

Pharmacovigilance Plan Review -PVP, August 21, 2013 - ALPROLIX

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology

MEMORANDUM

Date: August 21, 2013

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Office of Blood Research and Review

Through: Christopher Jankosky, MD, MPH

Chief, Pharmacovigilance Branch

David Martin, MD, MPH

Director, Division of Epidemiology

Subject: Pharmacovigilance plan review for initial licensure

Applicant: Biogen Idec

Product: Coagulation factor IX (Recombinant), Fc Fusion protein, also known as rFIXFc or Alprolix

Proposed Indication: Control and prevention of bleeding episodes in hemophilia B including perioperative management and routine prophylaxis.

Submission Type: BLA 125444

PVP Submission Date: January 29, 2013

Action Due Date: December 27, 2013

1. INTRODUCTION

a. Product Description

Recombinant coagulation factor IX Fc fusion protein (rFIXFc or Alprolix) is a recombinant coagulation factor IX Fc fusion protein consisting of human coagulation factor IX (rFIX) covalently linked to the Fc domain of human immunoglobulin G1 (IgG). The Fc component of rFIXFc binds to the neonatal Fc receptor (FcRn), which is present on many adult cell types. This binding of the Fc domain causes the degradation of rFIXFc to be delayed and, therefore, increases the circulating half-life of rFIX. This longer half-life results in a recommended dosing schedule of every 5-14 days instead of the usual schedule of approximately twice a week for currently licensed factor IX replacement products. rFIXFc is made in a human embryonic kidney (HEK) cell line. The sponsor of rFIXFc is submitting the product for initial approval for the indications of: the treatment of adults and children with hemophilia B for the control and prevention of bleeding episodes, routine prophylaxis to prevent or reduce the frequency of bleeding

episodes, and perioperative management (surgical prophylaxis). rFIXFc is formulated as a lyophilized powder for intravenous (IV) injection.

Currently, BeneFIX and Rixubis are the only two recombinant FIX products licensed in the US. Unlike rFIXFc, BeneFIX and Rixubis are both made in Chinese hamster ovary cells and have half-lives equivalent to the plasma-derived FIX products. rFIXFc would provide a third recombinant FIX option and could improve quality of life by lengthening the time between doses.

b. Regulatory History

This submission is the initial application for licensure of rFIXFc [coagulation factor IX (recombinant), Fc Fusion protein] in the U.S.

c. Objectives

This memorandum is in response to a request from the Office of Blood Research and Review (OBRR) to the Office of Biostatistics and Epidemiology (OBE) to review the Risk Management Plan submitted by Biogen Idec for the BLA 125444 submitted on January 29, 2013. The BLA is seeking initial licensing of the product rFIXFc (recombinant coagulation factor IX Fc Fusion protein) also referred to as Alprolix, for the indications of: the treatment of adults and children with hemophilia B for the control and prevention of bleeding episodes, routine prophylaxis to prevent or reduce the frequency of bleeding episodes, and perioperative management (surgical prophylaxis).

Please note that text in italics is verbatim from the BLA.

2. MATERIALS REVIEWED

Source	Subtype	Document Reviewed
Biogen Idec	BLA 125444	Risk Management Plan, 1.16, submitted Jan. 29, 2013
Biogen Idec	BLA 125444	Summary of Clinical Safety, 2.7.4, submitted Dec. 28, 2012
Biogen Idec	BLA 125444	Study 998HB102 Protocol, 5.3.5.2, submitted Dec. 28, 2012
Biogen Idec	BLA 125444	Study 998HB102 Study Report, 5.3.5.2, submitted Dec. 28, 2012
Biogen Idec	BLA 125444.16	Interim Clinical Pharmacology Report, Amendment 16, submitted Jun. 27, 2013
Biogen Idec	BLA 125444.22	Efficacy Information Amendment 22, 1.11.3, submitted Aug. 9, 2013
Wyeth	Package insert	BeneFIX Package Insert (Revised 11/2011)
Baxter	Package insert	Rixubis Package Insert (Approved 6/2013)
Amgen/Wyeth	Package insert	Etanercept Package Insert (Revised 6/2003)
Biogen	Package insert	Alefacept Package Insert (Revised 5/2011)
Bristol-Myers Squibb	Package insert	Abatacept Package Insert (Revised 12/2011)
Regeneron	Package insert	Riloncept Package Insert (Revised 4/2010)
Amgen	Package insert	Romiplostim Package Insert (Revised 5/2013)

Source	Subtype	Document Reviewed
Bristol-Myers Squibb	Package insert	Belatacept Package Insert (Revised 4/2013)
Regeneron	Package insert	Aflibercept Package Insert (Revised 6/2013)
FDA	Annual Surveillance Report	OBE Annual Surveillance Report for BeneFIX for 2/12/12 to 2/11/13
Other	Publication	Franchini M, Frattini F, Crestani S, Sissa C, Bonfanti C. Treatment of hemophilia B: focus on recombinant factor IX. <i>Biologics</i> . 2013;7:33-8. doi: 10.2147/BTT.S31582. Epub 2013 Feb 12.
Other	Publication	Martinowitz U, Shapiro A, Quon DV, et al. Pharmacokinetic properties of IB1001, an investigational recombinant factor IX, in patients with haemophilia B: repeat pharmacokinetic evaluation and sialylation analysis. <i>Haemophilia</i> . 2012 Nov; 18(6);881-7.
Other	Publication	Monahan PE, Liesner R, Sullivan ST, Ramirez ME, Kelly P, Roth DA. Safety and efficacy of investigator-prescribed BeneFIX prophylaxis in children less than 6 years of age with severe haemophilia B. <i>Haemophilia</i> . 2010 May; 16:460-8.
Other	Publication	Czajkowsky DM, Hu J, Shao Z, Pleass RJ. Fc-fusion proteins: new developments and future perspectives. <i>EMBO Mol Med</i> . 2012 Oct;4(10): 1015-28.
Other	Publication	Uprichard J, Adamidou D, Goddard NJ, Mann HA, Yee TT. HHFactor IX replacement to cover total knee replacement surgery in haemophilia B: a single-centre experience, 2000-2010 . <i>Haemophilia</i> . 2012 Jan;18(1):46-9
Other	Publication	HHYang RHH, HHZhao YHH, HHWang XHH, HHSun JHH, HHJin JHH, HHWu DHH, HHCharnigo RHH, HHO'Brien AHH, HHZhong ZHH, HHRendo PHH. Evaluation of the safety and efficacy of recombinant factor IX (nonacog alfa) in minimally treated and previously treated Chinese patients with haemophilia B. <i>HHHaemophilia</i> . 2012 Sep;18(5):e374-8.

3. PHARMACOVIGILANCE PLAN REVIEW

The Risk Management Plan was submitted on Jan 29, 2013. A review of the pharmacovigilance plan with supporting background clinical trial information from the BLA is included below.

a. Clinical Safety Database

The clinical safety database for rFIXFc includes two completed studies as well as an extension study for ≥12 year olds and an ongoing pediatric study for previously treated patients (PTPs) <12 years old.

Table 1: Clinical Studies for rFIXFc¹

Study Number (Phase)	Study Title	Number of Subjects	Status
SYN-FIXFc-07-001 (Phase 1/2a)	Open-label, multicenter, safety, dose-escalation study to evaluate safety and PK of a single dose of rFIXFc in PTPs with severe hemophilia B ($\leq 2\%$ endogenous FIX). All subjects were ≥ 18 years old and had ≥ 100 exposure days (EDs).	14	Completed
998HB102 (Phase 3)	Open-label, global, multicenter study to evaluate the safety, PK, and efficacy of rFIXFc in PTPs with severe hemophilia B ($\leq 2\%$ endogenous FIX). All subjects were ≥ 12 years old and had ≥ 100 EDs. Study compared two prophylactic treatment regimens to on-demand treatment.	123	Completed
9HB02PED (Phase 3)	Open-label, multicenter study to evaluate the safety (including frequency of inhibitor development), PK, and efficacy of rFIXFc in pediatric PTPs < 12 years old with severe hemophilia B ($\leq 2\%$ endogenous FIX). Subjects have ≥ 50 EDs.	24 subjects included in Interim Clinical Pharmacology Report with data cut-off date of Apr. 23, 2013	Ongoing
9HB01EXT (Phase 3 extension)	Open label, multicenter extension to 998HB102 and 9HB02PED to evaluate the long-term safety (up to 4 years) of rFIXFc for prophylaxis and episodic treatment.	87 enrolled at data cut-off	Ongoing

The clinical database for rFIXFc represented previously treated patients with severe hemophilia B. The sponsor states that *the extent of the patients exposed is robust and sufficient in size to assess inhibitor risk and the risk of very common (incidence of $\geq 1/10$) or common (incidence of $> 1/100$ to $< 1/10$) adverse events (AEs) associated with treatment with rFIXFc.*²

Study 998HB102 Safety Analysis Set: This phase 3 study included 123 subjects who received a least one injection of rFIXFc. The study was conducted in 50 centers in 17 countries, including 35 subjects in the US. The total person time monitored was 117.14 years. Fifty-six subjects were followed for ≥ 1 year and 2 subjects were followed for ≥ 2 years. A total of 60 subjects achieved at least 50 EDs. All of the subjects were male and were previously treated patients (PTPs). Eleven subjects were 12 – 17 years old. One hundred ten subjects were 18 to 64 years old and 2 subjects were ≥ 65 years old.³ The majority of the subjects (73 [59.3%]) were white, 29 (23.6%) were Asian, 10 (8.1%) were black, 1 (0.8%) was American Indian or Alaska Native, and the remaining 10 (8.1%) were other races not specified. Exclusion criteria included patients with: prior history of or current inhibitor (≥ 0.6 BU/mL or ≥ 1 BU/mL in laboratories with this historical lower sensitivity cut-off), other coagulation disorders in addition to hemophilia B, history of anaphylaxis with FIX or intravenous immunoglobulin, abnormal renal function (creatinine > 2.0 mg/dL), active hepatic disease, and several other criteria.

The primary safety endpoints were the incidence of inhibitor development, the incidence of AEs, and clinically notable changes from baseline in laboratory values. The study involved 4 arms:

- Arm 1 – weekly prophylaxis with an individualized dose for up to 52 weeks (N = 63 enrolled)
- Arm 2 – prophylaxis with an individualized dosing interval, at 100 IU/kg initially every 10 days or an interval derived from baseline PK data (N = 29 enrolled)
- Arm 3 – episodic (on demand) treatment (N = 27 enrolled)
- Arm 4 – perioperative treatment with a prophylactic regimen for major surgery, during postoperative period, surgery, and rehabilitation period (N = 12 enrolled with 14 major surgeries occurring)

Subjects were assigned to a treatment arm based on the clinical site’s standard of care and the Investigator’s decision following discussion with the subject. Of note, the study did not include a comparison to the currently labeled recombinant FIX product, BeneFIX, or to plasma-derived FIX. Laboratory assessments for the study included an inhibitor assay by the -----(b)(4)----- Bethesda method and anti-rFIXFc binding antibody testing at screening, baseline, and at each visit. A positive inhibitor test was defined as a neutralizing antibody value ≥ 0.6 BU/mL confirmed on retesting within 2 to 4 weeks. Anti-rFIXFc binding antibody was assessed. AEs occurring between the first dose of the study treatment and the follow-up telephone call at 30 days after the last dose were recorded. ⁴

Adverse events in Study 998HB102: Of the 123 subjects in the study, 94 (76.4%) reported at least 1 AE. The most common AEs observed in Arms 1, 2, and 3 combined were nasopharyngitis (15.1%), influenza (7.6%), arthralgia (6.7%), upper respiratory tract infection (URI) (5.9%), headache (5%), and hypertension (5%). All of the infections were assessed by the reporting investigator as being unrelated to rFIXFc. There were no deaths reported in the study.⁵ Table 2 below lists the Treatment-Emergent adverse events separated by study arm and totaled. Arm 4 with perioperative patients was not included in this analysis as it was considered to be a unique clinical situation. Subjects are counted once if they report multiple events in the same preferred term.

Table 2: Treatment-Emergent Adverse Events (TEAEs) with Incidence $\geq 3\%$ in Study 998HB102⁶

Preferred Term	Arm 1 (weekly prophylaxis) (N=63)	Arm 2 (individualized prophylaxis) (N=29)	Arm 3 (episodic) (N=27)	Total rFIXFc (N=119)
Total number of TEAEs	158	76	52	286
Number of subjects with ≥ 1 TEAE	45 (71.4%)	23 (79.3%)	20 (74.1%)	88 (73.9%)
Nasopharyngitis	13 (20.6%)	4 (13.8%)	1 (3.7%)	18 (15.1%)
Influenza	5 (7.9%)	0	4 (14.8%)	9 (7.6%)
Arthralgia	6 (9.5%)	2 (6.9%)	0	8 (6.7%)
URI	4 (6.3%)	2 (6.9%)	1 (3.7%)	7 (5.9%)
Headache	2 (3.2%)	2 (6.9%)	2 (7.4%)	6 (5.0%)
Hypertension	3 (4.8%)	2 (6.9%)	1 (3.7%)	6 (5.0%)
Dizziness	3 (4.8%)	2 (6.9%)	0	5 (4.2%)

Preferred Term	Arm 1 (weekly prophylaxis) (N=63)	Arm 2 (individualized prophylaxis) (N=29)	Arm 3 (episodic) (N=27)	Total rFIXFc (N=119)
Sinusitis	3 (4.8%)	2 (6.9%)	0	5 (4.2%)
Diarrhea	3 (4.8%)	1 (3.4%)	0	4 (3.4%)
Musculoskeletal pain	2 (3.2%)	2 (6.9%)	0	4 (3.4%)
Rhinitis	3 (4.8%)	1 (3.4%)	0	4 (3.4%)

Of the 119 patients in the first 3 arms, the investigator-assessed severity of AEs was mild for 39 subjects (32.8%), moderate for 43 subjects (36.1%) and severe for 6 subjects (5.0%). The six subjects with severe⁷ AEs had a total of 7 events that were: arthralgia, hepatic neoplasm malignant, obstructive uropathy, peritonsillar abscess, road traffic accident, tonsillitis, and upper GI hemorrhage. The AEs observed in the study were consistent with medical events expected in the general hemophilia population.⁸ There were 6 subjects (out of the 119) who had hypertension. All of these subjects had the hypertension on the day of product infusion or the day after. Two of the 6 subjects had a history of hypertension, but none were on anti-hypertensive medication. One of the patients with prior history of hypertension, as well as another patient, had a history of diabetes mellitus. All of these hypertensive events were assessed by the study investigator as nonserious, mild or moderate in severity, and either unrelated or unlikely related to the rFIXFc treatment. It is possible that the monitoring of blood pressure during factor infusion visits led to an increase in diagnosis of hypertension at the time of these visits. The presence of confounding conditions further complicates the evaluation of a possible relation between rFIXFc infusion and hypertension. The sponsor concluded there was not an association between hypertension and rFIXFc therapy.⁹ Considering the confounding factors, the low number of affected patients in the study, and the high underlying prevalence of this condition, no clear connection could be drawn between rFIXFc and hypertension.

Of the 119 subjects in Study 998HB102, there were 15 serious adverse events (SAEs) in 13 subjects (10.9%) [not including SAEs during the perioperative management period]. The SAEs are listed in Table 3 below.

Table 3: Serious Adverse Events in Study 998HB102^{10, 11}

Subject ID	Preferred Study Arm	Age (yr)	Preferred Term	Judged Relationship to rFIXFc	Onset Day in relation to study entry (rFIXFc was past medical history ongoing)	Comment on AE and/or patient's history
110-001	Arm 1	68	Arthralgia	Unrelated	348	Extensive history of joint disease
118-001			Inguinal hernia	Unrelated	297	History of recurrent right inguinal

Subject ID Study Arm Age (yr)	Preferred Term	Judged Relationship to rFIXFc	Onset Day in relation to study entry (rFIXFc was ongoing)	Comment on AE and/or patient's past medical history
Arm 3 62 150-007				hernia
Arm 3 37 300-006	Cellulitis	Unrelated	255	Cellulitis of the left jaw
Arm 3 19	Road traffic accident	Unrelated	119	Motorcycle accident
521-001 Arm 3 19	Small intestinal obstruction	Unrelated	30	History of exploratory laparotomy for excision of an abdominal hematoma
	Intestinal obstruction	Unrelated	200	
522-004 Arm 1 62	Hepatic neoplasm malignant	Unrelated	310	History of chronic hepatitis C with liver cirrhosis
556-001 Arm 1 58	Cellulitis	Unrelated	83	Right forearm phlegmon with history of right elbow hemarthrosis
863-001 Arm 2 20	Peritonsillar abscess	Unrelated	304	History of pharyngitis and diabetes
871-003 Arm 1 50	Device related infection	Unrelated	136	Endoprosthesis infection of right knee
872-003 Arm 1 24	Abdominal adhesions	Unrelated	366	History of appendectomy
892-002 Arm 1 71	Angina pectoris	Unlikely related	124	History of coronary bypass, myocardial infarction. Had restenosis and required restenting.
	Angina pectoris	Unrelated	213	
901-004 Arm 2 53	Upper GI hemorrhage	Unrelated	3	History of hypertension and irritable bowel syndrome; possible symptoms prior to rFIXFc dose (prior low hemoglobin, short onset time after infusion)
903-002 Arm 2 41	Obstructive uropathy	Possibly related	496	Hematuria with clot formation in the ureter

As seen in Table 3, the majority of subjects with SAEs had pre-existing conditions that were related to the SAE. All of the subjects with SAEs continued the assigned rFIXFc treatment except for subject 300-006 (road traffic accident) and 871-003 (device related infection). The two exceptions had the drug withdrawn because the events occurred in countries where the study treatment was not able to be imported. The one case determined by the investigator as possibly related to rFIXFc (subject 903-002) involved a patient who had several days of painless hematuria before developing colicky pain. He was determined to have blood clotting in the urinary collecting system and pain resolved with passing of clots. The specific cause of the hematuria in this patient was not determined, but hematuria can be a complication of the patient's underlying hemophilia.

There were 12 subjects who participated in the perioperative management in Arm 4 of Study 998HB102 with 3 of those subjects (25%) reporting at least 1 SAE during the surgery and rehabilitation period. The 6 SAEs which occurred in the 3 subjects are listed on Table 4 below. All of the perioperative SAEs were considered unrelated to the study drug and did not lead to discontinuation of rFIXFc.

Table 4: Serious AEs During the Surgery/Rehabilitation Period of Study 998HB102¹²

Subject ID Study Arm Age (yr)	Preferred Term	Judged Relationship to rFIXFc	Onset Day in relation to study entry (rFIXFc was ongoing)	Comment
102-004 Arm 4 61	Bacterial sepsis	Unrelated	290	Gram negative sepsis 2 days after dental surgery
	Tachycardia	Unrelated	313	
813-002 Arm 1 with surgical events in Arm 4 24	Bacterial sepsis	Unrelated	313	
	Pilonidal cyst	Unrelated	165	
881-004 Arm 1 with surgical events in Arm 4	Tooth abscess	Unrelated	194	
	Limb crushing injury	Unrelated	330	Mining accident

Events of Special Interest in Study 998HB102:

There were no deaths that occurred during Study 998HB102. There were no inhibitors detected. There were also no SAEs of allergic reactions or anaphylaxis reported. There was one subject who had 2 episodes of dizziness and 1 episode of oral paresthesia (mild) that could have been signs of a hypersensitivity reaction. The patient continued on the treatment regimen without further problems and did not develop inhibitors. There

were no AEs of vascular thrombotic events. Transmission of infectious agents is not expected with rFIXFc because it is a recombinant protein made in a human cell line without any additional human or animal derived components. During Study 998HB102, there were no AEs of suspected transmission of an infectious agent due to a medicinal product.¹³ There was a 20 year old subject from Poland (863-001) who had a negative anti-hepatitis C (HCV) antibody test at screening but then was found to a positive HCV antibody test with elevated liver enzymes during the study. The sponsor notes that there were no known risk factors for HCV in this patient other than his hemophilia, but the patient had a history of injections for 100 bleeds in the year prior to the study. He, therefore, had significant recent exposure risks prior to enrollment in the study potentially with a slightly delayed seroconversion.¹⁴

While the presence of central venous access devices used in hemophiliacs receiving frequent factor infusions is a baseline risk for bacterial infections for any patient, rFIXFc could potentially pose an additional risk. It is possible that the Fc fusion component of rFIXFc could affect IgG total or subclass levels or influence IgG biological recycling. Of the 119 subjects in Study 998HB102, 46 (40.3%) had at least 1 AE that was in the infections and infestations SOC (system, organ, class). All of these events were judged by the investigator to be unrelated or unlikely related to rFIXFc treatment. The majority of the events involved the upper respiratory tract. As outlined in Table 2, the most common events were nasopharyngitis, influenza, upper respiratory tract infections, sinusitis, and rhinitis. These illnesses are common in the general population and are not indicative of immune compromise or increased risk of infection.¹⁵ Further exploration of a theoretical effect on IgG levels showed that there were no clinically meaningful changes observed in the mean actual value or mean change from baseline over time in the total IgG or any of the 4 IgG subclasses in any treatment arms or in arms 1, 2, and 3 combined.¹⁶

There were 4 of the 123 subjects in study 998HB102 who had positive tests for rFIXFc binding proteins (referred to by the sponsor as anti-rFIXFc drug antibody or ADA) at some point during the study. Three of the subjects had a low positive ADA test at screening and at baseline and then reverted to negative during the study. The fourth subject (115-001) was in Arm 2 and had a negative test at screening. At study completion (Day 338), he had a borderline positive result. The sponsor notes that even though the subject had a negative test at screening, at varying points prior to rFIXFc exposure, he had an ADA confirmatory assay value of 4.8% - 28.2% (with 19.7% as the threshold for ADA confirmation). During the study, the subject had values which ranged from 2.0% to 23.5%. The subject did not have any signs of a hypersensitivity reaction or a bleeding episode during the study.¹⁷

Study SYN-FIXFc-07-001: This phase 1/2a, open-label, single dose safety and PK study enrolled 15 patients and had 14 patients complete the study. The study was based in 7 centers in 2 countries and included 14 subjects from the US. Subjects ranged in age from 18 – 76 years old. There were 7 subjects (50%) who reported at least 1 AE in study SYN-FIXFc-07-001. AEs reported by more than 1 subject were: sinusitis (2 subjects) and increased thrombin-antithrombin (TAT) complex (2 subjects). There were 2 subjects in the study who had SAEs. One subject with an SAE had a history of laparotomy and excision of an abdominal hematoma and developed moderate abdominal adhesions. The second subject had a history of bipolar disorder and

depression and during the study experienced an SAE of mild depression. There were no positive inhibitor tests or confirmed anti-rFIXFc binding antibodies in the study.

Extension Study 9HB01EXT: As of Oct. 9, 2012, there were 87 subjects enrolled in this extension study. At the data lock point, there were 4 SAEs reported: convulsion in a patient with a history of a convulsion and a history of an intracranial hemorrhage as a child, ureteric calculus in a patient with a history of bilateral nephrolithiasis, cellulitis of the leg in a patient with a recent history of cellulitis, and a subdural hemorrhage 2 days after being hit by a car. The preliminary safety data from this extension study does not indicate any new safety concerns.¹⁸

Study 9HB02PED: This pediatric study is an ongoing open-label, multicenter study of the safety, pharmacokinetics, and efficacy of rFIXFc for routine prophylaxis and control of bleeding in previously treated patients <12 years of age. Safety data on 24 patients was included in the Interim Clinical Pharmacology Report with a data cut-off date of Apr. 23, 2013. The median duration of treatment for the interim report was 21.3 weeks with a range of 1.1 week to 45.7 weeks. The study will continue for approximately 50 doses of weekly prophylactic treatment with rFIXFc. At the time of the interim report, 9 of the enrolled children were <6 years of age and 15 were 6 to <12 years of age. The only SAEs reported were a fall and a head injury in a 2-year-old male patient who fell out of bed. Following the fall, the patient had a red spot visible on his right temple and vomited twice. He was admitted to the hospital for observation and was given a dose of rFIXFc in addition to his usual prophylactic schedule. He was not found to have any further complications and was discharged the next day. The Investigator considered the events to be unrelated to the study treatment. At the time of the data cut-off, there were no inhibitors detected, no vascular thrombotic events reported, and no grade 2 or higher hypersensitivity reactions.¹⁹ The study is ongoing, but there were no new safety issues identified in the interim report.

b. Safety Concerns

i. Safety Concerns from the Risk Management Plan

Inhibitor Formation: Historically, inhibitors (neutralizing antibodies to factor IX) have been detected in previously treated patients receiving factor IX products. The formation of these antibodies can lead to lack of effect for the product as well as allergic reactions. There were no inhibitors found in subjects during the clinical trials for rFIXFc. The sponsor states that *in Study 998HB102, the inhibitor incidence rate (95% CI) among 55 subjects with at least 50 EDs and a valid inhibitor test after 50 EDs was 0% (0%, 6.49%), which is within the prespecified reference range for inhibitor risk (upper limit of 95% CI of 10.65%).*²⁰ Thus, this product does not appear to have a higher risk of inhibitor development than other hemophilia B treatment products, but there is an inherent risk with all of the FIX products.

Hypersensitivity: Hypersensitivity reactions are a possible concern following the infusion of exogenous proteins like FIX. Hypersensitivity reactions may be due to inhibitor development or other antibody development. Antibodies may form in response to the FIX or to residual traces of animal protein in a product. rFIXFc is made in HEK cells and is animal protein free. There were no allergic reactions and no anaphylaxis during the clinical trials. The sponsor proposes that rFIXFc may be less immunogenic than commercially available FIX because of rFIXFc's composition of FIX genetically fused to the Fc domain of the human IgG.²¹

Thromboembolic Events: In prior studies, factor IX complex concentrates have been associated with the development of thromboembolic complications including disseminated intravascular coagulation (DIC). Factor IX given without the additional coagulation factors found in the factor IX complex concentrates could pose a lower risk of thrombosis. Also, patients with hemophilia B who receive factor IX would be expected to be at a lower risk of thrombosis than non-hemophiliac patients who receive factor IX complex concentrates for warfarin-reversal. In vitro data suggest that rFIXFc has an activated FIX level of one-tenth of that of BeneFIX which may give rFIXFc a lower thrombotic risk.^{22, 23} There were no cases of vascular thrombosis during the rFIXFc clinical program. The sponsor states that evaluation of rFIXFc compared to BeneFIX and Profilnine using the Wessler Stasis Model in rabbits demonstrated that rFIXFc had a low thrombogenic risk. A subset of patients in study 998HB102 had D-dimer, TAT, and F1+2 measured during the study and there were no clinically relevant changes observed.²⁴

Areas of Missing Information: Children <12 years old were not included in study 998HB102, and there were only 2 patients ≥65 years old. There is an ongoing study, 9HB02PED, which includes previously treated pediatric patients less than 12 years of age. The clinical studies also did not include pregnant women. Any congenital anomalies or birth defects in children born to male subjects during the study period were required to be reported. There were no cases reported.

ii. Additional Safety Concerns from the Summary of Clinical Safety

Lack of Effect/Bleeding Episodes: Patients receiving treatment and having less than expected therapeutic effect are at risk of serious bleeding episodes due to the inherent nature of the underlying disease. Decreased efficacy of any factor replacement can potentially be due to, amongst other causes, inhibitor development or lack of compliance with dosing. The proposed PI includes instructions for testing for inhibitor development and for adjusting the rFIXFc dose if necessary.

Infection Events/Effects on Immune Response: Since rFIXFc contains the Fc portion of the IgG molecule, there is a theoretical risk that its presence would affect the natural levels of IgG in the recipient. The information from the clinical trials did not indicate an increased risk for infection or a change in circulating IgG levels in the subjects.

Immunogenicity: As mentioned in the section on hypersensitivity, there is a risk that FIX binding antibodies could cause an allergic reaction or affect the half-life of the product by altering the FIX clearance rate in the subject. In study 998HB102, there were 4 subjects who had a positive anti-rFIXFc antibody test. Three of the 4 were positive at screening. The fourth had a history of a positive anti-rFIXFc antibody test prior to rFIXFc treatment but then tested negative at screening. There were no clinical correlations seen with these antibodies, and the patients did not have rising levels of antibodies.

Viral Transmission: rFIXFc is a fully recombinant product made in HEK cells which reduces the risk of transmission of infective agents such as viruses. The manufacturing process contains a viral clearance step of nanofiltration. During the clinical trials, there was a subject from Poland who had a negative hepatitis C test at screening and then a positive hepatitis C antibody test with elevated liver function tests during the study. He had a history of multiple bleeding episodes prior to the study that would have increased his exposure risk. The hepatitis C test was felt by the investigator to be unrelated to the

study product. Transmission of human viruses is not expected in fully recombinant products.

iii. Additional Safety Concern from the FDA Review Team

Dosing errors: The current U.S. licensed FIX products have a significantly shorter half-life than rFIXFc. If rFIXFc is dosed according to a more frequent schedule than recommended, the FIX levels may become too high and potentially increase the risk of serious adverse events such as thromboembolism. The sponsor states that *medication errors with rFIXFc are unlikely to occur and rFIXFc has no known special risks increasing the potential for medication errors.*²⁵ This reviewer feels that the significant difference in half-life of rFIXFc compared to the current factor IX replacement products is a potential risk for increased medication errors.

Nephrotic Syndrome: There are literature reports of nephrotic syndrome following high doses of a plasma-derived factor IX being used in immune tolerance induction (ITI, also called immune tolerance therapy or ITT). Use of rFIXFc for immune tolerance is not a proposed indication for this product, but there is a history of other FIX products being used for ITT without a specific indication for it. There is a potential serious risk of nephrotic syndrome if rFIXFc is used for ITT as well.

c. Sponsor's Proposed Actions

The sponsor did not find any known identified risks during the clinical trials. Important potential risks the sponsor listed are inhibitor formation, hypersensitivity reactions, and thromboembolic events. The sponsor has provided information on all of these risks in the package insert and has expedited reporting. The sponsor also has ongoing phase 3 studies that will add to the safety database for these events. Targeted questionnaires will be used to gain information on these potential risks. In response to the FDA information request dated July 1, 2013, the sponsor added development of anti-FIX binding antibodies, dosing errors, and nephrotic syndrome following attempted immune tolerance induction and the planned actions regarding these issues to the list of important potential risks as is outlined in Table 5 below.

The sponsor has identified the following areas where there is important missing information regarding rFIXFc: pediatric patients <12 years of age and geriatric patients. These areas of missing information are all addressed in the proposed package insert and routine pharmacovigilance is planned for these areas. In addition, there is an ongoing study, 9HB02PED, for use in pediatric patients <12 years old. In response to an FDA information request, the sponsor added the use of rFIXFc for immune tolerance and use during pregnancy, labor and delivery, and lactation in women with hemophilia B to the areas of important missing information. Table 5 below outlines the sponsor's proposed pharmacovigilance plan for the important potential risks and missing information for rFIXFc.

Table 5: Summary of Safety Concerns and Planned Pharmacovigilance Actions²⁶

²⁷,

Safety concern

Planned actions

Important Potential Risks

Inhibitor Formation

Routine pharmacovigilance

Safety concern	Planned actions
Allergic reactions or anaphylaxis	Pediatric study 9HB02PED Safety extension study 9HB01EXT Extended pharmacovigilance: --Expedited reporting of inhibitors --Targeted follow-up questionnaire for inhibitor formation Routine pharmacovigilance Pediatric study 9HB02PED Safety extension study 9HB01EXT Extended pharmacovigilance: --Expedited reported of allergic reactions and anaphylaxis --Targeted follow-up questionnaire for allergic reactions and anaphylaxis Routine pharmacovigilance
Thrombotic events	Pediatric study 9HB02PED Safety extension study 9HB01EXT Extended pharmacovigilance: --Expedited reporting of thrombotic events Targeted follow-up questionnaire for thrombotic events Routine pharmacovigilance:
Development of anti-FIX binding (non-neutralizing) antibodies to rFIXFc	--Testing for anti-FIX antibodies to rFIXFc in Pediatric study 9HB02PED and extension study 9HB01EXT Enhanced pharmacovigilance: --If anti-FIX binding antibodies to rFIXFc are detected in clinical trials, a review of safety, efficacy and PK data will be performed Routine pharmacovigilance: --Cumulative analyses in Periodic Safety Update Reports (PSURs)
Dosing errors due to the prolonged half-life of rFIXFc	--Pediatric study (9HB02PED) --Extension study (9HB01EXT) Enhanced pharmacovigilance: --Targeted follow-up of dosing errors from spontaneous reports, other programs with solicited data and all clinical trial AE reports of dosing errors Routine pharmacovigilance:
Nephrotic syndrome with attempted immune tolerance induction with rFIXFc	--Cumulative analyses in PSURs Enhanced pharmacovigilance: --Targeted follow-up of nephrotic syndrome from spontaneous reports and other programs with solicited data
Important Missing Information	
Pediatric patients <12 years of age	Routine pharmacovigilance Pediatric Study 9HB02PED Limited data from safety extension study 9HB01EXT
Patients ≥65 years old	Routine pharmacovigilance Limited data from safety extension study 9HB01EXT
Use of rFIXFc for immune tolerance	Routine pharmacovigilance:

Safety concern

Planned actions

Use during pregnancy, labor and delivery, and lactation in women with hemophilia B

--Cumulative analyses in PSURs
Routine pharmacovigilance:
--Cumulative analyses in PSURs

4. OTHER INFORMATION FROM MANAGED REVIEW PROCESS

While the chromatographic and nanofiltration viral clearance steps used in manufacturing are felt to be very effective, the review team is working with Chemistry, Manufacturing, and Controls (CMC) and the sponsor to add a -----(b)(4)----- step to the manufacturing process. This may be conducted as a CMC postmarketing commitment (PMC).

The clinical review team in OBRR has discussed plans to have the extension study 9HB01EXT converted to a clinical PMC.

5. POST-LICENSURE SAFETY REVIEW

a. Recombinant FIX products

rFIXFc is not currently approved or marketed in any country. BeneFIX and Rixubis are the two currently U.S. licensed factor IX (recombinant) products. Rixubis was just approved in June 2013, and therefore does not yet have postmarketing data available. The Rixubis package insert (PI) includes warnings regarding hypersensitivity reactions, inhibitor development, nephrotic syndrome with immune tolerance induction, and thromboembolic complications.

BeneFIX has been on the U.S. market for 15 years. Postmarketing adverse reactions reported in the package insert for BeneFIX are: inadequate factor IX recovery, inadequate therapeutic response, inhibitor development, anaphylaxis, angioedema, dyspnea, hypotension and thrombosis. BeneFIX is made in Chinese hamster ovary cells and contains trace amounts of CHO proteins. The BeneFIX package insert states that patients receiving BeneFIX may develop hypersensitivity to these non-human mammalian proteins. BeneFIX's package insert warns that the safety of BeneFIX administered by continuous infusion has not been established. Some of the postmarketing reports of thromboembolic events described the AE occurring during BeneFIX continuous infusion. The BeneFIX label also states that nephrotic syndrome has been reported following use of FIX products for immune tolerance induction.

The FDA internal annual surveillance report for BeneFIX covering the time period of 2/12/12 – 2/11/13 included an annual Adverse Event Reporting System (AERS) search which found 46 worldwide adverse events with 37 of those being serious. There were no deaths reported during this surveillance period. For the serious cases, the most common preferred terms were hemorrhage, fall, hemarthrosis, drug ineffective, allergic reaction, anaphylactic reaction, arthropathy, bleeding, contusion, and dizziness. The number of AE reports to AERS has increased significantly in 2013 due to an ongoing non-clinical study program called the Hemophilia Patient Chart Study. The reports in AERS made in conjunction with this study describe typical hemophilia disease complications including break-through bleeding, joint injury, and arthropathy. The most

common PTs seen in AERS are typical medical sequelae of hemophilia B as it is a chronic coagulation disorder that often results in bleeding, especially into the joints. A literature search on BeneFIX and recombinant factor IX on June 12, 2013 revealed five recent articles related to safety (PubMed search for “recombinant factor IX” and “safety” and “BeneFIX” and “safety” covering the past 5 years). The most recent article is by Franchini et al.²⁸ and reviews the use of recombinant FIX. It concludes that the licensed recombinant FIX product (BeneFIX) has an excellent safety profile and excellent clinical efficacy for halting and preventing bleeding in hemophilia B patients. A second article²⁹ describes a study of safety and efficacy of BeneFIX prophylaxis in children with severe hemophilia. The article states that approximately 7,000 patients worldwide have used BeneFIX. A prospective, open-label clinical study included 25 subjects, with 10 of these subjects accruing more than 50 exposure days. Only two of the subjects had adverse events felt to be related to BeneFIX. One had a mild rash and the other patient had an allergic reaction that was associated with a low-titer FIX inhibitor. The inhibitor titers spontaneously decreased and were undetectable 2 and 3 months later. The patient received premedication and did not have allergic reactions with subsequent doses. There were no reports of thrombosis in the study. Two subjects had elevated thrombogenic markers, but they had no associated clinical symptoms. In the study, factor IX inhibitor and anti-FIX antibody assessments were conducted at baseline and every 1 - 3 months thereafter. The one inhibitor subject was the only patient found to be anti-FIX ELISA positive. The article did not mention the potential development of anti-CHO antibodies. The authors concluded that safety was established for BeneFIX due to the low incidence of treatment-related adverse events. A third article³⁰ describes a study of an investigational recombinant factor IX named IB1001. The study was a randomized, double-blind, non-inferiority, cross-over study in patients ≥ 12 years old with severe or moderately severe hemophilia B. The study focused on the pharmacokinetics of the investigational product and compared it to BeneFIX. There were eight adverse events in each arm of the study (IB1001 and BeneFIX). Most of the events were mild or moderate and all except two cases of headache were considered unrelated to the study drug. There was one serious AE reported, and it involved an ankle hemarthrosis after BeneFIX treatment. The authors of the study concluded that IB1001 was well tolerated and without safety concerns. A fourth article was a manufacturer-sponsored study assessing the efficacy and safety of BeneFIX in China.³¹ F Thirty-five patients were treated with BeneFIX. There were 21 AEs in 13 patients, and none were felt by the investigators to be related to the study drug. One patient was found to be positive for FIX inhibitors at study entry and was subsequently withdrawn from the study. There were no cases of new FIX inhibitor development during the study. There were no new safety concerns identified in the study. A final relevant article³² FF described a retrospective study that reviewed 13 knee replacement surgeries in 11 patients with hemophilia B performed by the same surgeon over a ten-year period. Ten patients received plasma-derived Factor IX and the remaining one received BeneFIX. Seven of the patients received continuous infusions of Factor IX. Across all the cases, there was no excess hemorrhage, no thrombosis and no infections.

b. Fc Fusion Protein Products

There have been seven Fc Fusion protein products approved by the FDA. The first product, etanercept, was approved in 1998 and the last two products were approved in 2012³³. Most of these products contain the Fc portion of IgG fused to immunosuppressive agents for the treatment of rheumatoid arthritis. As a result, the package inserts for these products include warnings regarding the risk of serious infections. Romiplostim is an example Fc Fusion protein that includes a thrombopoietin analogue peptide. Romiplostim's PI does not list infection as a risk, presumably because the potential effects of the Fc portion were not found to significantly affect the immune system (as hypothesized above in section 3.b.ii). rFIXFc could be considered similar to romiplostim as the factor fused to the Fc protein is not an immunomodulator. Of note, several of the Fc Fusion protein products (including etanercept, romiplostim, and alefacept) include sections in the PI discussing immunogenicity and antibody formation. All three of these products had some patients in the clinical trials develop binding antibodies to the recombinant protein (approximately 5% in each of product). It was noted that other than the 2 patients (0.4%) in the romiplostim trial who showed neutralizing activity, the rest of the antibodies did not show a correlation with clinical effectiveness or a safety concern.

6. INTEGRATED RISK ASSESSMENT

rFIXFc is a recombinant FIX product that is made in HEK cells and provides the benefit of an extended half-life by being fused to the Fc portion of the IgG molecule. There are two currently licensed recombinant FIX products which are made in CHO cells. BeneFIX has been licensed in the US for over 15 years with an excellent safety profile. The clinical program for rFIXFc included over 120 subjects and did not show any inhibitor development, severe allergic reactions, thrombotic events, or other unexpected events. The sponsor acknowledges and documents in the proposed package insert that there is missing safety data for use in children <12 years old, elderly patients (≥65 years old), and pregnant and lactating women.

The proposed pharmacovigilance plan includes routine pharmacovigilance, quarterly periodic adverse event reports for three years, 15-day expedited reports for serious, unlabeled adverse events as well as specific events of interest, and completion of the pediatric study 9HB02PED and the safety extension study 9HB01EXT. The reviewed safety data do not substantiate a need for a post-marketing requirement (PMR) or a risk evaluation and mitigation strategy (REMS).

7. RECOMMENDATIONS

1. OBE supports OBRR's proposal for a supplemental information sheet/Patient Package Insert to further explain the new dosing schedule with rFIXFc. The currently licensed FIX replacement products have shorter half-lives than rFIXFc. This difference creates the risk that physicians and patients may use rFIXFc according to a more traditional prophylactic schedule of twice a week dosing and then potentially have increased complications from the high levels. A communication to patients included with the PI would highlight the different half-life and recommended dosing for rFIXFc.
2. OBE agrees with the sponsor's submitted Risk Management Plan with the alterations included in the Efficacy Information Amendment 1.11.3 submitted Aug. 9, 2013 as 125444 amendment 22.

Footnotes

- ¹ Adapted from BLA 125444, Risk Management Plan, p. 9.
- ² BLA 125444, Risk Management Plan, p. 10.
- ³ BLA 125444, Risk Management Plan, p. 11.
- ⁴ BLA 125444, Summary of Clinical Safety, p. 14-16.
- ⁵ BLA 125444, Summary of Clinical Safety, p. 36-37.
- ⁶ BLA 125444, Summary of Clinical Safety, p. 42.
- ⁷ Severe AE is defined in Study 998HB102 Protocol, p. 82 as: symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.
- ⁸ BLA 125444, Summary of Clinical Safety, p. 46.
- ⁹ BLA 125444, Summary of Clinical Safety, p. 43.
- ¹⁰ Serious AE is defined as: results in death, in the view of the Investigator, places the subject at immediate risk of death (a life-threatening event), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or results in a congenital anomaly/birth defect.
- ¹¹ BLA 125444, Summary of Clinical Safety, p. 52-53.
- ¹² BLA 125444, Summary of Clinical Safety, p. 77.
- ¹³ BLA 125444, Summary of Clinical Safety, p. 55-56.
- ¹⁴ BLA 125444, Summary of Clinical Safety, p. 58.
- ¹⁵ BLA 125444, Summary of Clinical Safety, p. 57.
- ¹⁶ BLA 125444, Summary of Clinical Safety, p. 71.
- ¹⁷ BLA 125444, Summary of Clinical Safety, p. 72.
- ¹⁸ BLA 125444, Summary of Clinical Safety, p. 87-88.
- ¹⁹ BLA 125444.16, Interim Clinical Pharmacology Report (Study 9HB02PED), p. 23.
- ²⁰ BLA 125444, Risk Management Plan, p. 14.
- ²¹ BLA 125444, Risk Management Plan, p. 14.
- ²² Buyue Y, Chhabra ES, Wang L. The effect of factor IXa on thrombin generation activity determination: rFIXFc vs. BeneFIX® [abstract]. *Blood*. 2011;118(21):#2266.
- ²³ Peters RT, Low SC, Kamphaus GD, et al. Prolonged activity of factor IX as a monomeric Fc fusion protein. *Blood*. 2010;115(10):2057-64. Epub 10 Jan 7.
- ²⁴ BLA 125444, Risk Management Plan, p. 14.
- ²⁵ BLA 125444, Risk Management Plan, p. 38.
- ²⁶ BLA 125444, Risk Management Plan, p. 27-28.
- ²⁷ BLA 125444.22, Efficacy Information Amendment 1.11.3, p. 1-5.
- ²⁸ Franchini M, Frattini F, Crestani S, Sissa C, Bonfanti C. Treatment of hemophilia B: focus on recombinant factor IX. *Biologics*. 2013;7:33-8. doi: 10.2147/BTT.S31582. Epub 2013 Feb 12.
- ²⁹ Monahan PE, Liesner R, Sullivan ST, Ramirez ME, Kelly P, Roth DA. Safety and efficacy of investigator-prescribed BeneFIX prophylaxis in children less than 6 years of age with severe haemophilia B. *Haemophilia*. 2010 May; 16:460-8.
- ³⁰ Martinowitz U, Shapiro A, Quon DV, et al. Pharmacokinetic properties of IB1001, an investigational recombinant factor IX, in patients with haemophilia B: repeat

pharmacokinetic evaluation and sialylation analysis. *Haemophilia*. 2012 Nov; 18(6);881-7.

³¹ HHYang RHH, HHZhao YHH, HHWang XHH, HHet al.H Evaluation of the safety and efficacy of recombinant factor IX (nonacog alfa) in minimally treated and previously treated Chinese patients with haemophilia B. HH*Haemophilia*.HH 2012 Sep;18(5):e374-8.

³² Uprichard J, Adamidou D, Goddard NJ, Mann HA, Yee TT. Factor IX replacement to cover total knee replacement surgery in haemophilia B: a single-centre experience, 2000-2010. *Haemophilia*. 2012 Jan;18(1):46-9.

³³ Czajkowsky DM, Hu J, Shao Z, Pleass RJ. Fc-fusion proteins: new developments and future perspectives. *EMBO Mol Med*. 2012 Oct;4(10): 1015-28.

Related Memo

- [Addendum to pharmacovigilance plan review, January 30, 2014 - ALPROLIX \[ARCHIVED\]](#)