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

MEMORANDUM

Date:	May 27, 2014
From:	Bethany Baer, MD Medical Officer, Pharmacovigilance Branch (PVB), Division of Epidemiology (DE), Office of Biostatistics and Epidemiology (OBE)
To:	Chava Kimchi-Sarfaty, Chair of BLA 125426 Review Team, Office of Blood Research and Review
Through:	Craig Zinderman, MD, MPH Acting Chief, PVB, DE, OBE Scott Winiecki, MD Acting Director, DE, OBE
Subject:	Pharmacovigilance Plan Version 2 review for initial licensure
Applicant:	Cangene/Emergent BioSolutions
Product:	Recombinant Factor IX Concentrate, Ixinity (IB1001)
Proposed Indication:	Control and prevention of bleeding, peri-operative management in patients with hemophilia B, and secondary, tertiary, or intermittent prophylaxis to reduce the frequency of bleeding episodes in adults and children ≥12 years of age with hemophilia B.
Submission Type:	BLA 125426
PVP Submission Date:	Jan 27, 2014
Action Due Date:	Jul 29, 2014

1. INTRODUCTION

a. Product Description

Coagulation factor IX (Recombinant), IB1001 (also referred to as Ixinity), is a purified recombinant form of the human coagulation factor IX protein. It is produced in Chinese Hamster Ovary (CHO) cells and is a single chain glycoprotein with an amino acid sequence identical to the Thr148 allelic form of plasma-derived factor IX. It is used to treat patients with hemophilia B. It is functionally and structurally similar to BeneFIX (a recombinant factor IX currently marketed in the United States), and would provide an alternative to the factor IX products already approved in the U.S. Following a Complete Response letter in 2013, the sponsor added a (b) (4) step to the manufacturing process (referred to as the "modified process") to remove host cell proteins (HCPs). The sponsor refers to the product that has undergone the modified process with (b) (4) as the "polished" product.

b. Regulatory History

The study IB1001-01 under the IND 13551 was placed on clinical hold by the FDA on July 5, 2012 due to concerns regarding the development of anti-CHO antibodies in 18 of 68 subjects in the trial.[1] Subsequently, the initial application for licensure was issued a Complete Response (CR) letter on Feb 1, 2013. The Division of Epidemiology (DE) reviewed the initial application for IB1001 in a memo dated Dec 12, 2012. The Complete Response letter listed 25 comments, of which 16 were related to Chemistry, Manufacturing, and Controls issues. The main concern from the review team centered on the level of CHO proteins and associated immunogenicity. Following the addition of the (b) (4) step to remove host cell proteins, the clinical hold was lifted on IND 13551 on Jul 26, 2013. On Jan 27, 2014, the sponsor (now Cangene/Emergent BioSolutions instead of the original sponsor, Inspiration Biopharmaceuticals) resubmitted the application with responses to the CR letter, an updated IB1001-01 study report with a data lock date of Mar 1, 2013, an updated summary of clinical safety, and a new pharmacovigilance plan.

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 Cangene with the BLA 125426/0.18. The BLA is seeking initial licensing of IB1001 for the indications of:

1. control and prevention of bleeding,
2. peri-operative management in patients with hemophilia B, and
3. secondary, tertiary, or intermittent prophylaxis to reduce the frequency of bleeding episodes in adults and children ≥12 years of age with hemophilia B.

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

2. MATERIALS REVIEWED

Source	Subtype	Document Reviewed

[1] IND 13551, FDA Clinical Hold Letter, dated Jul 5, 2012

Inspiration	BLA 125426/0	Summary of Clinical Safety (original submission)
Inspiration	BLA 125426/0.7	Pharmacovigilance Plan (United States) Version 0.1
Inspiration	BLA 125426/0.8	BLA Amendment
Cangene	BLA 125426/0.18	Resubmission Cover letter
Cangene	BLA 125426/0.18	Pharmacovigilance Plan Version 2.0
Cangene	BLA 125426/0.18	Summary of Clinical Safety (resubmission with data lock date of Mar 1, 2013)
Cangene	BLA 125426/0.18	Immunogenicity Risk Assessment, IB1001, Appendix 16.1.12
Cangene	BLA 125426/0.23	Phase I/II/III Pharmacokinetic and Outcome Study of Ixinity (IB1001), a Recombinant Factor IX Product, in Subjects with Hemophilia B – Supplemental Clinical Study Report
Cangene	BLA 125426/0.27	Response to FDA Information Request Dated May 09, 2014
Cangene	IND 13551/0.72	Protocol IB1001-02, dated Jun 26, 2013
Cangene	IND 13551/0.72	Summary of Changes Study Protocol IB1001-01, dated June 26, 2013
Cangene	IND 13551/0.80	Protocol IB1001-04 v 1.3, dated Dec 13, 2013
Wyeth	Package insert	BeneFIX Package Insert
FDA	Internal Surveillance Report	OBE Internal Surveillance Reports for BeneFIX and Rixubis
FDA	IND 13551	Clinical Hold Letter, dated Jul 5, 2012
FDA	IND 13551	Release from Clinical Hold Letter, dated Jun 26, 2013
FDA	Review Memo	Division of Epidemiology Pharmacovigilance Plan Version 0.1 review by Bethany Baer, MD, dated Dec 12, 2012
Other	Publication	Franchini M, Frattini F, Crestani S, Sissa C, Bonfanti C. Treatment of hemophilia B: focus on recombinant factor IX. Biologics. 2013;7:33-8. Epub 2013 Feb 12.
Other	Publication	Ingerslev J. Christiansen K, Ravn HB et al. Antibodies in heterologous proteins in hemophilia A patients receiving recombinant factor VIII (Recombinate). Thromb Haemost 87:626-34, 2002.
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. Haemophilia. 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. Haemophilia. 2010 May: 16:460-8.
Other	Publication	Powell JS, Pasi KJ, Ragni MV, et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. N Engl J Med. 2013 Dec 12;369(24):2313-23. Epub 2013 Dec 4.
Other	Publication	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
Other	Publication	Windyga J, Lissitchkov T, Stasyshyn O, et al. Efficacy and safety of a recombinant factor IX (Bax326) in previously treated patients with severe or moderately severe haemophilia B undergoing surgical or other invasive procedures: a prospective, open-label, uncontrolled, multicentre, phase III study. Haemophilia. 2014 Apr 3. [Epub ahead of print].
Other	Publication	Yang R, Zhao Y, Wang X, Sun J, Jin J, Wu D, Charnigo R, O'Brien A, Zhong Z, Rendo P. Evaluation of the safety and efficacy of recombinant factor IX (nonacog alfa) in minimally treated and previously treated Chinese patients with haemophilia B. Haemophilia. 2012 Sep;18(5):e374-8.

3. PHARMACOVIGILANCE PLAN REVIEW

The Pharmacovigilance Plan (United States) Version 0.1 was received on August 29, 2012 and reviewed in a DE memo in Dec 2012. With the application resubmission following the CR letter, the sponsor submitted Pharmacovigilance Plan Version 2 on Jan 27, 2014. A review of Pharmacovigilance Plan Version 2 with supporting clinical trial information from the updated Summary of Clinical Safety is included below.

a. Non-clinical Study with "Polished Product"

A non-clinical study was performed to evaluate the manufacturing changes that were made to reduce the host cell proteins associated with the anti-CHO antibodies. Using the "polished product" that resulted from the modified manufacturing process, an immunogenicity study (1914-008) was conducted in (b) (4) rabbits. In this study, *it was observed that the incidence of immunogenicity (based on reactivity) had been significantly reduced. . . . Thus, the "polished product" should reduce the anti-CHO response seen historically in clinical trials.*[2]

b. Clinical Safety Database

Study IB1001-1

The single clinical trial available at the initial application submission, Protocol IB1001-01 Phase I/II/III is titled Pharmacokinetic and Outcome Study of Inspiration's Recombinant Factor IX Product, IB1001, in Subjects with Hemophilia B. The majority of the data from this study pertains to the IB1001 product resulting from the original manufacturing process. Patients in clinical studies IB1001-01 (adults ≥12 years of age) and IB1001-02 (pediatric patients <12 years of age) are being transitioned to the "polished" product which has undergone the modified process to remove host cell proteins.

Briefly, subjects entered into either the pharmacokinetic (PK) or recovery phase of the Study IB1001-01 and progressed to 6 months of treatment with either an on-demand or prophylaxis schedule, and then if desired, to a continuation phase, where they could continue on IB1001 until product licensure or for up to one year, depending upon the approval by the applicable regulatory agency. The study also included a surgery sub-study phase in which subjects could participate separately, without a requirement for participation in the other study phases.[3]

With a data lock date of Mar 1, 2013, there were 77 subjects participating in any phase of Study IB1001-01 that had received at least one dose of IB1001 and were thus included in the safety analysis. All of the safety data pertains to IB1001 before the modified manufacturing process was put into place to create the polished IB1001.
There were 68 subjects in the treatment/continuation phase of the trial, including 45 subjects with >100 exposure days (ED). *In total, 43 subjects enrolled in the*

[2] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 12.
[3] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 4.

Treatment/Continuation phase had discontinued the study as of March 01, 2013. Certain subjects had enrolled for a limited period ((b) (6)*) while others (*(b) (6)*) discontinued due to a move. Five subjects were terminated for lack of compliance (*(b) (6)*). One subject (*(b) (6)* withdrew because of a perceived lack of efficacy. A number of subjects withdrew following the clinical hold issued by the FDA in July 2012. Subjects at site 40 were withdrawn based on the investigator's decision to join a competing study on a long acting factor IX product. Some subjects were withdrawn from the study due to positive CHOP* [Chinese hamster ovary protein] *responses.*[4]

There was a total of 449 adverse events (AEs) reported in 58 (75.3%) of the 77 subjects. Of the 449 AEs reported, 67.7% were considered mild, 26.9% were moderate, and 5.1% were severe. There were 14 serious adverse events (SAEs) which were all assessed by the study team as being unrelated to the study drug. The AEs that were reported in >10% of study subjects were headache (16.9%), arthralgia (15.6%), pyrexia (13.0%), nasopharyngitis (11.7%), and limb injury (10.4%).[5]

For Study IB1001-01, all of the 68 patients in the treatment phase were male. 79.4% were Caucasian, 10.3% were Asian, 4.4% were Black, 2.9% were Native Hawaiian, and 2.9% were other race. The mean age was 30 years old, with a range from 7 to 64 years of age.[6]

Adverse Events in Clinical Study:

Pharmacokinetic (PK) phase: The pharmacokinetic phase involved a crossover study with BeneFIX as a control. While the goal of this phase of the study was not a safety assessment, the cross-over design does provide a comparison between IB1001 and the only licensed recombinant factor IX product at the time, BeneFIX. With the updated data lock date of Mar 1, 2013, there was a total of 24 AEs in 15 subjects. Fourteen of the AEs were in the BeneFIX control group and 10 of the events were in the IB1001 group. None of the AEs were considered serious. Two of the events (nephrolithiasis and hemarthrosis) were considered severe and both occurred in patients during the BeneFIX arm of the pharmacokinetic study.[7]

Table 1: Adverse Events in PK Phase[8]

Preferred Term	BeneFIX Phase n=32 n	IB1001 Phase n=32 n
Number of AE's	14 AEs in 10 subjects	10 AEs in 5 subjects
Headache	3	3
Migraine	1	0
Abdominal discomfort	1	0

[4] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 41.
[5] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 41, 53.
[6] BLA 125426/0.18, Summary of Clinical Safety, p. 23.
[7] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 61-67.
[8] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 62.

Diarrhea	0	1
Vomiting	0	1
Back pain	1	1
Hemarthrosis	3	0
Pyrexia	2	1
Viral gastroenteritis	0	1
Nasopharyngitis	1	0
C-reactive protein increased	0	2
Nephrolithiasis	1	0
Skin hemorrhage	1	0

Treatment/Continuation Phase:
For the treatment phase, 68 subjects were enrolled with 59 initially in the prophylaxis group and 9 in the on-demand group. Five subjects shifted between the two treatment groups and were assessed in their original enrollment group. There were 406 events reported in 57 subjects with 14 of the AEs being SAEs.[9]

Prophylaxis Regimen: There was a total of 347 AEs in 49 subjects during the prophylaxis phase. Fourteen of the AEs were serious and are discussed in Table 2 below. The most common AEs were arthralgia (19.0%), headache (17.2%), limb injury (12.1%), insomnia (10.3%), and nasopharyngitis (10.3%). All of these events were considered unrelated to IB1001 with the exception of 4 events of headache.[10]

On-Demand Regimen: There were 59 AEs reported in 8 of the 9 subjects receiving the on-demand regimen. None of the AEs were serious. The most common AEs were headache, nasopharyngitis, nasal congestion, oropharyngeal pain, wound, and pain in the extremity.

With the updated data lock date of Mar 1, 2013, there were 20 (29%) out of 68 study subjects who were found to have seroconverted to be positive for anti-CHO antibodies during the study. This was an increase of 2 patients compared to the previous data lock date used in the initial submission. There were an additional 11 patients (16%) who were positive at baseline, had sporadic anti-CHOP results or had indeterminate results. In 8 of the 9 subjects who had follow-up samples available, there were declining titers for anti-CHOP antibodies. There were no adverse events, including inhibitor development, associated with the anti-CHOP response. [11] There has been a median of 414 days of follow-up after seroconversion for the affected patients. These subjects continue to be followed in the continuation phase of study IB1001-01.[12]

Surgery Sub-Study:

[9] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 67.
[10] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 68-9.
[11] BLA 125426/0.18, Immunogenicity Risk Assessment, p. 4.
[12] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 87.

There were 22 surgical procedures completed in 17 subjects during the surgery sub-study. Thirteen of the subjects received IB1001 as a bolus and 4 received it as a continuous infusion. Twenty of the procedures were major surgery and 2 were minor procedures. There was a total of 33 AEs reported in 10 subjects in the study. None of the AEs were serious. Pyrexia was the most common AE and occurred in 17.6% of patients. The other AEs were constipation, diarrhea, nausea, vomiting, peripheral edema, procedural pain, wound hemorrhage, abdominal wound dehiscence, incision site hematoma and hemorrhage, incision site pain, wound secretion, arthritis, back pain, decrease joint range of motion, decrease hemoglobin, insomnia, vaginal discharge, pulmonary congestion, ecchymosis, rash pruritic, and scar.[13]

Serious Adverse Events:
There were 14 serious adverse events (SAEs) reported in 10 subjects during all phases of study IB1001-01. These events, which all occurred during the treatment phase of the study, are summarized in Table 2 below. Many of these events had other known causal factors as are listed in the table.

Table 2: Serious Adverse Events in Study IB1001-01[14]

Subject	Preferred Term	Outcome	Intensity	Causality
(b) (6)	Hematoma	Resolved	Moderate	Unrelated – from fall
(b) (6)	Diverticulitis	Resolved	Moderate	Unrelated
	Diverticulitis	Resolved	Severe	Unrelated
	Diverticulitis	Resolved	Severe	Unrelated
(b) (6)	Skin laceration	Resolved	Mild	Unrelated – from motor vehicle accident (MVA)
(b) (6)	Periprosthetic fracture	Resolved with sequelae	Severe	Unrelated
(b) (6)	Joint injury	Resolved	Severe	Unrelated
(b) (6)	Limb injury	Resolved	Moderate	Unrelated - hit with bat during baseball game
(b) (6)	Abdominal pain	Resolved	Moderate	Unrelated
(b) (6) (in previous report listed as (b) (6))	Mental status change	Resolved	Moderate	Unrelated - after eye trauma from hockey puck
(b) (6)	Lumbar vertebral fracture	Resolved	Severe	Unrelated – all were result of an MVA caused by a seizure in patient with a prior seizure disorder.
	Wound infection	Resolved	Life-threatening	
(b) (6)	Femur facture	Resolved	Severe	Unrelated
	Postoperative	Resolved	Severe	Unrelated

[13] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 69-70.
[14] BLA 125426/0.18, Summary of Clinical Safety, p. 83-84.

	wound infection			

The lack of significant safety findings, specifically lack of any detected inhibitors in subjects followed for up to 24+ months, and lack of detection of all other serious class specific adverse events [thromboembolic events, hypersensitivity (including anaphylaxis) and nephrotic syndrome] provide strong support that the safety profile of IB1001 is acceptable and desirable for use in the treatment of subjects with hemophilia B.[15] There will be additional safety information provided through the long-term follow-up of study IB1001-01. There are no new safety concerns raised by the reported adverse events, and as pointed out by the sponsor, many specific potential risks associated with this type of factor product were not seen in the clinical trials (thromboembolic events, hypersensitivity, and nephrotic syndrome).

The sponsor states that an evaluation of the safety data with a data lock date of Mar 1, 2013 from clinical study IB1001-01 *reveals that reported ADRs* [adverse drug reactions] *associated with the use of IB1001 are mild to moderate, and are in line with the expected safety profile for a recombinant factor IX product for treatment of bleeding in hemophilia B patients.*[16]

Supplemental Data from Patients Transitioned to Polished Product:
On Apr 15, 2014, the sponsor submitted a supplemental clinical study report for study IB1001-01 which included data from 7 subjects who had been transitioned from the original IB1001 product to the polished product (data lock date of Feb 28, 2014).[17] These patients were all on the prophylaxis regimen and had 3 months of follow-up on the polished product at the time of the supplemental report. In the follow-up period, a total of 146 infusions of the polished product were given. The median number of exposure days was 23 with a range of 10 – 28 ED on the polished product. Consistent with the original product, there was no inhibitor development in these 7 patients during the available follow-up period. In these 7 patients, the anti-CHOP antibody status remained stable. The 5 subjects that were negative for anti-CHOP antibodies on the original product remained negative on the polished product. The one patient who had seroconverted to anti-CHOP antibody positive while receiving the original product remained positive with a stable titer on the polished product. The one subject who had tested positive for anti-CHOP antibodies at baseline (before receiving IB1001), had indeterminate results while on the original IB1001 and then continued to have indeterminate results while on the polished product. There was one subject who tested positive for non-inhibitory FIX antibodies after receiving the polished product. He had 3 follow-up tests which were all negative for non-inhibitory FIX antibodies.

There was a total 14 AEs in 4 patients during the follow-up period on the polished product. None of these events met the criteria to be considered serious. There were no allergic reactions observed.

[15] BLA 125426/0.18, Summary of Clinical Safety, p. 89.
[16] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 12.
[17] BLA 125426/0.23, Supplemental Clinical Study Report for IB1001-01.

A response to an Information Request dated May 9, 2014 reported that 5 additional patients had been transitioned to the polished product but data was not yet available for these patients.[18]

Events of special interest in IB1001-01:
There were no deaths during the study IB1001-1. There were also no allergic reactions reported during the study. There were, however, other events that may be signs of allergic reaction including asthma (n=2), lethargy (n=1), rash including rash pruritic (n=3), cough (n=6), shortness of breath (n=1), rhinitis allergic (n=2), and chest tightness or pain (n=1). Only one of these events (rash pruritic) was considered related to the study drug.

There were also no reports of anaphylaxis, thrombogenicity, or nephrotic syndrome during the clinical trials with IB1001. [19] Cases of immunogenicity are discussed below in section c.

c. Safety Concerns
Thrombogenicity: There were no cases of thrombotic events (TEs) reported in the IB1001-01 clinical program. *In the PK phase of Study IB1001-01, laboratory parameters monitored included thrombogenic markers prothrombin fragment 1+2 (F1+2), d-dimer and thrombin-antithrombin complex (TAT). There was no concurrent increase in all three markers noted at any time point and no correlation of TEs or thrombotic markers with IB1001 administration was observed.*[20] Thrombosis is a theoretical concern with any substance that affects the clotting cascade. There were no clinical adverse events or thrombosis in the clinical trials for IB1001, but the trials are limited in number of patients. As is common for this category of product, this type of rare adverse event would need to be monitored in a larger population.

Lack of Effect: Due to the nature of hemophilia, patients receiving treatment and having less than expected therapeutic effect are at risk of serious bleeding episodes. Decreased efficacy of any factor replacement can potentially be due to inhibitor development or lack of compliance with dosing. It is difficult to account for the effect of lack of compliance with dosing, but instructions are given in the package insert to adjust the dose if bleeding is seen on the current dose. Inhibitor formation is addressed in the immunogenicity section below.

Immunogenicity – Hypersensitivity, including anaphylaxis: There were no hypersensitivity or allergic reactions reported with the use of IB1001 in hemophilia B patients, including anaphylaxis. There were cases of asthma, lethargy, rash, cough, and chest tightness or pain that could have been signs of hypersensitivity.[21] Allergic reactions are a common concern for this type of factor replacement. There was no sign of increased risk for this product during the clinical trials, but the full significance of the

[18] BLA 125426/0.27, Response to FDA Information Request Dated May 09, 2014.
[19] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 74-76.
[20] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 77.
[21] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 78.

anti-CHO antibody development is not known. This antibody formation could theoretically increase risk of hypersensitivity events.

Immunogenicity – Anti-Factor IX Antibodies: Version 2 of the PVP updated the clinical study information to a data lock date of Mar 1, 2013 and confirmed that there had been no cases of inhibitor development reported in subjects from study IB1001-01. Inhibitor development is an expected event with use of all factor replacement products. It is included on the proposed label for IB1001 and other factor IX products. The lack of inhibitor development seen in this study provides reassurance that inhibitors may not occur in substantial numbers with this product, but small size of the study limits definitive conclusions.

There were non-inhibitory antibodies to factor IX found in 21(27%) of the 77 subjects in study IB1001-01. Five of the 21 subjects who tested positive for the non-inhibitory factor IX binding proteins were positive at screening. The antibodies were sporadic in some patients and more persistent in others. A correlation between these non-inhibitory factor IX antibodies could not be found with anti-CHOP, lack of efficacy, or clinical AEs.[22]

Immunogenicity - Anti-CHO Antibodies: The sponsor states that *as a consequence of the manufacturing process, trace quantities of CHO cell protein are present in IB1001. While studies of marketed recombinant factor products produced in CHO cells suggest that antibodies against such proteins can sporadically be detected in patients as well as non-hemophilic subjects (Ingerslev J et al, 2002), there has been no clinical evidence that this is typical or is associated with any clinical consequences.*[23] Of note, the Ingerslev article[24] referenced describes a study on Recombinate, a recombinant human factor VIII synthesized in Chinese Hamster Ovary cells that was first introduced in 1992, and the conclusions on safety may not fully apply to IB1001. Different processing can lead to varying levels of CHO protein between products. With 18 patients of the 68 (26%) tested in the IB1001-01 study seroconverting for anti-CHO antibodies, the FDA clinical review and Chemistry, Manufacturing and Controls (CMC) teams expressed great concern that the level of CHO protein in IB1001 was greater than in other similar products. There has also been limited follow-up on these patients with anti-CHO antibodies in study IB1001-01. The sponsor reports that there were no clinical characteristics or patient medical histories that appeared to be related with seroconversion. The data suggest that higher doses may be a risk factor. The significance of these antibodies is unclear as there has been no evidence of allergic reactions or other adverse events related to the antibody formation.[25]

Following the CR letter, the sponsor implemented the CMC changes described above to add a step to remove residual host cell proteins. At the time of the updated PVP,

[22] BLA 125426/0.18, Immunogenicity Risk Assessment, p. 18-19.
[23] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 34-35.
[24] Ingerslev J. Christiansen K, Ravn HB et al. Antibodies in heterologous proteins in hemophilia A patients receiving recombinant factor VIII (Recombinate). Thromb Haemost 87:626-34, 2002.
[25] BLA 125426, Pharmacovigilance Plan, p. 32.

immunogenicity to CHO proteins has been observed in 20 out of 68 (29%) subjects in study IB1001-01, and the sponsor states that currently there is no published data to suggest any safety concerns associated with this observation.[26] This data is for patients who received the unpolished IB1001 in the clinical trials. Since October 2013, the sponsor has been transitioning patients to the polished IB1001. With the modified manufacturing process, the polished product has less host cell proteins and should presumably cause less antibody formation. There is currently data for 7 patients in the clinical trial that had been switched to the new polished product. The sponsor plans to continue following these patients and to conduct study IB1001-04 to look at patients who have been treated with other factor IX replacement products but are naïve to IB1001. The subjects will receive polished IB1001product only, but data from this study is not yet available.

Nephrotic Syndrome: There have been reports in the literature of nephrotic syndrome following high doses of a plasma-derived factor IX being used in immune tolerance therapy (ITT) in hemophilia B patients with factor IX inhibitors and a history of allergic reactions. IB1001 has not been studied for use in immune tolerance therapy. There were no cases of nephrosis in the clinical studies. Of note, the sponsor is not currently applying for the indication for IB1001 to include use for ITT. The proposed label specifically addresses the lack of safety information with ITT.

d. Additional Areas for Special Consideration

Pregnancy: IB1001 has not been studied in pregnant or lactating subjects. Due to the X-linked recessive inheritance pattern of this disease, there are extremely few affected females.

Viral Transmission: As IB1001 is a recombinant product, there is less risk of transmission of blood-borne viral pathogens compared to products produced from pooled human plasma. In addition, the manufacturing process of IB1001 contains *two dedicated viral reduction/inactivation steps as well as virus testing and viral inactivation assessments throughout the manufacturing process, hence, safety of IB1001 with regard to viral contamination is reasonably assured.*[27]

e. Sponsor's Proposed Actions

During the clinical trials, the sponsor did not find any known important identified risks. The sponsor has identified the following important potential risks: immunogenicity (inhibitor development)/lack of efficacy, thrombogenicity, hypersensitivity (including anaphylaxis), and nephrotic syndrome. These adverse events were not seen during the clinical trials for IB1001, but they have been reported following the administration of other marketed factor IX products.[28] Areas of important missing information are: pregnant or lactating women, elderly patients (>65 years old), patients with hepatic insufficiency, patients with renal insufficiency, children (<12 years old) previously treated with factor IX products, children previously untreated with factor IX products,

[26] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 13.
[27] BLA 125426/0.18 Summary of Clinical Safety, p. 6.
[28] BLA 125426, Pharmacovigilance Plan, p. 32.

and patients administered IB1001 for use as immune tolerance therapy in patients who have developed inhibitors to factor IX. Table 3 below outlines the sponsor's pharmacovigilance plan for the important risks and missing information for IB1001, and Table 4 describes the 4 ongoing and planned clinical studies for IB1001. The sponsor is planning to continue the study IB1001-01 for long-term monitoring of adults and adolescents. This continuation phase includes the assessment of antibodies to CHO cells and inhibitor testing. The sponsor also has ongoing and planned studies in previously treated children (IB1001-02) and previously untreated children (IB1001-03).[29] With the second version of the PVP, the sponsor has also added a new study (IB1001-04). This study will evaluate polished IB1001 safety and efficacy in previously treated hemophilia B patients ≥12 years of age.

Table 3: Summary of Safety Concerns and Planned Pharmacovigilance Actions[30]

Important Potential Risks	Planned Actions
Immunogenicity	• Routine pharmacovigilance • Long-term safety study IB1001-01 Continuation Phase • Hypersensitivity Reaction Reporting form requesting patients with hypersensitivity reactions provide a sample for assessment of antibodies to CHO cells and inhibitor testing • Clinical studies IB1001-02, -03 and -04 • Cumulative review in all DSURs/PSURs
Lack of Efficacy Thrombogenicity	• Routine pharmacovigilance • Long-term safety study IB1001-01 Continuation Phase • Clinical studies IB1001-02, -03 and -04 • Cumulative review in all DSURs/PSURs
Hypersensitivity (including anaphylaxis)	• Routine pharmacovigilance • Long-term safety study IB1001-01 Continuation Phase • Clinical studies IB1001-02, -03, and -04 • Implementation of Hypersensitivity Reaction Reporting form • Cumulative review in all DSURs/PSURs
Nephrotic Syndrome	• Routine pharmacovigilance • Cumulative review in all DSURs/PSURs
Important Missing Information	**Planned Actions**
Elderly patients (>65 years old) Patients with hepatic insufficiency Patients with renal insufficiency	• Routine pharmacovigilance • Cumulative review in all DSURs/PSURs
Children (<12 years old) previously treated patients (PTPs)	• Routine pharmacovigilance • Clinical study IB1001-02 – Phase III/IV Pediatric Study in pediatric subjects with hemophilia B previously treated with Factor IX products • Cumulative review in all DSURs/PSURs
Children previously untreated patients (PUPs)	• Routine pharmacovigilance • Clinical study IB1001-03 – Phase III/IV Pediatric Study in children with hemophilia B previously untreated with Factor IX products • Cumulative review in all PSURs/DSURs
IB1001 use in immune tolerance therapy	• Routine pharmacovigilance

[29] BLA 125426, Summary of Clinical Safety, 2.7.4, p. 30.
[30] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 116-118.

(ITT)	• Clinical study IB1001-03–Phase III/IV Pediatric Study in children with hemophilia B previously treated with Factor IX products-to identify inhibitor incidence & determine need to evaluate ITT; Need for further evaluation to be determined based upon outcome of IB1001-03 • Cumulative review in all DSURs/PSURs

Table 4: Ongoing and Planned Clinical Studies for IB1001[31]

Study	Title/Description	Milestone dates
IB1001-01 Continuation phase	Phase I/II/III Pharmacokinetic and Outcome Study of Recombinant Factor IX Product, IB1001, in Subjects with Hemophilia B. Includes enhanced anti-CHOP monitoring, safety and efficacy for subjects transitioning to polished IB1001. Includes testing for inhibitory FIX antibodies, non-inhibitory FIX antibodies, and anti-CHOP antibodies.[32]	Study Report Safety and Efficacy (50 subjects x 50 ED): May 2012 Study Report Safety and Efficacy (50 subjects x 100 ED): TBD
IB1001-02	Study of Recombinant Factor IX Product, IB1001, in Pediatric Subjects with hemophilia B (Phase III/IV). Use in children <12 years old who have been previously treated with factor IX (PTPs). Includes Hypersensitivity Reaction Reporting Forms and evaluation of anti-CHO, non-inhibitory factor IX antibody response, and/or factor IX inhibitor formation.[33]	Initiation Q2 2011 Study Report: TBD
IB1001-03	Study of Recombinant factor IX Product, IB1001, in Previously Untreated Patients (PUPs) with hemophilia B (Phase III/IV). Use in children <6 years old who have previously not been treated with any factor IX (PUPs). Includes Hypersensitivity Reaction Reporting Forms and evaluation of anti-CHO and/or factor IX inhibitor formation.	Initiation: TBD Study Report: TBD
IB1001-04	Study of Safety and Efficacy of Recombinant Factor IX Product, IB1001, in Patients with Severe hemophilia B (Phase III). Includes patients ≥12 years of age who are naïve to IB1001. Goal to include up to 18 subjects with 12 subjects completing study. Includes testing for inhibitory FIX antibodies, non-inhibitory FIX antibodies, and anti-CHO antibodies.[34]	Initiation: Jan 2014 Study Report: TBD

4. OTHER INFORMATION FROM MANAGED REVIEW PROCESS

With the initial application, the review team was concerned about the unknown nature of the risk of relatively high levels of anti-CHO antibodies. This resubmission includes a manufacturing change to decrease the amount of CHO protein in polished IB1001. The review team is discussing these manufacturing changes and the effects on the product.

[31] BLA 125426/0.18, Pharmacovigilance Plan Version 2, p. 121-125.
[32] IND 13551/0.72, Summary of Changes Study Protocol IB1001-01, dated June 26, 2013.
[33] IND 13551/0.72, Protocol IB1001-02, dated Jun 26, 2013.
[34] IND 13551/0.80 IB1001-04 Protocol v 1.3.

5. POST-LICENSURE SAFETY REVIEW

BeneFIX and Rixubis are two currently approved factor IX (recombinant) products. Alprolix is a third recombinant FIX product which was approved in Mar 2014 but differs from IB1001 and the two other FIX recombinant products because the recombinant human coagulation factor IX is covalently linked to the Fc domain of human immunoglobulin G1. Alprolix is made in human embryonic kidney (HEK) cells. Like IB1001, BeneFIX and Rixubis are made in Chinese Hamster Ovary cells and contain trace amounts of CHO proteins. BeneFIX was first approved in 1997, and Rixubis was more recently approved in Jun 2013. The BeneFIX package insert states that patients receiving BeneFIX may develop hypersensitivity to non-human mammalian proteins.[35] 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. Also, cases of anaphylaxis could theoretically have been caused by antibodies to CHO or to other substances.

Ongoing CBER surveillance for BeneFIX and Rixubis include monitoring FAERS reports, data mining scores, literature review and periodic adverse experience reports submitted by the sponsors. This surveillance has not identified any new safety concerns. Monitoring for Alprolix is just beginning as it was only recently approved.

A literature search of "recombinant factor IX" and "safety" performed in PubMed on May 6, 2014 included the following relevant articles:

A publication by Franchini et al.[36] 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 article[37] 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 -

[35] BeneFIX package insert, section 5.2

[36] Franchini M, Frattini F, Crestani S, Sissa C, Bonfanti C. Treatment of hemophilia B: focus on recombinant factor IX. Biologics. 2013;7:33-8. Epub 2013 Feb 12.

[37] 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.

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.

Multiple articles describe the clinical trials for IB1001, BAX326 (Rixubis), and Alprolix.[38,39,40]

An additional article was a manufacturer-sponsored study assessing the efficacy and safety of BeneFIX in China.[41] 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, and there were no new safety concerns identified in the study.

A final relevant article[42] describes 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 were no excess hemorrhages, no thromboses and no infections.

6. INTEGRATED RISK ASSESSMENT

Initially, the primary concern regarding IB1001's safety was the unknown significance of antibody formation in a high percentage of trial subjects. There was a seroconversion rate of 29% of clinical study patients developing anti-CHO antibodies. There was also 27% of subjects who tested positive for non-inhibitory factor IX binding proteins during the study. In response to the anti-CHO antibodies, the sponsor made a manufacturing change to decrease the residual CHO protein in the product, and a PK comparability study was performed. Neither of these antibodies was found to be associated with adverse events, including hypersensitivity reactions or inhibitor formation. This resubmission included additional follow-up on patients who had tested positive for anti-

[38] 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.

[39] Windyga J, Lissitchkov T, Stasyshyn O, et al. Efficacy and safety of a recombinant factor IX (Bax326) in previously treated patients with severe or moderately severe haemophilia B undergoing surgical or other invasive procedures: a prospective, open-label, uncontrolled, multicentre, phase III study. Haemophilia. 2014 Apr 3. [Epub ahead of print].

[40] Powell JS[1], Pasi KJ, Ragni MV, et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. N Engl J Med. 2013 Dec 12;369(24):2313-23. Epub 2013 Dec 4.

[41] Yang R, Zhao Y, Wang X, et al. Evaluation of the safety and efficacy of recombinant factor IX (nonacog alfa) in minimally treated and previously treated Chinese patients with haemophilia B. Haemophilia. 2012 Sep;18(5):e374-8.

[42] 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.

CHO antibodies and provided some reassurance that no clinical adverse events were found to be associated with the longer observation period. Additionally, it showed that titers of anti-CHO antibodies decreased over time in the majority of patients. The sponsor confirmed that there were lower levels of CHO protein in the polished product, and there is limited data available to demonstrate that this results in fewer patients developing anti-CHO antibodies. Information regarding the non-inhibitory FIX binding antibodies and the anti-CHO antibodies seen in the clinical trials has been included in the draft labeling.

While there is very limited clinical data on the polished product, the available data on the outcome of patients with anti-CHO antibodies and non-inhibitory factor IX binding antibodies is reassuring. Multiple other factor replacement products have been found to have antibodies of unknown significance associated with them. Some of these products are having specific antibody testing continued as part of ongoing clinical postmarketing commitment studies. The approach of monitoring the development of anti-CHO antibodies, factor IX inhibitors, and non-inhibitory factor IX binding antibodies in the 4 ongoing and planned studies is acceptable. There has been no demonstrated clinical effect of anti-CHO antibodies. Additionally, the mechanism for removing the host cell antigenic material is expected to be effective, and there was a demonstrated decrease in anti-CHO seroconversion in animal models. There was also no demonstrated clinical effect of anti-factor IX binding antibodies and no correlation with developing inhibitors. Throughout the clinical trial, there were no inhibitors observed, and this product is not expected to have a higher rate of inhibitor development than approved similar factor products. Therefore, the reviewed safety data do not substantiate a need for a safety PMR or a risk evaluation and mitigation strategy (REMS).

7. RECOMMENDATIONS

1. The pharmacovigilance plan Version 2 is acceptable. The four ongoing and planned studies will provide additional safety and efficacy information for this product.
2. OBRR could consider asking the sponsor to increase the study size for study IB1001-04 from the proposed 18 subjects. Since this study is a clinical trial and has already been negotiated under the IND, OBE will defer to OBRR regarding adjustments to the protocol.