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CBER Received Date	August 30, 2012
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Division / Office	DH /OBRR
Priority Review	No
Reviewer Name(s)	Stephanie O. Omokaro, MD
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Baxter Healthcare Corporation
Established Name	Coagulation Factor IX (Recombinant)
(Proposed) Trade Name	Rixubis
Pharmacologic Class	Coagulation factor
Formulation(s), including Adjuvants, etc	Intravenous injection
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder for Injectable Solution, Intravenous
Dosing Regimen	Calculated by body weight. Available in 250, 500, 1000, 2000, 3000 IU single use vials
Indication(s) and Intended Population(s)	Control and prevention of bleeding episodes in adults 16 years or older with hemophilia B Perioperative management in adults 16 years or older with hemophilia B Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults 16 years or older with hemophilia B

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Glossary

Abbreviation	Definition
ABR	Annualized bleeding rate
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
aPTT	Activated partial thromboplastin time
AUC	Area under the plasma concentration versus time curve
AUC _{0-72 h}	Area under the plasma concentration versus time curve from 0 to 72 hours post-infusion
AUC _{0-∞} or AUC _{0-inf}	Area under the plasma concentration versus time curve from time 0 to infinity
BDS	Bulk Drug Substance
BE	Bleeding episode
BU	Bethesda Unit
CHO	Chinese hamster ovary
CIC	Circulating immune complexes
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CRM	Cross-reacting material
CRT	Case report tabulation
CTM	Clinical Trial Material
DIC	Disseminated intravascular coagulation
DMC	Data Monitoring Committee
eCRF	Electronic case report form
EC	Ethics committee
ED	Exposure day
EDCS	Electronic data capture system
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency

Abbreviation	Definition
ER	Emergency room
FAS	Full Analysis Set
FDP	Finished Drug Product
FIX	Factor IX
GCP	Good clinical practice
GP	General practitioner
h	Hour(s)
HAV	Hepatitis A virus
anti-HBs	Antibody to hepatitis B surface antigen
anti-HBc	Antibody to hepatitis B core antigen
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRP	Horseradish peroxidase
HR QoL	Health-related quality of life
hs-CRP	High-sensitive C-reactive protein
ICF	Informed consent form
ICH	International Conference on Harmonisation
iCSR	Interim clinical study report
Ig	Immunoglobulin
INR	International normalized ratio
IP	Investigational product
IR	Incremental recovery
ITI	Immune tolerance induction
IU	International units
IVRS	Interactive Voice Response System
LSO	Last subject out
MRT	Mean residence time
MRL	Master Randomization List

Abbreviation	Definition
NOAEL	No observable adverse event level
PK	Pharmacokinetic
PKFAS	Pharmacokinetic Full Analysis Set
PKPPAS	Pharmacokinetic Per Protocol Analysis Set
PTP	Previously treated patients
SAE	Serious adverse event
SAER	Serious adverse event report
SIC	Subject identification code
SOC	System organ class
SPC	Summary of product characteristics
STD	Standard deviation
SWFI	Sterile water for injection
TAT	Thrombin-antithrombin
T _{1/2}	Elimination phase half-life
VAS	Visual analog scale
V _{ss}	Volume of distribution at steady state

Page numbers: All page numbers in this document refer to the electronic page number from the digital documents as numbered by Adobe Acrobat.

1. Executive Summary

Rixubis (BAX326) is a lyophilized recombinant human factor IX manufactured in Chinese hamster ovary (CHO) cells. Rixubis is intended for intravenous administration as a replacement therapy or prophylaxis for adult patients 16 years or older with hemophilia B, including control and prevention of bleeding episodes, peri-operative management and routine prophylaxis.

Data from a single combined phase 1/3 study that included subjects on prophylactic and on-demand treatment as well as subjects undergoing surgery were submitted in support of licensure for the proposed indications. The clinical development program for Rixubis included a randomized cross-over comparative PK study with BeneFIX; a non-randomized open-label treatment phase where subjects received either prophylaxis or on-demand treatment for at least 50 exposure days (ED), and a peri-operative prophylaxis study. A study in pediatric subjects is ongoing and complete data is not yet available.

A total of 86 subjects were enrolled in one or more study phases and 73 of these subjects were used for analysis of safety and efficacy in the treatment phase. Overall, Rixubis was effective in preventing bleeding in hemophilia B subjects with a twice weekly prophylactic dose. The majority

of subjects were dosed with 40-60 IU/kg twice weekly with a mean annualized bleeding rate of 4.26 in the prophylaxis arm (N=56) and 33.87 in the on-demand arm (N=14).

The adverse event profile of Rixubis was most commonly low-titer binding antibodies to FIX and/or rFurin (8-18%) of no clinical significance, nasopharyngitis (9%), pharyngitis (5.5%), pyrexia (4.4%) and arthralgia (4.4%).

Although formation of FIX inhibitors was not observed, non-neutralizing FIX antibodies of low-titer were seen in 12 subjects at any time-point other than screening and similarly development of low-titer anti-rFurin antibodies was seen in 16 subjects (N=91 including subjects in continuation study). These findings were transient in some subjects especially when considering only those who were positive at the time of data cut-off. At data cut-off, there were 7 subjects positive for rFurin antibody and no subjects with binding FIX antibody. FIX and rFurin antibodies were considered of indeterminate specificity by Baxter because they were below the threshold pre-specified for positivity and within the limits of assay variability. In order to further evaluate the potential clinical significance of these antibodies and to conduct a root cause analysis of this finding, a risk analysis assessment addressing potential safety concerns was requested from Baxter. Healthy subject data provided by Baxter using the same assay in the pivotal study demonstrated similar reactivity without exposure to the investigational product. Additionally, the risk assessment analysis showed no associated clinical findings including no adverse events, lack of therapeutic effect or alterations in pharmacokinetics in study subjects that developed these low-titer antibodies.

The potential consequences of an immune reaction can range from development of binding antibodies without any clinical significance to rare but severe life-threatening conditions, including allergic reactions. The benefit to risk profile for Rixubis remains favorable despite the low titer non-inhibitory binding antibodies to FIX and rFurin as there was no observed clinical significance. Postmarketing pharmacovigilance through implementation of a cohort event monitoring safety and efficacy PMC study is recommended for approval.

Recommendation:

An approval is recommended.

Letter-Ready Comments:

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia B (Christmas disease) is a rare hereditary blood disorder caused by deficiency or dysfunction of factor IX resulting in bleeding secondary to abnormal clot formation. The hemophilia B gene is located on the X chromosome with an X-linked recessive inheritance pattern, affecting 1 in 100,000 male births and rare females.

4.2 Table of Studies/Clinical Trials

The clinical trial is summarized in the Table below

<p>Table 1 Listing of Clinical Studies in the BAX326 Clinical Development Program</p>					
Study Number	Type of Study	Study Status	Subjects in ISS ^a	Criteria	Dose Range and Frequency
250901	Pivotal Phase 1/3	Operationally completed	73	PTP 12 to 65 y	<u>Prophylactic treatment</u> : 50 IU/kg twice weekly, (range: 40 to 60 IU/kg) which may be increased up to 75 IU/kg twice weekly, or <u>On-demand treatment</u> : per Protocol 250901 Section 8.6.3.2 . <u>Acute bleeding episodes</u> : to be treated with BAX326 per 250901 Protocol Section 8.6.3.2 .
251001	Continuation Phase 3	Ongoing	44	PTP (completed 250901) 12 to 65 y for 250901 or < 12 y for 251101	<u>Prophylactic treatment</u> : 50 IU/kg twice weekly, (range: 40 to 60 IU/kg) which may be increased up to 75 IU/kg twice weekly in subjects ≥ 12 years of age; (range: 40-80 IU/kg) in pediatric subjects < 12 years); <u>Modified prophylaxis</u> : determined by the investigator; or <u>On-demand treatment</u> <u>Acute bleeding episodes</u> : to be treated with BAX326
251002	Surgery Phase 3	Ongoing	3	PTP Meets criteria for 250901, 251001, or 251101, or 12 to 65 y	<u>Surgical prophylaxis</u> : 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	<u>Prophylactic treatment</u> : 50 IU/kg twice weekly, (range: 40 to 80 IU/kg) <u>Acute bleeding episodes</u> : to be treated with BAX326

^aData cut-off was 2012 Mar 27 for pivotal study 250901 and 2012 23 Mar for ongoing studies 251001, 251002 and 251101.

4.3 Consultations

No consultations were requested by the clinical team.

4.4 Advisory Committee Meeting (if applicable)

N/A

4.5 External Consults/Collaborations

N/A

5. Applicable Literature

Montgomery RR, Gill JC, Scott JP. Hemophilia and von Willebrand's Disease (2003). In: Nathan and Oski's Hematology of Infancy and Childhood, 6th, Nathan DG, Orkin SH, Ginsberg D, Look AT (Eds), WB Saunders, Philadelphia.

European Medicines Agency. (2011, July 21). Guideline on clinical investigation of recombinant and human plasma-derived factor IX products (EMA/CHMP/BPWP/144552/2009). Retrieved from <http://www.ema.europa.eu>

Xue, L., Johnson, R., & Gorovits, B. (2010). Prevalence and isotypic complexity of the anti-chinese hamster ovary host cell protein antibodies in normal human serum. *The AAPS Journal*, 12(1), 98-106.

Guidelines for the Management of Hemophilia (2005). *World Federation of Hemophilia*, www.wfh.org.

Bullinger, M., Globe, D., Wasserman, J., Young, N.L., & von Mackensen, S. (2009). Challenges of Patient-Reported Outcome Assessment in Hemophilia care- a State of the Art Review. *Value In Health*, 12(5), 808-820.

Johnson, K.A. & Zhou, Z-Y. Cost of care in Hemophilia and Possible Implications of Health Care Reform. ASH Education Book (2011), 413-418. *American Society of Hematology*, <http://asheducationbook.hematologylibrary.org/content/2011/1/413.full.pdf>

Bourne, G.L. & Grainger, D.J. (2011). Development and characterization of an assay for furin activity. *Journal of Immunological Methods*, 364, 101-108.

Wasley, L.C. et al. (1993). PACE/Furin can process the vitamin K-dependent pro-factor IX precursor within the secretory pathway. *The Journal of Biological Chemistry*, 268(12), 8458-8465.

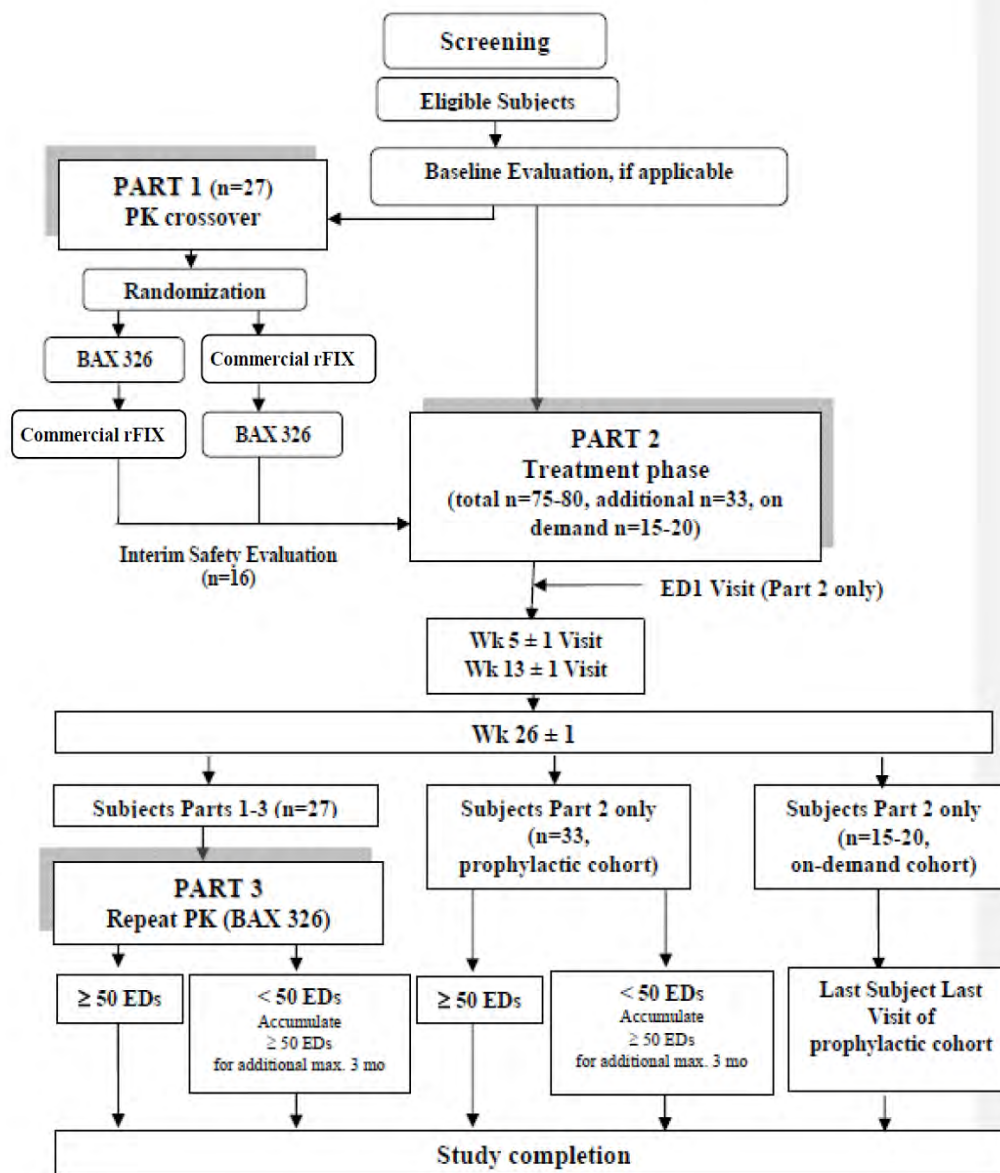
Ornatowski, W. et al. (2007). Elevated furin levels in human cystic fibrosis cells result in hypersusceptibility to exotoxin A-induced cytotoxicity. *The Journal of Clinical Investigation*, 117(11), 3489-3497.

Saenko, E.L. et al. (2002). The future of recombinant coagulation factors. *Journal of Thrombosis and Haemostasis*, 1, 922-930.

6. Discussion of Individual Studies/Clinical Trials

The trial provides data as of the cut-off date of March 27, 2012 on the pivotal study and March 23, 2012 for the surgery, pediatric and continuation studies. A schematic of the pivotal trial design is depicted in the figure below.

Study Design for Baxter Clinical Study 250901 (Pivotal)



[Source: BLA 125446/0 Full Clinical Study Report Amendment 3]

6.1 Trial #1

Pharmacokinetic Study, Rixubis, in Subjects with Hemophilia B

No safety issues were identified in this study.

The pharmacokinetic (PK) results are covered in the review conducted by clinical pharmacology.

6.1.1 Objectives (Primary, Secondary, etc)

To evaluate the pharmacokinetic parameters for Rixubis in previously treated subjects with hemophilia B, compare them with Benefix, determine PK equivalence and gather initial human safety data.

6.1.2 Design Overview

The phase 1 study is a dual arm, randomized, blinded crossover study (Part 1). Rixubis or BeneFIX were given in randomized order to non-bleeding subjects, separated by at least 5 days but preferably 7 days of washout and up to a maximum of 28 days. Identical single intravenous doses of 75 ± 5 U/kg were administered. The PK study was repeated (Part 3) in subjects who participated in Part 1 and had accumulated at least 30 EDs to Rixubis during the treatment phase (Part 2).

Factor IX levels and evidence of prior inhibitor development were gathered prior to infusion. Clinical and laboratory assessments were analyzed for the presence of safety signals. These included thrombotic markers (D-dimer, F1+2, and TAT) that were evaluated pre-infusion and at multiple times post infusion.

6.1.3 Population

Requirements for this study included severe (FIX activity <1%) or moderately severe (FIX activity 1-2%) deficiency. Subjects also had at least 150 prior exposure days with a FIX product.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Single 75 U/kg intravenous doses of Rixubis and BeneFIX were administered and evaluated sequentially. Only 500 IU potency vials from a single lot were used per PK infusion. No other products were specified by the protocol.

6.1.5 Directions for Use

A single intravenous dose of FIX product was given for each arm. An unblinded pharmacist or infusionist gave the drug. Other study personnel were blinded. No other special instructions were used.

6.1.6 Sites and Centers

The trial was a multi-investigator, multicenter, international study. Sites from Europe (Bulgaria, Czech Republic, Germany, Poland, Romania, Spain, Sweden, UK, Ukraine), Russia, South America (Argentina, Brazil, Chile, Colombia) and Japan were included.

6.1.7 Surveillance/Monitoring

The safety of this study was reviewed by an independent data and safety monitoring board (DSMB), composed of 5 experts in the field of hemophilia clinical care and research as well as an independent biostatistician who met at least annually at specified time points for data review including June 8, 2011 for review of PK data. Screening assessments were provided in Table 21.3 (see below) in amendment 7 of the protocol document. Physical examinations, medical histories, and concomitant medications were assessed. Adverse events and vital signs were recorded at each PK time point. The total duration for PK assessment was 72 hours, with evaluation of thrombogenicity pre- and post-infusion.

21.3 Schedule of Study Procedures and Assessments

Procedures/ Assessments	Screening Visit	Baseline ^a	Part 1 for Infusions 1 and 2 (Duration 2-4 Weeks)			Part 2 Study Visits (Duration 26 ± 1 Weeks) ^b				Part 3 (Duration ~ 1 Week)			Study Completion/ Termination Visit ^f
			Pre-Infusion	In-fusion	Post-Infusion	ED 1 ^c	Week 5 ± 1 EDs 10-15 ^d	Week 13 ± 1	Week 26 ± 1 ^e	Pre-Infusion	In-fusion	Post-Infusion	
Informed consent ^g	x												
Eligibility criteria	x												
Medical history	x												
Medications and non-drug therapies	x	x	x	x	x	x	x	X	x	x	x	x	x
Physical examination	x ^h		x			x	x	X	x	x ^h			x
Adverse events	x	x	x	x	x	x	x	X	x	x	x	x	x
Laboratories ⁱ	x	x	x		x	x	x	X	x	x		x	x
Vital signs ^j	x	x	x		x	x	x	X	x	x		x	x
Randomization		x ^k											
IP treatment ^l		(x)		x ^m		x	x	X	x		x		x
Hand out subject diary	x				x	x	x	X	x ⁿ			x ⁿ	
Review subject diary		x	x		x	x	x	X	x	x		x	x
HR QoL					x ^o	x ^c			x			x ^o	

6.1.8 Endpoints and Criteria for Study Success

The pharmacokinetic trial was conducted as a non-inferiority trial comparing Rixubis and BeneFIX. The primary pharmacokinetic endpoint was area under the plasma concentration vs. time from 0 to 72 hours. The secondary endpoints were total AUC/dose, MRT, CL, IR, elimination phase half-life and Vss. Clinical safety was assessed using descriptive statistics. Other than PK, there is no efficacy component to this part of the trial.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The estimated sample size was 27 and 31 subjects were enrolled.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Inclusion criteria included:

1. Severe or moderately severe hemophilia B (factor IX activity $\leq 1-2\%$)
2. Previously treated subjects with a minimum of 150 exposure days to a factor IX preparation

Exclusion criteria included:

1. History of factor IX inhibitor ≥ 0.6 Bethesda units
2. Existence of another coagulation disorder

The overall population assessed in the PK portion was 28 subjects. There were three subjects with major protocol deviations including incorrect lots or potency used that were excluded.

6.1.10.1.1 Demographics

Average age was 30 years; age range was 18-59 years. Eighty-five percent of the subjects were Caucasian with remaining subjects of African-American, Japanese, Latin-American, Mestizo and Arabic descent. All were male.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The two arms had similar average baseline levels of factor IX. The study excluded subjects with significant concurrent illnesses and subjects receiving drugs such as chemotherapy, aspirin, or other anticoagulants.

6.1.10.1.3 Subject Disposition

Thirty one subjects were enrolled. All were randomized and 28 completed both study periods with the 75 IU/kg dose.

6.1.11 Efficacy Analyses

Please refer to the clinical pharmacology memo. No clinical study of efficacy was performed as part of this segment of the trial.

6.1.11.1 Dropouts and/or Discontinuations

N=3 subjects discontinued from the study before treatment and 2 subjects discontinued after treatment for reasons including withdrawn consent and lost to follow-up.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety of study subjects was monitored in terms of adverse events (AEs), immunogenicity, viral safety and thrombotic markers. Immunogenicity testing included total binding antibodies to FIX, inhibitory antibodies to FIX, antibodies to CHO protein and rFurin. The protocol included pre-specified definitions of adverse reactions including severity, seriousness, and relatedness. A DSMB monitored the study.

Preinfusion levels of factor IX, inhibitory, and non-inhibitory antibodies were assessed. Routine laboratory tests were not assessed during the PK part of the study.

6.1.12.2 Overview of Adverse Events

There were no reports of severe allergic reactions, thrombosis or inhibitory antibodies. Thrombotic markers (D-dimer, F1+2, and TAT) were found to be elevated pre- and post-infusion in 10 of 28 (36%) subjects exposed to either Rixubis or BeneFIX. The abnormalities detected did not correlate with infusion time or infused product. The applicant attributes these findings to sampling technique, handling artifact or recent bleeding. Clinical review confirms this explanation and does not identify any associated safety signals. See integrated summary of safety for further details on overall observed adverse events.

6.1.12.3 Deaths

There were no deaths in subjects who received Rixubis.

6.1.12.4 Nonfatal Serious Adverse Events

Nonfatal serious adverse events were not reported for this phase of the protocol.

6.1.12.5 Adverse Events of Special Interest (AESI)

Events of special interest included thromboses, severe allergic reactions and immunogenicity. Inhibitor formation was monitored using the –b(4)----- of the Bethesda assay titer > 0.6 BU or total binding antibodies with a positive titer of 1:80.

6.1.12.6 Clinical Test Results

None of the subjects developed thromboses, anaphylactic reactions or inhibitor antibodies to Rixubis.

6.1.12.7 Dropouts and/or Discontinuations

N=3 subjects discontinued from the study before treatment and 2 subjects discontinued after treatment for reasons including withdrawn consent and lost to follow-up.

The number of discontinued subjects is within acceptable limits and clinical review of reasons for discontinuation is consistent with the applicant's assessment.

6.2 Trial #2

Safety and Efficacy of Rixubis in Subjects with Hemophilia B

6.2.1 Objectives (Primary, Secondary, etc)

The objective of this part of the trial was to evaluate the safety and efficacy of Rixubis in subjects with hemophilia B. Safety was assessed in terms of acute infusion reactions and inhibitor formation, while efficacy was determined by breakthrough bleeding during prophylaxis and on-demand treatments.

The detailed objectives of the trial were as follows:

- To monitor incremental recovery (IR) of Rixubis over time
- To evaluate the hemostatic efficacy of Rixubis in the prevention of acute bleeding episodes for a period of 6 months
- To evaluate the hemostatic efficacy of Rixubis in the treatment of acute bleeding episodes
- To evaluate safety in terms of Rixubis related adverse events (AEs), as well as clinically significant changes in routine laboratory parameters (hematology/clinical chemistry) and vital signs
- To evaluate immunogenicity for a minimum of 50 exposure days (EDs) with Rixubis

Exploratory objective:

- To evaluate changes in HR QoL and health resource use

6.2.2 Design Overview

The treatment phase of the trial was an open-label, non-randomized design intended as the pivotal trial for licensure. Similar to the PK study, a minimum of 150 exposure days to a factor IX preparation was a pre-enrollment requirement.

The choice of prophylaxis or on-demand treatment was at the discretion of the investigator and subject. Once enrollment in the prophylactic group was completed, subjects willing to receive on-demand treatment were recruited. Bleeding episodes in the prophylaxis group were also treated with Rixubis. Laboratory studies including assays for inhibitor, anti-rFurin and anti-CHO formation were done prior to initial infusion and at 1, 3 and 6 months. Exploratory endpoints of Health-Related Quality of Life (HRQoL) and health resource use were also evaluated. HRQoL was assessed using 4 questionnaires (Haemo-QOL, PedsQL, EQ-5D and VAS Pain Scale) and a total score was calculated for each subject with higher scores indicating a worse quality of life.

6.2.3 Population

Requirements for this trial included males aged 12 to 65 years with severe (FIX activity <1%) or moderately severe (FIX activity 1-2%) hemophilia B. Subjects also had at least 150 prior exposure days with a FIX product. A total of 59 subjects in the prophylactic cohort and 14 subjects in the on-demand group completed the study.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The planned prophylaxis regimen was an intravenous 50 IU/kg dose of Rixubis twice weekly for a period of six months or for at least 50 exposure days. Changes in dose and frequency could be made at the discretion of the investigator according to the PK and clinical profile of the individual subject with a dose range of 40-60 IU/kg up to a maximum of 75 IU/kg. Subjects in the on-demand arm were treated with Rixubis until the last subject of the prophylactic cohort had completed the study.

6.2.5 Directions for Use

The anticipated intravenous doses for prophylaxis were 50-75 IU/kg. On-demand treatment regimens were based on the BeneFIX Summary of Product Characteristics (SPC) with a dose ranging from 20-100 IU/kg. No special directions were needed.

6.2.6 Sites and Centers

The trial was a multi-investigator, multicenter, international study. Sites from Europe (Bulgaria, Czech republic, Germany, Poland, Romania, Spain, Sweden, UK, Ukraine), Russia, South America (Argentina, Brazil, Chile, Colombia) and Japan were included.

6.2.7 Surveillance/Monitoring

The safety of this study was reviewed by an independent data and safety monitoring board (DSMB), composed of 5 experts in the field of hemophilia clinical care and research as well as an independent biostatistician who met at least annually at specified time points for data review including November 2011 and May 2012. Screening assessments were provided in Table 21.3 (see section 6.1.7 BLA Memo). Physical examinations, medical histories, and concomitant medications were assessed. Adverse events were recorded in subject diaries and reviewed along with vital signs at each visit.

6.2.8 Endpoints and Criteria for Study Success

Efficacy endpoints included control of spontaneous bleeding in the prophylaxis arm and treatment of hemorrhagic bleeding episodes in both prophylaxis and on-demand settings. Safety was determined by reporting of adverse events by subjects and investigators. Subjects recorded adverse events in their diaries and were questioned at the scheduled evaluations.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Statistical plans for safety and efficacy were limited to descriptive statistics and examination by the reviewer. Annualized bleeding rates were calculated. Sample size calculations were presented in section 9.7.2 of final clinical study report. The planned sample size for the treatment study phase was up to 60 subjects on prophylaxis and up to 20 subjects using an on-demand schedule.

6.2.10. Results

6.2.10.1 Populations Enrolled/Analyzed

Inclusion criteria included:

1. Severe or moderately severe hemophilia B (factor IX activity $\leq 1-2\%$)
2. If the subject is to receive prophylactic treatment, the subject is willing to receive prophylactic treatment over a period of 6 months
3. If the subject is to receive on demand treatment, the subject has > 12 documented bleeding episodes requiring treatment within 12 months prior to enrollment and is willing to receive on-demand treatment for the duration of participation in this study
4. Previously treated subjects with a minimum of 150 exposure days to a factor IX preparation

Exclusion criteria included:

5. History of factor IX inhibitor ≥ 0.6 Bethesda units
6. Existence of another coagulation disorder

A total of 86 subjects were enrolled, including 59 subjects who enrolled in the prophylaxis arm and 14 in the on-demand schedule. Treatment phase analyses included all subjects who received at least one dose of Rixubis.

6.2.10.1.1 Demographics

Overall median age was 33 years with an age range of 12-59 years and three pediatric subjects aged 12, 13, and 15 years. All subjects were male and 85% were Caucasian.

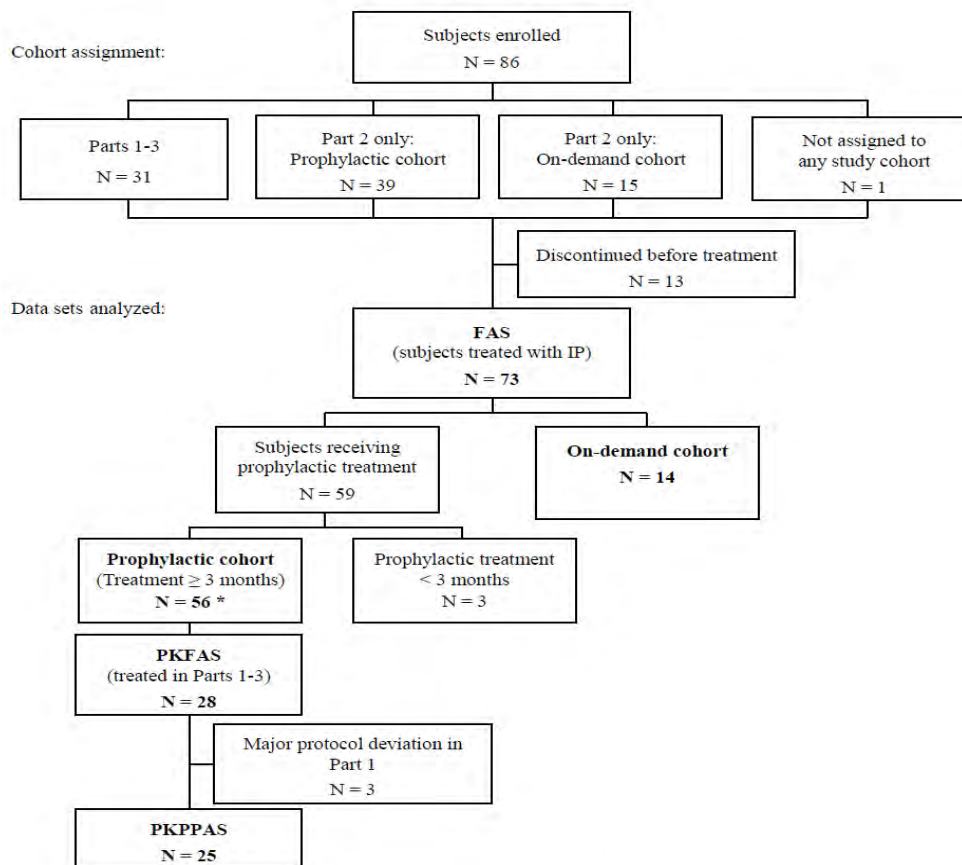
6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The 59 subjects on a prophylaxis regimen achieved a mean compliance of 90%. Compliance ranged from 89% to 99%, with the former result in subjects who experienced bleeds during prophylaxis.

6.2.10.1.3 Subject Disposition

Eighty-six subjects were enrolled. The full analysis set (FAS) was comprised of 73 subjects (N=14 on-demand and N=59 on prophylaxis).

Figure 10.1-1
Flow Chart for Study 250901



* Of 56 subjects who received prophylactic treatment for ≥ 3 months, 29 received prophylaxis for ≥ 6 months.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

Rixubis is effective in preventing bleeding in hemophilia B subjects. All prophylactic subjects were dosed at a median dose of 50.49 IU/kg twice weekly at a median treatment duration of 6.03 months. The mean annualized bleeding rate of 4.26 (See Table 7) in the prophylaxis arm (N=59) was 75% lower than the mean historical on-demand rate of 16.92. Of the 56 subjects on prophylaxis for at least 3 months duration, 48 had arthropathy at screening and a mean ABR of 3.16 compared to 1.02 in the remaining subjects who had no arthropathy. Whereas in the on-demand arm (N=14), the mean annual bleed rate was 38% greater than the mean historical on-demand rate of 24.50. This increased difference may be attributed to greater disease severity in subjects within the study. A comparison between both the prophylactic and on-demand cohorts was not done due to underlying baseline differences. Nonetheless, the results remain consistent with improvement in the bleeding frequency with prophylactic treatment. Rixubis is effective

in reducing bleeding compared to on-demand use when administered as routine prophylaxis in adult subjects 16 years or older with hemophilia B.

There were 134 bleeds recorded for on-demand subjects and 115 bleeds for subjects on prophylaxis totaling 249 bleeds during the study. 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. Of all 59 subjects on prophylaxis, 44% experienced no bleeds.

Table 7.
Efficacy of Prophylaxis with RIXUBIS in 56 PTPs

Treatment duration (months) Mean \pm SD Median (range)	6.0 \pm 0.65 6.0 (5.4 - 9.1)
Number of infusions per week* Mean \pm SD Median (range)	1.8 \pm 0.11 1.8 (1.5 - 1.9)
Dose per infusion (IU/kg) Mean \pm SD Median (range)	49.4 \pm 4.92 50.5 (40.0 - 62.8)
Total annualized bleeding rate (ABR) Mean \pm SD Median (range)	4.3 \pm 5.80 2.0 (0.0 - 23.4)
ABR for joint bleeds Mean \pm SD Median (range)	2.9 \pm 4.25 0.0 (0.0 - 21.5)
ABR for spontaneous bleeds Mean \pm SD Median (range)	1.7 \pm 3.26 0.0 (0.0 - 15.6)
Subjects with zero bleeding episodes % (n)	42.9% (24)

* The prophylactic regimen consisted of 40 to 60 IU/kg rFIX twice weekly. The individual dose could be increased up to 75 IU/kg twice weekly.

[Adapted from Rixubis Package Insert]

For each bleeding episode, subjects were asked to rate the efficacy of Rixubis on a four point scale of excellent to poor. Two percent of the bleeding episodes were reported as not rated for efficacy. Of those that were reported, 41% were rated as excellent, 55% as good, and 2% as fair. The mean total dose per bleed was 83.83 \pm 58.82 IU/kg (median: 62.29 IU/kg, range: 25.5-372.1 IU/kg). There were 3 subjects who were treated with more than 300 IU/kg but review of case reports detailed that dose corresponded to type of bleed and severity and did not reveal safety concerns.

6.2.11.2 Analyses of Secondary Endpoints

No significant differences in the HR QoL were observed in on-demand subjects between baseline and follow-up. In subjects on prophylaxis, statistically significant improvements between baseline and follow-up were seen only for the physical component score, bodily pain score and role physical domains of the SF-36 as well as the EQ-5D VAS score.

Overall for all subjects, HR QoL did not show a marked improvement and was considered underpowered and exploratory.

6.2.11.3 Subpopulation Analyses

Data for pediatric subjects is not available but a pediatric study is ongoing with 16 subjects <12 years currently enrolled. A deferral is requested and a pediatric indication will not be requested until pharmacokinetic data from at least 20 pediatric subjects is available.

6.2.11.4 Dropouts and/or Discontinuations

N=3 subjects discontinued from the study before treatment and 2 subjects discontinued after treatment for reasons including withdrawn consent and lost to follow-up.

The number of discontinued subjects is within acceptable limits and detailed review of reasons for discontinuation is consistent with the applicant's assessment.

6.2.12 Safety Analyses

6.2.12.1 Methods

Safety of study subjects was monitored in terms of adverse events (AEs), immunogenicity, history and physical examination, laboratory measurements, assessments of bleeding and viral safety. Although bleeding was monitored and considered an efficacy outcome, subjects were monitored for development of inhibitors that might predispose to bleeding. Immunogenicity testing by ELISA included total binding antibodies to FIX, inhibitory antibodies to FIX, antibodies to CHO protein and rFurin. The protocol included pre-specified definitions of adverse reactions including severity, seriousness, and relatedness. A DSMB monitored the study.

Preinfusion baseline levels of factor IX, inhibitory, and non-inhibitory antibodies were also assessed.

6.2.12.2 Overview of Adverse Events

Overall, there were 90 adverse events throughout the pivotal study and 3 non-serious related AEs (1 case of transient pain in hand of unknown causality considered related by default, and 2 cases of transient dysgeusia in 1 subject). There were no deaths as well as no cases of nephrotic syndrome, inhibitors, or anaphylaxis.

There were no patterns of increased consumption or other patterns suggestive of inhibitor formation. Formation of binding antibodies against FIX (non-neutralizing) and rFurin proteins is discussed in section 6.2.12.5.

There were 37 subjects (51%) of the FAS population that experienced an adverse event during the study but no treatment-emergent adverse events (TEAE) were observed within 24 hours after infusion. The most frequently occurring events were low-titer binding antibodies to FIX and /or rFurin (8-18%), nasopharyngitis (9%), pharyngitis (5.5%), pyrexia (4.4%) and arthralgia (4.4%). Causality of the majority of adverse events by Rixubis did not seem plausible during the clinical review given the common occurrence in the general population.

In the integrated safety analysis, there were 161 AEs reported. Of these, 6 were SAEs (duodenal ulcer hemorrhage, intestinal obstruction, cervical vertebral fracture, traumatic hematoma, convulsion and hepatitis B core antibody positive) that were unlikely related to Rixubis based on review of case reports.

[Source: p. 32, Integrated Analysis of Safety, BLA 125446/0]

6.2.12.3 Deaths

No deaths occurred in this population.

6.2.12.4 Nonfatal Serious Adverse Events

There were 6 SAEs reported and none were considered related to treatment. There were no patterns suggestive of inhibitor formation. The SAEs included duodenal ulcer hemorrhage, intestinal obstruction, cervical vertebral fracture, traumatic hematoma, convulsion and hepatitis B core antibody positive and are unlikely to be caused by Rixubis.

6.2.12.5 Common Adverse Events

Approximately 51% of subjects experienced at least one adverse event. The most common adverse reaction were low-titer binding antibodies to FIX and /or rFurin (8-18%), nasopharyngitis (9%), pharyngitis (5.5%), pyrexia (4.4%) and arthralgia (4.4%).

6.2.12.6 Adverse Events of Special Interest (AESI)

Events of special interest included thromboses, hemolysis, transmitted infections, and immunogenicity. No case of confirmed inhibitor, thrombosis or hemolysis was detected.

Seventeen out of 91 subjects in the entire trial including the continuation study developed binding antibodies against FIX and/or rFurin of indeterminate specificity (1:20 and 1:40 titers) on at least one time-point during the study. No clinically relevant abnormalities were reported in these subjects. A written information request was made to Baxter regarding a comprehensive risk assessment analysis on the formation of these antibodies. The antibody formation was considered indeterminate as confirmatory assay was negative in all but 2 subjects.

Throughout all 4 studies (pivotal, surgery, pediatric and continuation), 91 subjects had been treated with Rixubis as of 09/03/2012. A validated screening and confirmatory ELISA assay was used to detect antibodies against CHO, FIX and rFurin. No anti-CHO antibodies were detected during the study. Sixteen subjects were positive for rFurin at one or more time points during the study. Four of these subjects had rFurin antibodies present at screening and of these, one subject was positive both before and after Rixubis treatment. Additionally, there was 1 subject who developed rFurin antibody after treatment with Benefix but prior to Rixubis during the PK study. Overall, a total of 7 subjects had low titer rFurin antibodies detected after screening and after treatment with Rixubis. Only two subjects reached the lower limit of 1:80 for the confirmatory assay, the remainder of the subjects were negative for rFurin antibody by default using the confirmatory assay since their titers were too low for the assay to be done.

Binding antibodies to FIX were detected in 12 subjects at one or more time points during the study but none were neutralizing. None of the subjects were positive for binding antibodies to FIX at the time of data cut-off. Six subjects had simultaneous positivity for rFurin and FIX at one point during the study but in-depth review of these subjects showed no associated clinical abnormalities.

All but 2 subjects with rFurin and/or FIX binding antibodies were still receiving treatment with Rixubis as of the data cut-off date in either the continuation or pediatric study without clinical sequelae. The applicant's conclusion that low-titer antibodies (1:80) and indeterminate antibodies (1:20 and 1:40) had no impact on safety and efficacy, no temporal association with adverse events and no impact on pharmacokinetic parameters is well supported by the data and risk assessment analysis.

6.2.12.7 Clinical Test Results

Aside from the antibodies of low-titer and indeterminate specificity to FIX and rFurin, there were no patterns of clinically significant laboratory abnormalities that could be ascribed to Rixubis. Similarly, no patterns of abnormal vital signs or physical examination findings were noted.

None of the subjects displayed significant hypereosinophilia. IgE levels were not assessed during the study or determined for any of the antibody positive subjects.

6.3 Trial #3

Name of trial: Safety and Efficacy of Rixubis in Subjects with Hemophilia B Undergoing Surgical or Other Invasive Procedures

6.3.1 Objectives (Primary, Secondary, etc)

The objective of the surgery substudy was to evaluate the safety and efficacy of Rixubis in the peri- and post-operative setting in subjects with severe or moderately severe (factor IX activity $\leq 1-2\%$) hemophilia B undergoing major or minor elective and emergency surgical, dental or other invasive procedures.

The specific study objectives are as follows:

- To determine the actual intra- and post-operative blood loss at the end of surgery and until drain removal, if applicable, compared to the estimated volume of expected average and maximum blood loss as predicted post-operatively by the operating surgeon
- To determine the intra- and post-operative hemostatic efficacy at the end of the surgery, at the time of drain removal, if applicable, or at post-operative day 3 (approximately 72 hour post-operatively) in case of major surgery and no drain employed, and at the time of discharge from the hospital on a scale of “excellent”, “good”, “fair” and “none”.
- To calculate the daily and total weight-adjusted dose of Rixubis per subject
- To record the number of units and amount (in mL) of blood product transfused
- To record the development of inhibitory and total binding antibodies to FIX
- To determine AEs related to Rixubis
- To determine the occurrence of thrombotic events

6.3.2 Design Overview

The surgery study is an ongoing phase 3, prospective, open-label, uncontrolled, multicenter trial intended to evaluate the hemostatic efficacy and safety of Rixubis in 30 subjects with severe or moderately severe hemophilia B undergoing major or minor surgical, dental or other invasive procedures. Subjects were allowed to participate in the surgery study only or could transfer between the treatment arms as desired.

6.3.3 Population

Many complications of hemophilia require surgical intervention including chronic destructive arthropathy or acute intracranial hemorrhage. Control of bleeding during and after surgery is an important determinant of surgical morbidity in this population.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Exact dosing regimens were tailored for each patient based on serial measurement of factor IX levels. The treatment regimen was determined by the type of surgery, the intensity and duration of the hemostatic challenge, and consistent with the study site’s standards of care for surgical management of hemophilia B subjects.

6.3.5 Directions for Use

Doses of Rixubis were administered such that factor IX levels were 30-60% for minor surgeries and 80-100% of normal for major surgeries.

6.3.6 Sites and Centers

The trial was a multi-investigator, multicenter, international study (Bulgaria, Poland, Russia and Ukraine).

6.3.7 Surveillance/Monitoring

Efficacy and safety assessments were done as outlined in tables 20.3-1 and 20.4-1 below from the amended protocol dated 10/11/2011. Factor IX levels were determined before and after infusion. Study duration ranged from 4-93 days. Inhibitory and non-inhibitory antibodies to factor IX were assessed at end of study visit or sooner if clinically indicated.

20.3 Schedule of Study Procedures and Assessments

Table 20.3-1 Schedule of Study Procedures and Assessments						
Procedures/ Assessments	Screening Visit ^a	PK assessment ^b	Study Visits			End of Study Visit: Discharge
			Preoperative procedures	Intraoperative procedures	Postoperative: Daily procedures	
Informed consent ^c	x					
Eligibility criteria	x					
Medical history ^d	x					
Medications and non-drug therapies	x	x	x	x	x	x ^e
Physical examination ^f	x	x	x		x ^g	x ^{e1}
Adverse events	x	x	x	x	x	x ^e
Laboratory assessments ^h	x	x	x	x	x	x ^e
Vital signs	x	x within 15 min pre, 15 to 30 min and 2 h ± 10 minutes post-dose	x 15 to 30 min post loading dose(s)			
IP treatment		x	x	x (as required)	x (as required)	
Hemostatic efficacy assessments				x	x ^h	x
Blood loss			x predicted	x	x	
Transfusion requirements				x	x	

Table 20.4-1
Clinical Laboratory Assessments

Note that in addition to the tests shown, parameters should also be evaluated whenever clinically indicated or according to the site's standard of care.

Assessments	Screening Visit ^a	(PK assessment ^b	Study Visits			End of Study Visit: Discharge ^c
			Preoperative procedures	Intraoperative procedures	Postoperative: Daily procedures	
Factor IX activity	C ^d	C ^e	L and B: within 60 minutes prior to surgery and 15 ± 5 minutes after loading dose/rebolus, if applicable	L and B: only if excessive or unexplained bleeding	L and B: 30 minutes pre and 10 to 30 minutes post infusion, or if excessive bleeding	
aPTT			L: pre and 15 ± 5 minutes after loading dose/rebolus, if applicable ^f		L: 30 minutes pre and 10 to 30 minutes post infusion	
Fibrinogen		C				
FIX inhibitory and binding antibodies ^g	C ^h			C and B (L): if excessive or unexplained bleeding	C and B (L): if excessive or unexplained bleeding	C ^h (L)
Hematology ⁱ	C ^h		L ^j : within 60 minutes prior to surgery		L ^j : 30 minutes pre or 10 to 30 minutes post infusion (differential weekly only)	C (L)
Clinical Chemistry ^k	C ^h				L: weekly	C (L)
Urinalysis	C ^h					C
Additional tests	C ^l	C: If a subject develops a severe allergic reaction or anaphylaxis ^m				

6.3.8 Endpoints and Criteria for Study Success

Criteria for efficacy success were determined by the surgeons' assessment of hemostatic control during and after the operation based on a 4-point rating scale from excellent to poor. Separate assessments for peri- and post-operative hemostasis were made. Safety

was determined from reports of adverse events by subjects and investigators. Adverse events which occurred during the perioperative hospitalization were also included.

6.3.9 Statistical Considerations & Statistical Analysis Plan

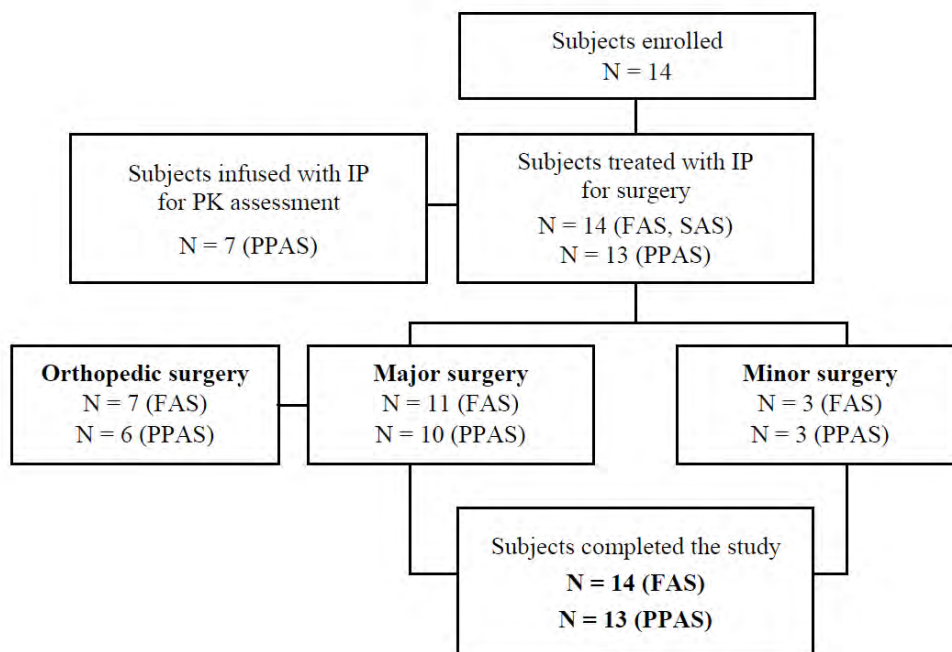
Statistical plans for efficacy were limited to descriptive statistics including median, range, frequency counts, proportions and examination by the reviewer. A sample size of at least 30 elective or emergency surgical, dental or other invasive procedures in 30 subjects was planned. At least 10 of the procedures had to be major surgeries in 10 unique subjects.

6.3.10. Results

6.3.10.1 Populations Enrolled/Analyzed

Fourteen surgeries in 14 subjects were included in the interim analysis surgery study report. All subjects enrolled were analyzed. Other than surgery, the inclusion and exclusion criteria were similar to the treatment protocols. Figure 10.1-1 below details the population enrolled and analyzed.

Figure 10.1-1
Flow Chart for Study 251002



[Source: BLA 125446/0 Full Clinical Study Report Amendment 3]

The major procedures performed included 7 orthopedic, 2 abdominal, 1 dental surgery and 1 excision of neurofibroma. The minor surgeries were 2 dental procedures and 1 intraarticular infusion.

6.3.10.1.1 Demographics

The demographics are presented in Table 11-1 in the surgery study report. The cohort consisted of 14 Caucasian males; ranging in age from 19-54 years.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

The efficacy of Rixubis to control bleeding during surgery was evaluated according to the surgeon's assessment of the: a) estimated blood loss intra-operatively, b) post-operative blood loss, c) hemostatic efficacy intra-operatively and d) hemostatic efficacy post-operatively.

Surgery phase analyses included 14 subjects who underwent 11 major surgeries and 3 minor. The types of procedures are listed below in Table 9 adapted from the package insert along with the assessment of hemostatic response to Rixubis. Perioperative factor IX replacement was by bolus infusion. Continuous infusion was not evaluated.

Table 9.
Efficacy of RIXUBIS for Surgical Procedures in PTPs (Full Analysis Set)

Procedure (category, # 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
Excision neurofibroma (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

* Where no drain was employed, response was assessed on postoperative day 3.

Subjects who had major surgery received bolus infusions at an initial pre-surgery dose of 134-296 IU/kg with subsequent dosing ranging from 20-237 IU/kg. The mean incremental recovery at 30 minutes was 1.06. Factor IX activity levels ranged generally between 65-136% at 15 minutes post bolus infusion.

Hemostasis control and blood loss were considered excellent or good in all procedures and acceptable factor IX levels were achieved in the peri-, intra-, and post-operative periods with transfusion support required in 4 subjects who underwent orthopedic surgery and had a mean post-operative blood loss of 704 mL expected for this type of surgery. The mean volume transfused post-operatively was 575 mL.

6.3.12 Safety Analyses

6.3.12.1 Methods

Screening and perioperative assessments are provided in amendment 1 of the study protocol in Figure 20.2-1 and Table 20.3-1. The quality of life assessments were not done for this subset. Safety assessments included reports of adverse events by investigators and subjects.

6.3.12.2 Overview of Adverse Events (AEs)

The adverse events were presented in Tables 24, 26 and 27 of the interim clinical study report 251002. In the 14 subjects analyzed, there were no inhibitors to FIX or total binding antibodies, no severe allergic reactions, thrombotic events or deaths. Fourteen adverse events reported as non-serious included pyrexia, procedural pain, arthralgia, and increased ALT in a subject with pre-existing chronic hepatitis B and C. There were no serious adverse events reported.

6.3.12.3 Deaths

There were no deaths in the surgery clinical trial 251002.

6.3.12.4 Nonfatal Serious Adverse Events

None.

6.3.12.5 Adverse Events of Special Interest (AESI)

Events of special interest included thromboses, hemolysis, transmitted infections, and immunogenicity. No AESI occurred during the perioperative surgery substudy.

7. Integrated Overview of Efficacy

7.1 Methods of Integration

A total of 86 subjects were enrolled in one or more study phases and 73 of these subjects were used for analysis of safety and efficacy in the treatment phase. Overall, Rixubis is effective in preventing bleeding in hemophilia B subjects.

7.2 Demographics and Baseline Characteristics

The baseline characteristics of the substudy populations are sufficiently alike that pooling data for safety is reasonable. The efficacy targets for each substudy are all different and are therefore best evaluated separately.

7.3 Efficacy Conclusions

Rixubis is effective in adults for control and prevention of bleeding, routine prophylaxis and peri-operative prophylaxis.

8. Integrated Overview of Safety

8.1 Safety Assessment Methods

The population undergoing integrated analysis of safety is the population from three of the substudies of the Rixubis development program.

The safety issues of interest were adverse events in general, thrombogenicity, inhibitors, and formation of low-titer binding antibodies to FIX and rFurin. The integrated safety population includes all subjects in all phases. Since all safety assessments were descriptive, no additional methods were required to pool them together.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Four substudies (PK, treatment, surgery, continuation) were used to evaluate safety.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Study enrollment closed in May 2011. As of September 2012, 91 subjects had received at least 1 infusion of Rixubis with 6 subjects < 6 years of age, 10 subjects 6-12 years of age and 3 adolescents (12-<16 years of age). The remaining 72 subjects were adults (16 years of age and older). The median number of exposure days per subject was 83 with a median study duration of 13 months.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Based upon similarities in the subpopulation patient characteristics, it is reasonable to pool the data together as the applicant has done.

8.4 Safety Results

A total of 161 adverse events were reported in 48 of the 91 subjects. Of these, 6 were SAEs (duodenal ulcer hemorrhage, intestinal obstruction, cervical vertebral fracture, traumatic hematoma, convulsion and hepatitis B core antibody positive) that were unlikely related to Rixubis based on review of case reports. The majority of the non-serious AEs were related to mild infections, gastrointestinal disease, arthralgia and low-titer binding antibodies to FIX and/or rFurin.

8.4.1 Deaths

There were no fatalities in this trial.

8.4.2 Nonfatal Serious Adverse Events

There were 6 SAEs (duodenal ulcer hemorrhage, intestinal obstruction, cervical vertebral fracture, traumatic hematoma, convulsion and hepatitis B core antibody positive) that were unlikely related to Rixubis based on detailed review of case reports.

8.4.3 Study Dropouts/Discontinuations

Two subjects were withdrawn from the study for emergent treatment of SAEs (road traffic accident and intestinal surgery).

8.4.4 Common Adverse Events

The summary table of adverse reactions below is adapted from the Rixubis package insert.

Summary Table of Adverse Reactions

System Organ Class (SOC)	Events	Number of ARs (n)	Number of Subjects N = 91 n (%)	Percent per Infusion N=7353
Infections and Infestations	Bronchitis	1	1 (1.1%)	0.01%
	Gastroenteritis	2	2 (2.2%)	0.03%
	Influenza	1	1 (1.1%)	0.01%
	Nasopharyngitis	2	2 (2.2%)	0.03%
	Pharyngitis	3	3 (3.3%)	0.04%
	Rhinitis	1	1 (1.1%)	0.01%
	Super infection bacterial	1	1 (1.1%)	0.01%
	Upper respiratory tract infection	1	1 (1.1%)	0.01%
Nervous System Disorders	Convulsion	1	1 (1.1%)	0.01%
	Dysgeusia	2	1 (1.1%)	0.03%
	Headache	2	2 (2.2%)	0.03%
Vascular Disorders	Hypertension	1	1 (1.1%)	0.01%
Gastrointestinal Disorders	Constipation	1	1 (1.1%)	0.01%
	Diarrhea	4	2 (2.2%)	0.05%
	Dyspepsia	1	1 (1.1%)	0.01%
	Gingivitis	1	1 (1.1%)	0.01%
Musculoskeletal and Connective Tissue Disorders	Arthralgia	1	1 (1.1%)	0.01%
	Arthropathy	1	1 (1.1%)	0.01%
	Bone Pain	1	1 (1.1%)	0.01%
	Pain in extremity	2	1 (1.1%)	0.03%
General Disorders and Administration Site Conditions	Malaise	2	1 (1.1%)	0.03%
	Pyrexia	3	3 (3.3%)	0.04%
Investigations	rFurin antibody test positive*	1	1 (1.1%)	0.01%
	Increased blood pressure	1	1 (1.1%)	0.01%
	FIX or rFurin antibodies of indeterminate specificity **	9	7 (7.7%)	0.12%

8.4.5 Clinical Test Results

No safety signals were seen in the routine laboratory results, physical examinations, or vital signs. The results of immunogenicity studies are provided in section 8.5.

8.4.6 Adverse Events of Special Interest

Events of special interest included thromboses, hemolysis, transmitted infections, and immunogenicity. No episodes of thrombosis, hemolysis, or product-transmitted infection occurred during any part of the trial.

8.5 Additional Safety Evaluations

8.5.1 Immunogenicity (Safety)

There was no pattern of increased consumption of product, the absence of which is evidence against clinically significant immunogenicity mediated by neutralizing antibody against the therapeutic protein.

Although formation of FIX inhibitors was not observed, non-neutralizing FIX antibodies of low-titer were seen in 12 subjects on at least one time-point other than screening and similarly development of low-titer anti-rFurin antibodies was seen in 16 subjects (N=91 including subjects in continuation study). Some of these findings were transient and when considering only subjects who were positive at the time of data cut-off, there were 7 subjects with rFurin antibodies and none with binding FIX. FIX or rFurin antibodies were considered indeterminate specificity by Baxter because they were below the threshold pre-specified for positivity and within the limits of assay variability. Two subjects reached the threshold for positivity at a titer of 1:80 for rFurin antibody but positivity was transient in one subject and there were no associated adverse events in either.

In order to further evaluate the potential clinical significance of binding antibodies to FIX and/or rFurin and to conduct a root cause analysis of these findings, a risk analysis assessment addressing potential safety concerns was requested from the applicant. In response, Baxter provided data from 500 healthy subjects from 5 different geographies in Austria who were screened for the prevalence of rFurin antibodies using the same assay in the pivotal study. Forty-one healthy subjects were found to be reactive (8.2%) without prior exposure to the investigational product. Of these, 7% had titers of 1:20 or 1:40 and 1.2% had higher titers ranging from 1:80 to 1:320. A review of the literature was also provided describing the historical knowledge of self-reactive rFurin antibodies that are of unclear origin but of no associated pathology. The theorized mechanism is the creation of an immunological homunculus that maintains immune homeostasis as well as binds apoptotic cells thereby facilitating uptake and clearance by dendritic cells.

The risk assessment analysis showed no associated clinical findings in study subjects with low-titer or indeterminate titer binding antibodies during the development program for Rixubis including no adverse events, lack of therapeutic effect or alterations in pharmacokinetics.

8.6 Safety Conclusions

Twelve subjects out of 91 developed low-titer non-neutralizing antibodies to FIX and 16 subjects had low-titer binding antibodies to rFurin host cell proteins. Only 2 subjects reached the true limit of detection for rFurin antibody and this finding was transient in

one subject. No clinically significant adverse reactions could be ascribed to these antibodies, though the long-term consequences are unknown.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Not studied.

9.1.2 Use During Lactation

Not studied.

9.1.3 Pediatric Use and PREA Considerations

Safety and efficacy in children has yet to be established. A pediatric study is ongoing with 16 subjects <12 years currently enrolled. A deferral is requested and a pediatric indication will not be requested until pharmacokinetic data from at least 20 pediatric subjects is available.

9.1.4 Immunocompromised Patients

Not studied.

9.1.5 Geriatric Use

Not applicable because of younger age of this population.

10. Conclusions

Rixubis is effective in control and prevention of bleeding, routine prophylaxis and peri-operative prophylaxis in adults –b(4)- years or older with hemophilia B. The applicant's calculations were reproduced and confirmed by both the clinical, pharmacology and statistical reviewers. In 91 subjects, development of inhibitory antibodies against the product was not observed.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Hemophilia B is a rare condition with variable deficiency of coagulation factor IX. Hemophilia is accompanied by bleeding into tissues and joints which can be spontaneous, post-traumatic, or perioperative. Bleeding can be acutely devastating, such as intracranial bleeding, or chronically destructive such as hemophilic arthropathy. 	<ul style="list-style-type: none"> Hemophilia B is a serious, progressive, life-threatening disease. The bleeding associated with hemophilia can cause clinically significant complications. Current treatment is expensive and carries risks of infection or adverse reactions.
Unmet Medical Need	<ul style="list-style-type: none"> There is one other recombinant factor IX product licensed for use by FDA. Numerous other plasma-derived factor IX products exist, but carry the same risks as other human plasma products, such as infection with known or unknown agents, acute hypersensitivity reactions, or immunogenicity with resistance. 	<ul style="list-style-type: none"> Although alternative recombinant therapy exists for Hemophilia B, it is expensive with the average on-demand treatment ranging from ~\$130,000-300,000/year and even higher costs for those on prophylactic therapy. Increasing the number of available licensed products could have a positive impact and allow options for hemophilia patients who remain untreated due to high costs.
Clinical Benefit	<ul style="list-style-type: none"> Rixubis was shown to be effective for treatment of, and prevention against spontaneous or traumatic bleeding by both prophylactic or on-demand regimens Rixubis was shown to be effective in the perioperative setting for reduction of bleeding during surgery. 	<ul style="list-style-type: none"> Rixubis is similarly effective to the currently licensed recombinant product.
Risk	<ul style="list-style-type: none"> Twelve subjects out of 91 developed low-titer non-neutralizing antibodies to FIX and 16 subjects had low-titer binding antibodies rFurin host cell proteins. No associated clinical sequelae were noted. The long term consequences of indeterminate or low-titer binding FIX and/or rFurin antibodies is unknown though cross-reactivity with innate proteins is possible. 	<ul style="list-style-type: none"> The risks of long-term exposure to immunogenic proteins with Rixubis are largely unknown but increasing or very high titers could theoretically result in allergic reactions, anaphylaxis, serum sickness, autoimmunity, and immunogenicity.
Risk Management	<ul style="list-style-type: none"> An approval with condition of PMC implementation is recommended. 	<ul style="list-style-type: none"> An adequately designed PMC cohort event safety and efficacy monitoring study would help to better understand potential aspects of the process of immunogenicity development. Recipients would need to be routinely evaluated in order to monitor for reactivity and complications, many of which are unknown at this point requiring broad surveillance.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Summary and Assessment

Although formation of FIX inhibitors was not observed, non-neutralizing FIX antibodies of low-titer were seen in 12 subjects on at least one time-point other than screening and similarly development of low-titer anti-rFurin antibodies was seen in 16 subjects (N=91 including subjects in continuation study). Some of these findings were transient and when considering only subjects who were positive at the time of data cut-off, there were 7 subjects with rFurin antibodies and none with binding FIX. FIX and rFurin antibodies were considered indeterminate specificity by Baxter because they were below the threshold pre-specified for positivity and within the limits of assay variability. Two subjects reached the threshold for positivity at a titer of 1:80 for rFurin antibody but positivity was transient in one subject and there were no associated adverse events in either.

A risk analysis assessment addressing potential safety concerns was requested from the applicant. In response, Baxter provided data from 500 healthy subjects from 5 different geographies in Austria who were screened for the prevalence of rFurin antibodies using the same assay in the pivotal study. Forty-one healthy subjects were found to be reactive (8.2%) without prior exposure to the investigational product. Of these, 7% had titers of 1:20 or 1:40 and 1.2% had higher titers ranging from 1:80 to 1:320. A review of the literature was also provided describing the historical knowledge of self-reactive rFurin antibodies that are of unclear origin but of no associated pathology. The theorized mechanism is the creation of an immunological homunculus that maintains immune homeostasis as well as binds apoptotic cells thereby facilitating uptake and clearance by dendritic cells.

The risk assessment analysis showed no associated clinical findings in study subjects with low-titer binding antibody formation during the development program for Rixubis including no adverse events, lack of therapeutic effect or alterations in pharmacokinetics.

Due to the effective hemostasis in control and prevention of bleeding episodes, routine prophylaxis and peri-operative prophylaxis in adult subjects b(4) years or older with hemophilia B, the benefits were considered to outweigh the risks of this product.

11.2 Discussion of Regulatory Options

The regulatory option discussed was approval of the indications of control and prevention of bleeding, routine prophylaxis and peri-operative prophylaxis in adults -(b)(4)- or older with hemophilia B. Implementation of a PMC is also recommended.

11.3 Recommendations on Regulatory Actions

An approval is recommended. Implementation of a PMC cohort event safety and efficacy monitoring study is also recommended.

11.4 Labeling Review and Recommendations

A labeling review with recommendations is under negotiation with Baxter.