.

8. Labeling

The proposed proprietary name of the product, RIXUBIS™, was determined to be acceptable. A copy of an acceptable Full Prescribing Information (FPI) is attached as Appendix 1. Carton and container labels submitted to BLA were considered acceptable.

The FPI was reviewed by the BLA team, including Advertising Promotional Labeling Branch, during the labeling review meeting on April 1, 2013. Initial comments regarding product promotion and labeling comprehension were conveyed to Baxter on April 19, 2013. Baxter provided a response on April 30, 2013. Additional comments were sent to Baxter on May 17, 2013.

9. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review committee recommends the approval of the BLA for Coagulation FIX (Recombinant), under the proprietary name of RIXUBIS™, for the following indications to treat adults with hemophilia B: (1) control and prevention of bleeding episodes, (2) peri-operative management and (3) routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

b) Risk/ Benefit Assessment

Hemophilia B is a blood clotting disorder caused by a mutation of the FIX gene, leading to a deficiency of FIX. Hemophilia B patients are at risk for acute bleeding episodes predominantly into joints, muscles, mucosa, body cavities, and central nervous system (CNS). The bleeding episodes can lead to disabling joint disease and may be life threatening. RIXUBIS™ temporarily replaces the missing clotting FIX needed for effective hemostasis in patients with Hemophilia B.

Benefits:

The efficacy of RIXUBIS™ has been established for control and prevention of bleeding episodes, peri-operative management and routine prophylaxis to prevent or reduce the frequency of bleeding episodes, in clinical studies that enrolled 91 subjects. The PK profile of RIXUBIS™ is comparable to that of a rFIX product that has been licensed for 15 years.

Risks:

RIXUBIS™ is a recombinant product synthesized by a genetically engineered well characterized CHO cell line. The manufacturing process includes two validated viral clearance steps. Other than the cell substrate, no materials of human or animal origin are employed in the manufacture, purification, or formulation of the final product, thereby reducing the risk of transmission of adventitious agents.

No subjects developed neutralizing antibodies, allergic reaction or thromboembolic complications. In addition, all 6 SAEs were considered unrelated to RIXUBIS™. Therefore, the safety profile of RIXUBIS™ is acceptable.

Neutralizing antibodies (inhibitors) are known to occur in PTPs treated with FIX containing product. Even though no subjects developed neutralizing antibodies to FIX in the pivotal clinical study, the potential for developing inhibitors is discussed in the Warnings and Precautions section of the Package Insert (PI).

As there have been reports in the literature showing an association between the occurrence of a FIX inhibitor and allergic reactions, the PI discusses the potential for allergic/hypersensitivity reactions in the Warnings and Precautions section. However, no subjects developed anaphylaxis or allergic symptoms in the pivotal clinical study.

Thirteen of 91 patients (14.3%) developed low-titer, non-neutralizing antibodies against FIX at one or more time points. Two of the 13 patients were found to have these antibodies at screening, prior to receiving RIXUBIS™. However, no clinical adverse findings were observed in any of these 13 patients. PK evaluations conducted after the development of these antibodies were within normal limits.

Thirteen of the total 91 subjects (14.3%) were found to have antibodies against Furin of indeterminate specificity. Two additional subjects developed specific anti-Furin antibodies. No clinical adverse findings were observed in any of these 15 patients. Their PK evaluations were within normal limits. The applicant concluded that anti-Furin antibodies may be naturally occurring based on the finding of these antibodies in a study of healthy individuals (see Safety Section).

In conclusion, the observation of low-titer binding antibodies was not associated with any adverse clinical findings including lack of therapeutic effect, or alterations in pharmacokinetics.

Overall, the risk benefit profile of RIXUBIS™ is favorable.

c) Recommendation for Postmarketing Risk Management Activities

The epidemiology reviewer identified no new safety issues arising from the clinical database for RIXUBIS™. This product is similar to a rFIX product made in CHO cells that has been licensed in the U.S. for over 15 years. There were no safety signals identified during the RIXUBIS™ clinical studies. With a data lock date of Sept. 3, 2012, the RIXUBIS™ clinical program included 91 treated patients and no observations of FIX inhibitor development, CHO-antibody development, severe allergic reactions, thrombotic events, or other unexpected events. Two study subjects developed anti-Furin antibodies above the confirmatory threshold level. However, these were not associated with adverse events. The sponsor acknowledges and documents in the package insert that there are insufficient safety data for use in children <12 years old, elderly patients (≥65 years old), pregnant and lactating women, or for use as continuous infusion for peri-operative management or immune tolerance induction.

The pharmacovigilance plan which includes routine pharmacovigilance, quarterly periodic adverse event reports for three years, 15-day expedited reports for serious, unlabeled adverse events, and completion of the pediatric study is adequate to monitor the safety of RIXUBIS™ postmarketing. The potential risks are outlined in the package insert under Contraindications and Warnings and Precautions sections. The reviewed safety data do not substantiate a need for a post-marketing requirement (PMR) or REMS.

d) Recommendation for Postmarketing Activities:

1. Baxter agreed to evaluate long-term efficacy and safety of RIXUBIS™ in 100 patients of all age groups with hemophilia B (as part of the continuation study), of which at least 25 subjects will be naïve to RIXIBIS™. Baxter has committed to the following timelines:

Final protocol submission date: July 31, 2013

Study/trial completion date: December 31, 2015

Final Report Submission date: June 30, 2016

2. Baxter commits to providing validation data to support the *Precision (Repeatability and Intermediate Precision)*, *Linearity* and *Range* for the test method, *Method No.* --b(4)-----, used to determine the ---b(4)----- in RIXUBIS™. Baxter will apply an approach similar to that used for --b(4)----- determination in validation report --b(4)-----, and will submit the final report to the FDA by November 30, 2013.
3. Baxter commits to place at least one RIXUBIS™ lot on the stability program annually, rotating among different dose strengths.

APPENDIX 1

Listing of Clinical Studies in the BAX326 Clinical Development Program					
Study Number	Type of Study	Study Status	Subjects in ISS	Criteria	Dose Range and Frequency
250901	Pivotal Phase 1/3	Completed	73	PTP 12 to 65 y	Prophylactic treatment: 50 IU/kg twice weekly, (range: 40 to 60 IU/kg) which may be increased up to 75 IU/kg twice weekly, or on-demand treatment
251001	Continuation Phase 3	Ongoing	14	PTP 12 to 65 y or < 12 y for	Prophylactic treatment: 50 IU/kg twice weekly, (range: 40 to 60 IU/kg) which may be increased up to 75 IU/kg twice weekly in subjects \geq 12 years of age; (range: 40-80 IU/kg) in pediatric subjects < 12 years)
251002	Surgery Phase 3	Ongoing	3	PTP Meets criteria for 250901, 251001, or 251101, or 12 to 65 y	Surgical prophylaxis: The dose will be tailored 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	Ongoing	1	PTP < 12 y	Prophylactic treatment: 50 IU/kg twice weekly, (range: 40 to 80 IU/kg), treatment of Acute bleeding episodes

APPENDIX 2

