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Food and Drug Administration
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Subject: Pharmacovigilance Plan Review

Applicant: CSL Behring, LLC

Product: Idelvion – Coagulation Factor IX (Recombinant), Albumin Fusion Protein
International Nonproprietary Name [INN]: albutrepenonacog alfa

Proposed Indication: Treatment of patients with hemophilia B (congenital Factor IX deficiency) for:
*Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
*Control and prevention of bleeding episodes
*Control and prevention of bleeding in the perioperative setting

Submission type: Original BLA

BLA number/Submission Date: STN 125582 / Submitted December 5, 2014

PVP Submission Date: Original PVP (Version 1.0)-As part of Initial Submission: December 5, 2014
PVP (Version 2.0): April 3, 2015

Action Due Date: Original-December 5, 2015;
Revised-March 5, 2016

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1 EXECUTIVE SUMMARY

Introduction

Hemophilia B is a rare X-chromosome-linked recessive genetic bleeding disorder that results in deficiency of coagulation Factor IX (FIX). The most common manifestation of hemophilia is recurrent spontaneous bleeding, most frequently in joints such as ankles, elbows and knees.^{1,2}

The primary aim of care for patients with hemophilia B is to prevent bleeding. Replacement therapy with exogenous FIX provides a temporary correction of the coagulation factor deficiency by increasing FIX levels and thereby reducing bleeding.³ Current replacement therapy includes both plasma-derived (pdFIX) and recombinant FIX (rFIX) products, indicated for both the prophylactic and acute treatment of bleeding episodes, including bleeding in the perioperative setting. Although these products are generally safe and effective, they are limited by relatively short half-lives, which require frequent infusions to prevent and control bleeding episodes.⁴

Recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP), Idelvion™, was developed to provide an effective FIX replacement product with an improved pharmacokinetic (PK) profile to support a longer dosing interval for routine prophylaxis treatment, along with effective acute and perioperative treatment of bleeding episodes.

Product Description and Indications

Idelvion, or CSL654 rIX-FP (international non-proprietary name (INN): albutrepenonacog alfa), is a purified protein generated by the genetic fusion of recombinant coagulation factor IX to recombinant albumin. rIX-FP effectively replaces the missing coagulation FIX needed for hemostasis and provides longer dose regimens. rIX-FP remains intact in the circulation until FIX is activated, whereupon albumin is cleaved off, releasing activated factor IX (FIXa) when it is needed for coagulation.

Idelvion is indicated for treatment of patients with hemophilia B (congenital Factor IX deficiency) for: routine prophylaxis to prevent or reduce the frequency of bleeding episodes; control and prevention of bleeding episodes; and control and prevention of bleeding in the perioperative setting.

BLA Epidemiology Review

The nonclinical toxicology studies demonstrated that single and repeat doses up to 500 IU/kg for up to 28 days were well-tolerated, with no findings indicative of adverse toxicity, prothrombogenic properties, or local intolerance. In addition, rIX-FP revealed no genotoxic properties as shown in two *in vitro* systems.

As of January 9, 2015, a total of 111 subjects with severe and moderate hemophilia B (FIX activity level $\leq 2\%$) had received at least 1 injection of rIX-FP in 5 clinical trials (ie, studies 2001, 2004, 3001, 3002 and ongoing extension study 3003) and comprise the safety population. A breakdown of treatment emergent adverse events is as follows:

- 111 subjects in the 5 BLA safety studies, all male
 - 662 TEAEs
 - The most frequently reported AEs by PT were nasopharyngitis, headache and arthralgia
 - 16 (in 9 subjects) deemed “related” (all non-serious)
 - 10 SAEs (in 8 subjects): 0 deemed “related”
 - 5 subjects withdrew:
 - 1 due to “hypersensitivity”, later deemed an infusion-related reaction
 - 1 due to headache
 - 1 due to repeat episodes (x5) of rash/exanthema
 - 1 due to right thigh/groin pain (arthritis vs. possible deep muscle bleed, drug ineffective)
 - 1 due to “gamma-glutamyl transferase increased” with exacerbation of underlying alcoholic liver disease

- 0 subjects developed FIX inhibitors or antibodies to rIX-FP or Chinese hamster ovary (CHO) cell proteins.
- 4 subjects (of 63) in pivotal trial 3001 with normal baseline urinalyses developed proteinuria after exposure to rIX-FP, although none developed a corresponding increase in creatinine or new hypertension and none developed rIX-FP inhibitors or antibodies to rIX-FP or Chinese hamster ovary (CHO) host cell proteins. 1 of these 4 subjects was lost to follow-up in March 2015; the remaining 3 will undergo follow-up testing.

Risk Management Plan

CSL Behring identified the following risks or missing information for Idelvion recipients and proposed the corresponding Action Plan for these items:

Important Identified Risks	Planned Risk Management / Pharmacovigilance Actions
None	–
Important Potential Risks	Planned Risk Management / Pharmacovigilance Actions
Hypersensitivity / anaphylactic reactions	<ul style="list-style-type: none"> ● Product labeling that includes: <ul style="list-style-type: none"> ○ A contraindication for individuals with known hypersensitivity to rIX-FP or its excipients, including hamster protein ○ Warnings/precautions for the possibility of allergic reactions and a recommendation regarding hypersensitivity ○ Patient counseling information to report any adverse reaction or issues following rIX-FP administration to their physician or healthcare provider; advice regarding the early signs of hypersensitivity reactions; advice on what to do if a hypersensitivity reaction should occur ● CSL654-3003 Phase IIIb including PUPs ● Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including specific follow-up questionnaire
Development of inhibitors to FIX	<ul style="list-style-type: none"> ● Product labeling that includes recommendations to evaluate patients regularly for FIX inhibitors ● CSL654-3003 Phase IIIb including PUPs ● Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up and specific follow-up questionnaire
Development of antibodies to product (rIX-FP)	<ul style="list-style-type: none"> ● Product labeling that includes recommendations to evaluate patients regularly for inhibitors to the product ● CSL654-3003 Phase IIIb including PUPs ● Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up and target questionnaire
Development of antibodies to CHO host cell proteins	<ul style="list-style-type: none"> ● A (b) (4) step is used in the production process to purify rIX-FP from process- and product-related impurities. ● CSL654-3003 Phase IIIb including PUPs ● Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up and target questionnaire
Dosing errors based on variability in the assays used during treatment monitoring of FIX levels	<ul style="list-style-type: none"> ● Product labeling that includes a statement in the Warnings/Precautions section to inform of the variability of reagent results ● CSL654-3003 Phase IIIb including PUPs ● Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up and target questionnaire
Important Missing Information	Planned Risk Management / Pharmacovigilance Actions
Experience in patients with a history of thrombosis	<ul style="list-style-type: none"> ● CSL654-3003 Phase IIIb including PUPs ● Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up and specific follow-up questionnaire
Experience of inhibitor formation in PUPs	<ul style="list-style-type: none"> ● CSL654-3003 Phase IIIb including PUPs ● Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up and specific follow-up questionnaire
Experience in pregnancy and lactation, including labor and delivery	<ul style="list-style-type: none"> ● Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up and pregnancy follow-up questionnaire
Experience in elderly patients (65 years and above)	<ul style="list-style-type: none"> ● Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up

Abbreviations: CHO = Chinese hamster ovary; FIX = coagulation factor IX; PUPs = previously untreated patients; rIX-FP: recombinant fusion protein linking coagulation FIX with albumin

Epidemiology Reviewer Recommendations

Based on the review of the pre-licensure safety data and CSL Behring's proposed pharmacovigilance plan, the Epidemiology reviewer agrees with the Risk Management Plan as proposed by CSL Behring (above) with the following actions for post-licensure safety surveillance activities of Idelvion:

- Routine pharmacovigilance to monitor AEs among Idelvion recipients in accordance with 21 CFR 600.80
- Completion and review of safety data for ongoing study 3003 (target number of subjects: 115; 85 from previous studies, 20 PUPs, 10 surgeries)
- Labeling to include: a contraindication for individuals with known hypersensitivity to rIX-FP or its excipients, including hamster protein; warnings/precautions for the possibility of allergic reactions and a recommendation regarding hypersensitivity; patient counseling information to report any adverse reaction or issues following rIX-FP administration to one's physician or healthcare provider; advice regarding the early signs of hypersensitivity reactions; advice on what to do if a hypersensitivity reaction should occur

2 INTRODUCTION

2.1 Background

Hemophilia B is a rare X-chromosome-linked recessive genetic bleeding disorder that results in deficiency of coagulation Factor IX (FIX), which is needed to amplify the production of activated Factor X, which then generates thrombin and stabilizes the fibrin plug for effective coagulation. The most common manifestation of hemophilia is recurrent spontaneous bleeding, most frequently in joints such as ankles, elbows and knees.¹ Because hemophilia B is an X-linked recessive disorder, it is more common in men (92%) than in women.³ The disorder is lifelong (i.e., occurs in all age groups) and is found in all ethnic groups.

2.2 Epidemiology of Hemophilia B

The best available source for worldwide data of hemophilia prevalence is the World Federation of Hemophilia (WFH) Global Survey. WFH's 2012 survey included 109 countries with a total population of 6,419,691,046 and identified 28,008 people with hemophilia B (0.4 per 100,000 individuals). The largest number of hemophilia B patients in one country is found in the United States (n=4,112) followed by Brazil (n=1,801), India (n=1,797), China (n=1,433) and the United Kingdom (n=1,171). The largest proportion per 100,000 individuals is found in Macedonia (5.04), Ireland (4.83), Australia (2.47), Norway (2.21), and Sweden (2.16).⁵

Hemophilia B is often divided into groups of severe (FIX activity level < 1% of normal), moderate (FIX activity level of 1-5%) or mild (FIX activity level of ≥5-40%) disease. Results of an American survey showed that approximately 37% of hemophilia B patients have severe hemophilia associated with the severest bleeding manifestations.⁶ These patients suffer frequent spontaneous bleedings as well as bleedings induced by trauma or surgical procedures. Persons with moderate disease constitute 33% of patients with hemophilia B and will manifest bleeding after minor trauma, but are unlikely to experience spontaneous bleedings. Persons with mild disease comprise 30% of all people with hemophilia B; these patients develop bleeding only after significant trauma or surgery.⁶

2.3 Morbidity and Mortality with Hemophilia B

Hemophilia B manifests as profuse bleeding into joints and muscles or internal organs, either spontaneously or as the result of accidental or surgical trauma. Recurrent joint bleeding can lead to chronic arthropathy, pain, and loss of function.⁷

Before clotting factor preparations were introduced as treatment for hemophilia in the 1960s, the life expectancy for these patients was <30 years, and most died of intracranial or other hemorrhages. However, improved treatment options have greatly increased the life expectancy of hemophilia B patients. In a Dutch study, life expectancy between 1992 and 2001 was calculated as 73 years in HIV negative patients with hemophilia B and 60 years for all patients with hemophilia B. The most common primary causes of death were AIDS, HCV, diseases of the circulatory system and malignancies.⁸

2.4 Rationale for Development of Factor IX, Albumin Fusion Protein

The primary aim of care for patients with hemophilia B is to prevent bleeding. Replacement therapy with exogenous FIX provides a temporary correction of the coagulation factor deficiency by increasing FIX levels and thereby reducing bleeding.³ Current replacement therapy includes both plasma-derived (pdFIX) and recombinant FIX (rFIX) products. These products are indicated for both the prophylactic and acute treatment of bleeding episodes, including bleeding in the perioperative setting. Although these products are generally safe and effective, they are limited by relatively short half-lives, which require frequent infusions to prevent and control bleeding episodes.⁴ A safe FIX replacement product with a pharmacokinetic (PK) profile that supports efficacy over a longer dosing interval has the potential to reduce treatment burden, improve compliance and enhance quality of life.

2.5 Product Description

Idelvion, or CSL654 rIX-FP (international non-proprietary name (INN): albutrepenonacog alfa), is a purified protein derived from a Chinese Hamster Ovary (CHO) cell line and produced by recombinant DNA technology, generated by the genetic fusion of recombinant coagulation factor IX to recombinant albumin. The recombinant factor IX portion is identical to the Thr148 allelic form of human plasma-derived factor IX. rIX-FP effectively replaces the missing coagulation FIX needed for hemostasis and provides longer dose regimens. The prolongation of the half-life and the enhanced systemic exposure are achieved by the fusion with albumin. Albumin is a natural, inert carrier protein in plasma with a long half-life of approximately 20 days that is not involved in immune defense or immune response. rIX-FP remains intact in the circulation until FIX is activated, whereupon albumin is cleaved off, releasing activated factor IX (FIXa) when it is needed for coagulation.

Idelvion is provided as a lyophilized powder in single-use glass vials containing nominally 250, 500, 1000 or 2000 international units (IU) of the active ingredient. Besides the active ingredient rIX-FP, each single use vial contains tri-sodium citrate, polysorbate 80, mannitol, and sucrose as excipients. For application by intravenous injection, the lyophilized drug product is reconstituted using 2.5 mL or 5 mL (for 2000 IU) of sterile water for injection (WFI).

2.6 Indications and Dosage

Idelvion is indicated for treatment of patients with hemophilia B (congenital Factor IX deficiency) for:

- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- Control and prevention of bleeding episodes
- Control and prevention of bleeding in the perioperative setting

Calculation of required dose:

One International Unit (IU) of FIX activity is equivalent to that quantity of FIX in one mL of normal human plasma.

Dosage for on-demand treatment:

The calculation of the required dose of rIX-FP is based on the empirical finding that 1 IU of rIX-FP per kg body weight (BW) is expected to increase the circulating level of FIX by an average of 1.3 IU/dL (1.3% of normal) in patients \geq 12 years of age and by 1.0 IU/dL (1.0% of normal) in patients < 12 years of age. The required dose of rIX-FP for the treatment of bleeding episodes is determined using the following formula:

Required dose (IU) = BW (kg) x desired FIX rise (% of normal or IU/dL) x (reciprocal of recovery [IU/kg per IU/dL])

OR

Increase in FIX IU/dL (or % of normal) = Dose (IU) x Recovery (IU/dL per IU/kg)/BW (kg)

The dose is adjusted based on the individual patient's clinical condition and response.

Details of the dosing that can be used for the control and prevention of bleeding episodes and perioperative management are presented in Table 1 and Table 2, respectively.

Table 1. Dosing for Control and Prevention of Bleeding Episodes

Type of bleeding episode	Circulating FIX level required (%) (IU/dL)	Frequency of doses (hours) / Duration of therapy (days)
Minor or moderate Hemarthrosis, muscle bleeding (except iliopsoas) or oral bleeding	30-60	Single dose should be sufficient for majority of bleeds. Maintenance dose after 48-72 hours, if there is further evidence of bleeding.
Major Life-threatening hemorrhages, deep muscle bleeding, including iliopsoas	60-100	Repeat every 48-72 hours for the first week. Maintenance dose weekly until bleeding stops or healing is achieved.

Table 2. Dosing for Perioperative Management

Type of Surgery	Circulating FIX level required (%) (IU/dL)	Frequency of doses (hours) / Duration of therapy (days)
Minor (including uncomplicated tooth extraction)	50-80	Single dose should be sufficient for a majority of minor surgeries. If needed, maintenance dose after 48-72 hours until bleeding stops and healing is achieved.
Major	60-100 (initial level)	Repeat dose every 48-72 hours for the first week. Maintenance dose 1-2 times per week until bleeding stops and healing is achieved.

Dosage for routine prophylaxis:

The recommended dose is 25 to 40 IU rIX-FP per kg body weight every 7 days or 50 to 75 IU rIX-FP per kg every 14 days. The dosing regimen can be adjusted based on the individual patient's clinical condition and response. The recommended dose regimen for pediatric patients is the same as for adults.

2.7 Regulatory History & Clinical Development Program

Idelvion (rIX-FP) is not yet licensed for use in any country. The rIX-FP clinical development program includes 5 open-label, prospective clinical studies with 111 unique subjects treated with rIX-FP for a mean (standard deviation, SD) of 614.8 (394.70) days. Four studies are complete and one is ongoing. At the January 9, 2015 data cut-off, a total of 8257 exposure days (EDs) to rIX-FP had been accumulated in the Overall Safety population. The mean (SD) number of EDs was 74.4 (49.23); 82 subjects (73.9%) had achieved ≥50 EDs, and 35 subjects (31.5%) had achieved ≥100 EDs.

2.8 Objectives/Scope of the Review

The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance or studies should the product be licensed in the US, and to evaluate the pharmacovigilance plan (PVP) submitted by CSL Behring for the Idelvion BLA.

3 MATERIALS REVIEWED

Submit Date	Source	Document Type	Document(s) Reviewed
12/05/2014	CSL	BLA	125582/0.0; Module 1.7.1, Priority Review Request
04/23/2015	CSL	BLA	125582/0.11; Module 1.11.3, Information Amendment-Clinical, Response to FDA 04/15/2015 Information Request (satisfactory; additional IR sent)
05/11/2015	CSL	BLA	125582/0.13; Module 1.11.3, Information Amendment-Clinical, Response to FDA 04/30/2015 Information Request (satisfactory; additional IR sent)
06/01/2015	CSL	BLA	125582/0.16; Module 1.11.3, Information Amendment-Clinical, Response to FDA 05/26/2015 Information Request (satisfactory; additional IR sent)
06/17/2015	CSL	BLA	125582/0.18; Module 1.11.3, Information Amendment-Clinical, Response to FDA 06/09/2015 Information Request (satisfactory; additional IR sent)
08/10/2015	CSL	BLA	125582/0.31; Module 1.11.3, Information Amendment-Clinical, Response to FDA 07/13/2015 Information Request (satisfactory; additional IR sent)
08/20/2015	CSL	BLA	125582/0.33; Module 1.11.3, Information Amendment-Clinical, Response to FDA 08/18/2015 Information Request (satisfactory; additional IR sent)
10/02/2015	CSL	BLA	125582/0.43; Module 1.11.3, Information Amendment-Clinical, (2 nd) Response to FDA 07/13/2015 Information Request (satisfactory)
12/05/2014	CSL	BLA	125582/0.0; Module 1.12.1, Orphan Designation Letter
07/30/2015	CSL	BLA	125582/0.26; Module 1.14.1, Labeling: Draft Labeling
12/05/2014	CSL	BLA	125582/0.0; Module 1.16, Risk Management Plan: Pharmacovigilance Plan, Version 1.0, dated 11/21/2014
04/03/2015	CSL	BLA	125582/0.8; Module 1.16, Risk Management Plan: Pharmacovigilance Plan, Version 2.0, dated 03/13/2015
12/05/2014	CSL	BLA	125582/0.0; Module 2.2, Introduction
12/05/2014	CSL	BLA	125582/0.0; Module 2.4, Non-clinical Overview
12/05/2014	CSL	BLA	125582/0.0; Module 2.5, Clinical Overview
04/03/2015	CSL	BLA	125582/0.8; Module 2.5, Clinical Overview, 4-Month Safety Update, dated 03/16/2015
12/05/2014	CSL	BLA	125582/0.0; Module 2.6, Non-clinical Written and Tabulated Summaries <ul style="list-style-type: none"> •Subsection 2.6.1: Introduction •Subsection 2.6.6: Toxicology Written Summary
12/05/2014	CSL	BLA	125582/0.0; Module 2.7, Clinical Summary <ul style="list-style-type: none"> •Subsection 2.7.3: Summary of Clinical Efficacy, version 1.0 •Subsection 2.7.4: Summary of Clinical Safety, version 1.0 •Subsection 2.7.6: Synopses of Individual Studies, version 1.0
04/03/2015	CSL	BLA	125582/0.8; Module 2.7, Clinical Summary <ul style="list-style-type: none"> •Subsection 2.7.3: Summary of Clinical Efficacy, version 2.0 •Subsection 2.7.4: Summary of Clinical Safety, version 2.0 <ul style="list-style-type: none"> ➤ Labeling Justification •Subsection 2.7.6: Synopses of Individual Studies, version 2.0
12/05/2014	CSL	BLA	125582/0.0; Module 5.2, Tabular Listing of All Clinical Studies, version 1.0
04/03/2015	CSL	BLA	125582/0.8; Module 5.2, Tabular Listing of All Clinical Studies, version 2.0
12/05/2014	CSL	BLA	125582/0.0; Module 5.3.3, Reports of Human Pharmacokinetic (PK) Studies <ul style="list-style-type: none"> •Subsection 5.3.3.2: Patient PK and Initial Tolerability Study Reports <ul style="list-style-type: none"> ➤ Study CSL654-2001: An open-label, multi-center, dose-escalation safety and pharmacokinetic study of a recombinant coagulation factor IX albumin fusion protein (rIX-FP) in subjects with hemophilia B

Submit Date	Source	Document Type	Document(s) Reviewed
12/05/2014	CSL	BLA	125582/0.0; Module 5.3.5, Reports of Efficacy and Safety Studies (Synopses, Study Report Bodies, Discontinued Patients, Adverse Event Listings, and Case Report Forms, Individual Laboratory Measurements Listed by Patient, when applicable) <ul style="list-style-type: none"> • Subsection 5.3.5.2: Study Reports of Uncontrolled Clinical Studies <ul style="list-style-type: none"> ➤ Study CSL654-2004: A Phase ½ Open-Label, Multicenter, Safety and Efficacy Study of Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B ➤ Study CSL-654-3001: A Phase 2/3 Open-Label, Multicenter, Safety and Efficacy Study of Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B ➤ Study CSL-654-3002: A Phase 3 Open-Label, Multicenter, Pharmacokinetics, Safety and Efficacy Study of Recombinant Fusion Protein Linking Coagulation Factor IX Albumin (rIX-FP) in Previously Treated Children with Hemophilia B ➤ Study CSL-654-3003: A Phase 3b Open-Label, Multicenter, Safety and Efficacy Extension Study of a Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B
04/03/2015	CSL	BLA	125582/0.8; Module 5.3.5, Reports of Efficacy and Safety Studies <ul style="list-style-type: none"> • Subsection 5.3.5.2: Study Reports of Uncontrolled Clinical Studies <ul style="list-style-type: none"> ➤ Study CSL654-2004: A Phase ½ Open-Label, Multicenter, Safety and Efficacy Study of Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B <ul style="list-style-type: none"> ▪ Demographic Data Listing ➤ Study CSL-654-3001: A Phase 2/3 Open-Label, Multicenter, Safety and Efficacy Study of Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B <ul style="list-style-type: none"> ▪ Addendum 1: dated 03/03/2015 ➤ Study CSL-654-3002: A Phase 3 Open-Label, Multicenter, Pharmacokinetics, Safety and Efficacy Study of Recombinant Fusion Protein Linking Coagulation Factor IX Albumin (rIX-FP) in Previously Treated Children with Hemophilia B <ul style="list-style-type: none"> ▪ Study Report Body, v 4.0; dated 01/15/2015
throughout	FDA	OBRR Clinical Reviewer	Collaborative discussions regarding safety issues; draft clinical review summary, distributed prior to Mid-cycle meeting (05/12/2015) with updated draft prior to Late-cycle meeting (08/24/2015)
05/14/2015	FDA	Renal Consult	Consult regarding four subjects with positive tests for urine protein
throughout	FDA	Product Labels	Alprolix PI, BeneFIX PI, IXinity PI, Rixubis PI
throughout	Other	References	Medical literature review (<i>see detailed listing at end of report</i>)

4 SAFETY FINDINGS AND PHARMACOVIGILANCE PLAN REVIEW

4.1 Nonclinical Safety Findings

The rIX-FP nonclinical program included pharmacological, pharmacokinetic (PK) and toxicological studies in addition to studies for genotoxicity, local tolerance and thrombogenic potential. The nonclinical toxicology studies demonstrated that single and repeat doses up to 500 IU/kg for up to 28 days were well-tolerated, with no findings indicative of adverse toxicity, prothrombogenic properties, or local intolerance. In addition, rIX-FP revealed no genotoxic properties as shown in two *in vitro* systems. Table 3 lists all relevant safety findings in the nonclinical program.

Table 3. Nonclinical Safety Issues for rIX-FP

Safety Issue	Nonclinical Findings	Relevance to Human Usage
Genotoxicity	<ul style="list-style-type: none"> ▪ Bacterial reverse mutation test (b) (4) and <i>in vitro</i> mammalian chromosome aberration test in human lymphocytes showed no evidence of mutagenic activity or increase in frequency of structural chromosome aberrations. 	<ul style="list-style-type: none"> ▪ Unlikely coagulation proteins such as FIX would interact directly with DNA or chromosomes within cells. ▪ Recombinant FIX and human albumin are normal constituents of human plasma and not expected to be genotoxic.
Carcinogenicity	<ul style="list-style-type: none"> ▪ Recombinant human FIX is a normal constituent of human plasma and acts like endogenous FIX; albumin is an endogenous protein with known clinical experience and no established carcinogenic properties. 	<ul style="list-style-type: none"> ▪ Recombinant FIX and human albumin are normal constituents of human plasma and not expected to be carcinogenic.
Reproductive & Developmental Toxicity	<ul style="list-style-type: none"> ▪ Not performed, due to heterologous nature of human FIX for animals ▪ Macro- and histopathological examination of male and female reproductive systems after single and repeated dose toxicity studies showed no adverse findings. 	<ul style="list-style-type: none"> ▪ Hemophilia B occurs almost exclusively in males, so no necessity for studies on embryotoxicity or effects on fetal development. ▪ Recombinant FIX and human albumin are normal constituents of human plasma and not expected to induce adverse effects on the reproductive system.
Effects in Juvenile Animals	<ul style="list-style-type: none"> ▪ Not conducted 	<ul style="list-style-type: none"> ▪ Recombinant FIX and human albumin are normal constituents of human plasma and not expected to induce adverse effects in children.
Single-dose Toxicity	<ul style="list-style-type: none"> ▪ Single doses in rats and monkeys of up to 500 IU/kg were well tolerated, with no findings indicative of toxicity. 	<ul style="list-style-type: none"> ▪ No toxicity was seen within the clinical dose range for humans.
Repeated-dose Toxicity	<ul style="list-style-type: none"> ▪ Repeated doses in rats and monkeys of up to 500 IU/kg/day for 4 weeks were well tolerated, with no findings indicative of toxicity; anti-human FIX and human albumin antibodies occurred in several animals. 	<ul style="list-style-type: none"> ▪ No toxicity was seen within the clinical dose range for humans. ▪ Antibody formation to foreign (human) protein in animals after long-term exposure is expected and should be interpreted with caution.
Local Tolerability	<ul style="list-style-type: none"> ▪ Single intra-arterial, intravenous (IV) or perivenous doses of rIX-FP were administered in rabbits for 4 days and were well tolerated, with no local or systemic reactions 	<ul style="list-style-type: none"> ▪ No reactions noted with IV administration, suggesting similar tolerability in humans for the intended clinical dose route and range.
Safety Pharmacology --Respiratory --Cardiovascular --Central Nervous System (CNS)	<ul style="list-style-type: none"> ▪ Administration of rIX-FP in rats (up to 500 IU/kg) showed no statistically significant effect on respiratory parameters. ▪ Repeat dose administration in monkeys of up to 500IU/kg for 4 weeks showed no effect on cardiovascular parameters. ▪ Single and repeat dosing in rats and monkeys showed no clinical changes or changes in macroscopic or histopathological evaluations of the CNS. 	<ul style="list-style-type: none"> ▪ Recombinant FIX and human albumin are normal constituents of human plasma; this, plus a lack of clinical changes in these safety pharmacology nonclinical studies, suggests no respiratory, cardiovascular, or CNS-specific toxicity is expected.
Immunogenicity	<ul style="list-style-type: none"> ▪ Repeated doses in rats and monkeys of up to 500 IU/kg/day for 4 weeks were well tolerated, with no findings indicative of toxicity; anti-human FIX and human albumin antibodies occurred in several animals. 	<ul style="list-style-type: none"> ▪ Antibody formation to foreign (human) protein in animals after long-term exposure is expected and should be interpreted with caution. ▪ As with all therapeutic proteins, there is potential for immunogenicity and the development of neutralizing and non-neutralizing antibodies in patients exposed to rIX-FP.
Drug Interactions	<ul style="list-style-type: none"> ▪ Not conducted 	<ul style="list-style-type: none"> ▪ Human FIX is catabolized in the same manner as endogenous FIX and is not expected to induce adverse effects with exogenous drugs
Thrombogenicity	<ul style="list-style-type: none"> ▪ Wessler stasis model in rabbits showed no thrombogenicity in doses up to 500 IU/kg 	<ul style="list-style-type: none"> ▪ Nonclinical thrombogenicity data for rIX-FP indicated no prothrombotic potential within the intended clinical dose range. ▪ Older, low-purity FIX products have been historically associated with thromboembolic events (TEE).

4.2 Clinical Safety Database

The safety analyses supporting the Risk Management Plan are comprised of data from 4 completed clinical studies (2001, 2004, 3001, 3002) and 1 ongoing clinical study (3003) with data through January 9, 2015. Table 4 summarizes the pertinent information, including key safety findings, for all 5 studies included in this BLA.

Table 4. 5 BLA Safety Studies for rFIX-FP (Idelvion) (data through 1/9/15)

Study #; Region	Study Objectives; Safety Variables Assessed	Study Design; Population Parameters	# of Subjects	(Safety Analyses) Treatment Arms & # Subjects/Exposure	Key Safety Findings
CSL654-2001 Austria, France, Germany, Israel, Italy, Spain	Safety & PK AEs, biochemistry, hematology, UA, activation of coagulation tests, FIX inhibitors, rIX-FP Abs, local tolerability, PE, VS	Phase 1, prospective, multi-center, open-label, dose escalation study Age (years): 15–58	25 (25 unique)	<ul style="list-style-type: none"> ▪ 25 IU/kg: 5/25 (20%) ▪ 50 IU/kg: 8/25 (32%) ▪ 75 IU/kg: 5/25 (20%) ▪ 25 & 50 IU/kg: 3/25 (12%) ▪ 25 & 75 IU/kg: 1/25 (4%) ▪ 50 & 75 IU/kg: 3/25 (12%) 	<ul style="list-style-type: none"> ▪ No deaths Related TEAEs ▪ 3 subjects w/ 4 related TEAEs: <ul style="list-style-type: none"> ○ 1 w/ constipation ○ 1 w/ erythema @ injection site ○ 1 w/ “feeling hot” & HA SAEs ▪ None Related SAEs ▪ None *AEs leading to withdrawal ▪ None Thrombogenic events/lab abnormalities ▪ 1 w/ mild, short-term increase in TAT and D-dimer after rIX-FP (NCS)
CSL654-2004 Bulgaria, Israel	Safety, Efficacy & PK AEs, biochemistry, hematology, UA, FIX inhibitors, rIX-FP Abs, local tolerability, PE, VS	Phase 1/2, prospective, multi-center, open-label study Age (years): 13–46	17 (15 unique) 2 from 2001	<ul style="list-style-type: none"> ▪ Prophylaxis: 15-35 IU/kg (max 75 IU/kg): 13/17 (76%) ▪ OD: min 25 IU/kg: 4/17 (24%) 	<ul style="list-style-type: none"> ▪ No deaths Related TEAEs ▪ None SAEs ▪ None Related SAEs ▪ None *AEs leading to withdrawal ▪ None
CSL654-3001 Austria, Bulgaria, France, Germany, Israel, Italy, Japan, Russia, Spain, US	Safety, Efficacy & PK AEs, biochemistry, hematology, UA, activation of coagulation tests, FIX inhibitors, rIX-FP Abs, Abs to CHO host cell proteins, local tolerability, PE, VS	Phase 2/3, prospective, multi-center, open-label study (pivotal) Age (years): 12–61	63 (40 unique) 8 from 2001 15 from 2004 4 in surgical substudy	<ul style="list-style-type: none"> ▪ Prophylaxis: 40/63 (63%) <ul style="list-style-type: none"> ➢ 7-day: 35-50 IU/kg (max 75 IU/kg) ➢ 10-day: 75 IU/kg ➢ 14-day: 75 IU/kg ▪ OD: min 35-50 IU/kg: 23/63 (37%) 	<ul style="list-style-type: none"> ▪ No deaths Related TEAEs ▪ 5 subjects w/ 11 related TEAEs: <ul style="list-style-type: none"> ○ 1 w/ “hypersensitivity”, later deemed infusion-related reaction* ○ 1 w/ mild dizziness ○ 1 w/ eczema, HA* x 2 ○ 1 w/ rash/exanthema x 5* ○ 1 w/ injection site hematoma SAEs ▪ 2 subjects w/ 1 SAE each <ul style="list-style-type: none"> ○ 1 w/ L knee synovitis (NR) ○ 1 w/ epileptic aphasia in subject w/ 40-year Hx of epilepsy (NR) Related SAEs ▪ None *AEs leading to withdrawal ▪ 1 w/ “hypersensitivity”, later deemed infusion-related reaction ▪ 1 w/ HA ▪ 1 w/ rash x 5, withdrew after 5th episode ▪ 1 w/ thigh/groin pain (arthritis vs. possible deep muscle bleed, drug ineffective w/ 3 doses rIX-FP) Surgical subject AEs ▪ 3 of 4 surgical subjects developed AEs <ul style="list-style-type: none"> ○ 1 w/ anemia & UTI (both NR) ○ 1 w/ GI injury, clot in stool (NR) ○ 1 w/ post-surgical bleeds 3 & 7 days post-op, treated w/ rIX-FP both times Other issues ▪ 4 w/ new proteinuria after receipt of rIX-FP Thrombogenic events/lab abnormalities ▪ None

Study #; Region	Study Objectives; Safety Variables Assessed	Study Design; Population Parameters	# of Subjects	(Safety Analyses) Treatment Arms & # Subjects/Exposure	Key Safety Findings
CSL654-3002 Australia, Austria, Canada, Czech Republic, France, Germany, Israel, Italy, Russia, Spain	Safety, Efficacy & PK AEs, biochemistry, hematology, FIX inhibitors, rIX-FP Abs, Abs to CHO host cell proteins, local tolerability, PE, VS	Phase 3, prospective, multi-center, open-label study (pediatric) Age (years): 1–10	27 <6yrs: 12 6–11yrs: 15 (27 unique) 2 in surgical substudy	■ 7-day prophylaxis: 35-50 IU/kg (max 75 IU/kg): 27/27 (100%)	<ul style="list-style-type: none"> ■ No deaths Related TEAEs ■ None SAEs ■ 4 subjects w/ 6 SAEs (all NR): <ul style="list-style-type: none"> ○ 1 w/ arthralgia secondary to fall x 2 ○ 1 w/ forearm fracture ○ 1 w/ head injury and groin pain ○ 1 w/ tongue laceration Related SAEs ■ None *AEs leading to withdrawal ■ None Surgical subject AEs ■ 1 of 2 surgical subjects developed AEs: <ul style="list-style-type: none"> ○ 1 w/ post-surgical bleed 15 days post-op, treated w/ rIX-FP x 1
CSL654-3003 Australia, Austria, Bulgaria, Canada, Czech Republic, France, Germany, Israel, Italy, Japan, Malaysia, Philippines, South Africa, Spain, US	Prophylaxis study: Safety Surgery substudy: Perioperative Safety & Efficacy AEs, biochemistry, hematology, FIX inhibitors, rIX-FP Abs, Abs to CHO host cell proteins, local tolerability, PE, VS	Phase 3b, prospective, multi-center, open-label study (extension) Age (years): 2–63	80 (ongoing) (4 unique) 52 from 3001 24 from 3002 7 in surgical substudy (5–56 yrs)	<ul style="list-style-type: none"> ■ Prophylaxis: <ul style="list-style-type: none"> ➢ 7-day: 25-50 IU/kg (max 50 IU/kg) ➢ 10-day: 50-75 IU/kg (max 75 IU/kg) ➢ 14-day: 75 IU/kg ➢ (b) (4) ■ OD: min 35 IU/kg (max 75 IU/kg) ■ Surgery: min 50-100 IU/kg 	<ul style="list-style-type: none"> (All data as of 1/9/15) ■ No deaths Related TEAEs ■ None SAEs ■ 2 subjects w/ 1 SAE each: <ul style="list-style-type: none"> ○ 1 w/ esophagitis (NR) ○ 1 w/ colonic polyp (NR) Related SAEs ■ None *AEs leading to withdrawal ■ 1 w/ GGT increased w/ exacerbation of underlying alcoholic liver disease (counted in Study 3001, but w/d in Study 3003) Surgical subject AEs ■ 4 of 7 surgical subjects developed AEs: <ul style="list-style-type: none"> ○ 1 w/ low Hgb (not clinically significant) 8 days post-op & post-op pain that resolved by 10 days post-op (NR) ○ 1 w/ polyps requiring resection (NR) ○ 1 w/ post-surgical bleed 10 days post-op, treated w/ rIX-FP x 1; also w/ anemia that resolved (NR) ○ 1 w/ blisters @ medial right thigh & lateral right thigh and perioperative wound infection, treated w/ Abx (NR)

Abbreviations: Abs=antibodies; Abx=antibiotics; AEs=adverse events; CHO=Chinese hamster ovary; FIX=Factor IX; GGT=gamma glutamyl transferase; GI=gastrointestinal; HA=headache; Hgb=hemoglobin; Hx=history; IU=International Units; kg=kilograms; NCS=not clinically significant; NR=not related; OD=on-demand treatment; pdFIX=plasma-derived Factor IX; PE=physical exam; PK=pharmacokinetics; rIX-FP=recombinant fusion protein linking coagulation Factor IX with albumin; rFIX=recombinant Factor IX; SAEs=serious adverse events; TAT=thrombin-antithrombin; TEAEs=treatment-emergent adverse events; UA=urinalysis; US=United States; UTI=urinary tract infection; VS=vital signs; w/=with

4.2.1 Ongoing Extension Study 3003

Design: Study 3003 is an ongoing Phase 3b long-term extension study that is evaluating the safety and efficacy of prophylaxis with rIX-FP administered at intervals of 7, 10, 14, and (b) (4) days in eligible subjects from previous rIX-FP lead-in studies. Subjects who have not previously received rIX-FP requiring non-emergency, major surgery, and previously untreated subjects are also eligible to enroll. A treatment period of up to 3 years is planned. A surgical substudy is also included.

Objectives: The primary objective of the study is to evaluate the safety of rIX-FP as measured by the development of inhibitors against FIX.

Additional safety assessments include the evaluation of AEs, biochemistry, hematology, antibodies to rIX-FP, antibodies to CHO host cell proteins, local tolerability, physical examination, and vital signs.

Study population: The Safety population as of January 9, 2015 consisted of 80 subjects who received at least 1 dose of rIX-FP during the study, having a mean (SD) duration of treatment of 206.5 (73.11) days.

4.2.2 Summary of Clinical Safety Data

Measurements of exposure and safety analyses were performed for all study subjects who received a dose of study medication as part of either PK evaluation, on-demand treatment of bleeding episodes, routine prophylaxis, or perioperative management of bleeding episodes. Safety assessments were based on adverse event (AE) reporting, including SAEs, and the assessment of biochemistry, hematology, coagulation activation markers (i.e., prothrombin fragment 1+2, thrombin-antithrombin (TAT), D-dimer), local tolerability, vital sign measurements, and physical examinations. Urinalyses were performed in Studies 2001, 2004, and 3001. Important identified and potential risks that are class effects for recombinant FIX concentrates include hypersensitivity/anaphylactic reactions, thromboembolic events, development of FIX inhibitors and development of antibodies against CHO host cell proteins. FIX inhibitors and non-neutralizing antibodies to rIX-FP were assessed in all studies, and antibodies to CHO host cell proteins were assessed in Studies 3001 and 3002.

As of January 9, 2015, a total of 111 subjects with severe and moderate hemophilia B (FIX activity level $\leq 2\%$) had received at least 1 injection of rIX-FP in 5 clinical trials (ie, studies 2001, 2004, 3001, 3002 and ongoing study 3003) and comprise the Safety population. The subjects enrolled in the rIX-FP clinical development program were representative of the overall hemophilia B population. Subjects were exposed to rIX-FP with an adequate number of EDs over an adequate period of time to provide valid data to support the 3 indications.

4.2.2.1 Summary of Adverse Events

- 5 BLA safety studies (2001, 2004, 3001, 3002, 3003 [ongoing])
- 111 subjects in the 5 BLA safety studies, all male
 - 662 TEAEs
 - The most frequently reported AEs were in the System Organ Class (SOC) categories of:
 - Infections and Infestations (110 events in 42.3% of subjects)
 - Musculoskeletal and Connective Tissue Disorders (61 events in 27.0% of subjects)
 - Injury, Poisoning and Procedural Complications (46 events in 26.1% of subjects)
 - Nervous System Disorders (47 events in 19.8% of subjects)
 - The most frequently reported AEs by PT were:
 - Nasopharyngitis (54 events in 21.6% of subjects)
 - Headache (47 events in 19.8% of subjects)
 - Arthralgia (43 events in 19.8% of subjects)
 - 16 TEAEs (in 9 subjects) deemed “related” (all non-serious) (see Table 5)
 - 10 SAEs (in 8 subjects): 0 deemed “related”
 - 5 subjects withdrew:
 - (Study 3001) 1 due to “hypersensitivity”, later deemed an infusion-related reaction
 - (Study 3001) 1 due to headache
 - (Study 3001) 1 due to repeat episodes (x5) of rash/exanthema
 - (Study 3001) 1 due to right thigh/groin pain (arthritis vs. possible deep muscle bleed, drug ineffective w/ 3 doses rIX-FP)*
 - (Study 3003) 1 due to “gamma-glutamyl transferase increased” with exacerbation of underlying alcoholic liver disease

* This patient listed in Table 5, but not included in Related or SAE counts, due to uncertain diagnosis

- 0 subjects developed FIX inhibitors or antibodies to rIX-FP or Chinese hamster ovary (CHO) cell proteins.
- 4 subjects (of 63) in pivotal trial 3001 had a normal screening urinalysis, then developed a positive test for protein in the urine without blood on more than one sample (see Table 6). None of the four subjects had a corresponding pattern of increasing serum creatinine or new hypertension with the proteinuria during the study. Follow-up urinalyses in each of the 3 subjects remaining in Study 3003 in August/September 2015 were all negative, with corresponding normal spot urine

protein/creatinine ratios for each. According to the sponsor, no inhibitors to rIX-FP and no antibodies to rIX-FP or CHO host cell protein were detected in any subject in this trial.

- Subject (b) (6): 54 year old Asian male with a history of Hepatitis C and hypertension; urinalysis (UA) for protein in study 3001 was negative at screening, positive @ weeks 12, 44, negative @ weeks 28, 60, 76, 92, and end of study (EOS); he had a few mildly elevated blood pressures @ screening and after receiving the previous FIX dose prior to receiving rIX-FP, and post-rIX-FP @ weeks 4, 8, 24, and 56; creatinine at screening was 0.55 mg/dL and remained relatively unchanged throughout study 3001 (0.52 mg/dL @ EOS). Urinalysis and spot urine protein/creatinine ratio were tested in extension study 3003 80 weeks after the EOS measurements for study 3001; urinalysis was negative and spot urine protein/creatinine ratio was normal, despite a low serum creatinine (0.38 mg/dL).
 - Subject (b) (6): 15 year old White male who developed proteinuria detected on a UA in study 3001 that was positive for protein @ weeks 12, 28, 44, 60 and EOS; screening UA was done ~1 year prior to the first evidence of proteinuria @ 12 weeks; screening creatinine = 0.9 mg/dL and was similar @ EOS (0.88 mg/dL); he had normal urine concentration and serum albumin throughout the study. Urinalysis and spot urine protein/creatinine ratio were tested in extension study 3003 58 weeks after the EOS measurements for study 3001; urinalysis was negative and spot urine protein/creatinine ratio was normal, with a normal serum creatinine (1.02 mg/dL).
 - Subject (b) (6): 43 year old White male with a history of Hepatitis C whose UA in study 3001 was negative for protein @ screening, 12, and 28 weeks, positive @ 44 weeks and EOS (>6 months later); his creatinine remained unchanged throughout the study; UAs were negative for blood and revealed normal urine concentrations; one serum albumin level was increased, while the rest were normal; the subject had 2 urinary tract infections (during weeks 16-40) and an episode of syphilis (weeks 56-68) for which he received antibiotics. Urinalysis and spot urine protein/creatinine ratio were tested in extension study 3003 62 weeks after the EOS measurements for study 3001; urinalysis was negative and spot urine protein/creatinine ratio was not tested due to low protein; the subject's serum creatinine on the same date was low (0.48 mg/dL), and this was not considered clinically significant.
 - Subject (b) (6): 26 year old White male who demonstrated proteinuria in study 3001 @ 12 and 28 weeks and EOS (3 months later); the screening UA was done <4 months prior to the first evidence of proteinuria @ 12 wks; the subject had normal urine concentration and serum albumin throughout. The subject was lost to follow-up in March 2015, 37 weeks after the EOS measurements for study 3001; his final serum creatinine on that date was normal (0.62 mg/dL).
- There were no other concerning clinical manifestations or lab values regarding safety issues.

Table 5. Related Adverse Events, Serious Adverse Events, and Events Leading to Withdrawal Among rIX-FP Recipients in the 5 BLA Studies

AE #	Study	Patient ID	Patient Event #	Country	Age (yrs)	Race	Preceding rIX-FP Dose (IU/kg)	TEAE	Related	SAE	W/D	Event
1	2001	(b) (6)	001	Germany	?	?	25	Y	Y	N	N	constipation; resolved within 1 day
2	2001	(b) (6)	001	Israel	?	?	75	Y	Y	N	N	erythema @ injection site 30 min post-infusion; resolved within 3 hrs
3	2001	(b) (6)	001	France	?	?	50	Y	Y	N	N	"felt hot" 50 min post-infusion; resolved within 5-10 min without Tx
4	2001	(b) (6)	002	France	?	?	50	Y	Y	N	N	mild HA 50 min post-infusion; resolved within 1 day
5	3001	(b) (6)	1 of 1	Germany	22	W	50	Y	Y	N	Y	"hypersensitivity" 1 min post-infusion (nausea, sweet taste in back of throat, "tachycardia" [HR 51-->60]); D/C'd infusion, given NS IV; resolved within 23 min; After review by IDMC, event deemed an infusion-related rxn
6	3001	(b) (6)	1 of 7	Germany	20	W	50	Y	Y	N	N	mild dizziness 4 min post-infusion; resolved within 1 hr 46 min without Tx
7	3001	(b) (6)	4 of 6	Japan	30	A	50	Y	Y	N	N	HA
8	3001	(b) (6)	5 of 6	Japan	30	A	50	Y	Y	N	N	eczema
9	3001	(b) (6)	6 of 6	Japan	30	A	50	Y	Y	N	Y	HA
10	3001	(b) (6)	8 of 14	Germany	26	W	37	Y	Y	N	N	rash / exanthem
11	3001	(b) (6)	9 of 14	Germany	26	W	37	Y	Y	N	N	rash / exanthem
12	3001	(b) (6)	10 of 14	Germany	26	W	37	Y	Y	N	N	rash / exanthem
13	3001	(b) (6)	11 of 14	Germany	26	W	37	Y	Y	N	N	rash / exanthem
14	3001	(b) (6)	14 of 14	Germany	26	W	37	Y	Y	N	Y	rash / exanthem
15	3001	(b) (6)	7 of 18	Spain	14	W	50	Y	Y	N	N	injection site hematoma; resolved within same day
16	3001	(b) (6)	1 of 2	Bulgaria	18	W	38	Y	N	Y	N	L knee synovitis
17	3001	(b) (6)	2 of 2	France	55	W	50	Y	N	Y	N	epileptic aphasia in subject w/ 40-year Hx of epilepsy; resolved after Tx with Levetiracetam
18	3001	(b) (6)	1 of 1	US	58	B	35	Y	*	*	Y	R thigh/groin pain w/ negative hip CT (deemed arthritis, per sponsor; possible deep muscle bleed and drug ineffective w/ 3 doses of rIX-FP [50, 34 & 30 IU/kg], per clinical reviewer)
19	3002	(b) (6)	7 of 15	Canada	5	W	65	Y	N	Y	N	arthralgia; pain in hip due to traumatic fall on ice; hospitalized
20	3002	(b) (6)	11 of 15	Canada	5	W	65	Y	N	Y	N	arthralgia; pain in hip due to fall on snowbank; seen at hospital
21	3002	(b) (6)	8 of 8	Italy	5	W	40	Y	N	Y	N	L forearm fracture; hospitalized x 4 days
22	3002	(b) (6)	1 of 6	France	8	H	43	Y	N	Y	N	inguinal pain with impact on walking; hospitalized x 4 days
23	3002	(b) (6)	4 of 6	France	8	H	43	Y	N	Y	N	head injury; hospitalized overnight
24	3002	(b) (6)	3 of 4	Spain	6	W	46	Y	N	Y	N	tongue laceration; hospitalized
25	3003	(b) (6)	3 of 12	Japan	56	A	75	Y	N	Y	N	(weight loss → hemoccult positive); colon polyps found on colonoscopy; hospitalized and underwent polyp resection
26	3003	(b) (6)	3 of 3	Israel	28	W	75	Y	N	Y	N	(heartburn/reflux); esophagitis on endoscopy
27	3003	(b) (6)	4 of 6	Japan	58	A	45	N	Y	N	Y	exacerbation of underlying alcoholic liver disease & ↑d GGT on lab test

Abbreviations: A=Asian; B=Black; CT=computed tomography scan; D/C'd= discontinued; GGT=gamma-glutamyl transferase; H=Hispanic; HA=headache; HR=heart rate; hrs=hours; Hx=history; IDMC=Independent Data Monitoring Committee; IU=international units; IV=intravenous; kg=kilograms; L=left; min=minutes; N=no; NS=normal saline; R=right; rxn=reaction; Tx=treatment; W=White; w/=with; Y=yes; yrs=years; ?=unknown

* Related and SAE status depends on final diagnosis (arthritis vs deep muscle bleed); subject therefore not included in final Related & SAE counts

Table 6. Line Listing of Pertinent Lab Values and Clinical Signs Among 4 Subjects with Treatment-Emergent Proteinuria

ID #	Age @ Start	Race	Study Week	Urine SG	Urine Protein	Urine Other	Serum Albumin (g/L)	Reference Range		Serum Protein (g/L)	Reference Range		Serum Creatinine (mg/dL)	Reference Range		SBP (mm Hg)	DBP (mm Hg)		
								Low	High		Low	High		Low	High				
(b) (6) Pt w/ underlying HTN	54	A	SCR	1.021	negative	2+ protein PSE ¹	41	38	53	67	67	83	0.55 ²	0.61	1.04	124	63		
			FIXPKa														150	86	
			FIXPKb															163	85
			FIXPKc															165	80
			rIXPKa															130	75
			rIXPKb															135	85
			rIXPKc															131	74
			4															149	98
			8															158	105
			12	1.033	trace		44	38	53	70	67	83	0.65	0.61	1.04	119	83		
			16															117	81
			20															116	80
			24															145	84
			28	1.023	negative		39	38	53	63 ²	67	83	0.47 ²	0.61	1.04	115	83		
			32															122	85
			36															115	82
			40															129	81
			44	1.034	1+		43	38	53	69	67	83	0.68	0.61	1.04	126	87		
			48															132	71
			52															108	85
56															145	94			
60	1.017	negative		43	38	53	64 ²	67	83	0.47 ²	0.61	1.04	116	68					
76	1.025	negative		41	38	53	64 ²	67	83	0.68	0.61	1.04	112	73					
92	1.018	negative		44	38	53	66 ²	67	83	0.47 ²	0.61	1.04	108	74					
EOS	1.016	negative		43	38	53	67	67	83	0.52 ²	0.61	1.04	133	82					
+80wks ³	1.025	negative	Normal spot P/C	43	38	53	66	65	83	0.38	0.61	1.04							
(b) (6)	15	W	SCR	1.011	negative		40	35	50	73	60	80	0.90 ²	0.20	0.70	117	63		
			12	1.017	+					72	60	80	0.90	0.60	1.20	104	54		
			28	1.021	+		40	35	50	72	60	80	1.00	0.60	1.20	127	62		
			44	1.026	+	2+ leukocytes	48	35	50	79	60	80	1.00	0.60	1.20	113	60		
			60	1.022	+		43	35	50	75	60	80	0.84	0.60	1.20	118	57		
			EOS	1.015	+		47	35	50	77	60	80	0.88	0.60	1.20	115	62		
			+58wks ³	1.020	negative	Normal spot P/C	45	35	50	78	60	80	1.02	0.60	1.20				
(b) (6) Pt w/ 2 UTIs & 1 episode syphilis during trial	43	W	SCR	1.010	negative		48	35	52	77	64	82	0.54 ²	0.67	1.18	118	75		
			12	1.010	negative		55 ²	35	52	79	64	82	0.52 ²	0.67	1.18	131	84		
			28	1.010	negative		51	35	52	75	64	82	0.49 ²	0.67	1.18	116	76		
			44	1.005	+(0.3g/L)		50	35	52	77	64	82	0.67	0.67	1.18	109	67		
			EOS	1.000	++ (1g/L)		48	35	52	73	64	82	0.63 ²	0.67	1.18	109	71		
			+62 wks ³	1.005	negative	P/C too low to test				79 ²	60	78	0.48 ²	0.72	1.18				
(b) (6)	26	W	SCR	1.025	negative		45	35	52	76	57	82	0.61	0.60	1.10	129	71		
			12	1.030	trace	+ leukocytes	45	35	52	72	57	82	0.67	0.60	1.10	115	69		
			28	1.025	1+ (0.3g/L)	+ ketones (0.4g/L)	47	35	52	79	57	82	0.76	0.60	1.10	125	65		
			EOS	1.020	trace/ negative	+ leukocytes	49	35	52	81	57	82	0.74	0.60	1.10	114	65		

Abbreviations: A=Asian; BP=blood pressure; EOS=end of study; hrs=hours; FIXPKa=prior to previous FIX PK dose; FIXPKb=30 minutes post-previous FIX PK dose; FIXPKc=3 hours post-previous FIX PK dose; HTN=hypertension; min=minutes; P/C=(urine) protein-to-creatinine ratio; PSE=prior to study entry; Pt=patient; rIXPKa=prior to rIX-FP PK dose; rIXPKb=30 minutes post-rIX-FP PK dose; FIXPKc=3 hours post-rIX-FP PK dose; SBP=systolic blood pressure; SCR=screening; SG=specific gravity; UTIs=urinary tract infections; W=White; w/=with
If cell is blank, no measurement was obtained in that category.

¹ Subject (b) (6) had 2+ protein on a urinalysis in 2008.

² Not clinically significant (per sponsor/Principal Investigator)

³ Measurement in Study 3003 at n # of weeks from EOS measurement in Study 3001

4.3 Sponsor's Assessment – Proteinuria Among 4 Subjects

4.3.1 Proteinuria in Relation to rIX-FP Dosing

The sponsor provided an argument against a causal association between rIX-FP and the proteinuria observed in these 4 subjects. First, the contribution of albumin from the rIX-FP product to the total protein in the blood is small. Each IU of rIX-FP contains (b) (4) mg albumin (or (b) (4) in 10,000 IU of rIX-FP), which is a small fraction of the total albumin content of 34-54 g/L of blood. An average adult male (70 kg, ~5.5L blood volume) on a prophylaxis regimen would receive 4,900 IU, containing only (b) (4) albumin, or (b) (4) of total albumin. This argues against an excess amount of albumin from the administered product causing the proteinuria. Second, while FIX replacement products have been associated with renal damage consistent with nephrotic syndrome, this has typically been observed among patients with FIX inhibitors who receive high daily doses (100-325 IU/kg FIX daily) for immune tolerance induction (ITI) (see Section 5.1) with an onset 8-9 months following the start of ITI.^{9,10} The dosing of rIX-FP is significantly lower (75 IU/kg every 14 days) and no signs or symptoms of nephrotic syndrome (edema, proteinuria [4+], hypoalbuminemia) have been reported for any subject during the clinical trials. Third, nonclinical studies evaluating repeat-dose toxicity in monkeys and rats revealed no renal damage in either species at any dose (up to 500 IU/kg/day rIX-FP). Finally, the extended half-life of rIX-FP results in an exposure and consumption of FIX that is approximately half that for patients' previous FIX products. Subjects in Study 3001, Arm 1 exhibited approximately 50% lower monthly consumption (median = 162 IU/kg) compared with previous FIX treatment (median = 256.55 IU/kg). This lower exposure is within the normal range (50-150 IU/dL) for a healthy human and unlikely to be associated with renal damage such as nephrotic syndrome.

4.3.2 Proteinuria As Measured by Urine Dipstick

The urine dipstick is an efficient and readily available method of measuring blood, protein, glucose, ketones and leukocytes in the urine in a semi-quantitative manner. However, results can vary based on urine concentration, sample pH, contamination and inadequate handling of the specimen. Data suggest that using the urine specific gravity to judge urine concentration may improve the ability to identify abnormal proteinuria with the dipstick. One study found that a urine dipstick for proteinuria of 2+ or higher was predictive of significant proteinuria regardless of the specific gravity; however, a urine dipstick for proteinuria of trace or 1+ was only predictive of significant proteinuria if the specific gravity was 1.025 or less.¹¹

4.3.3 Causes of Proteinuria

Transient proteinuria is common, particularly among younger individuals; it has been reported in nearly 20% of school children and in approximately 4% of college-aged individuals.^{12,13} It has also been observed following exercise in healthy adults.¹⁴ Additionally, several disease conditions (such as diabetes and hypertension), infections (such as human immunodeficiency virus (HIV), syphilis, hepatitis B and C) and medications (such as antibiotics, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs)) can also cause proteinuria.

4.3.4 Alternate Explanations for Dipstick-Measured Proteinuria Among These 4 Subjects

Subject (b) (6) is a 54 year old Asian male with hepatitis C and HIV who had been taking frequent NSAIDs due to "severe pain" from his hemophilic arthropathy. Both hepatitis C and HIV, as well as NSAID exposure, can increase the risk of proteinuria. Additionally, the positive protein tests occurred when his urine specific gravity was >1.030, making the urine dipstick results less predictive of significant proteinuria. Of note, the patient had a prior history of a positive urine dipstick for protein in 2008, before rIX-FP exposure. Follow-up urinalysis and spot urine protein/creatinine ratio 80 weeks after the end of study 3001 were both negative, demonstrating the transient nature of the previously detected proteinuria.

Subject (b) (6) is a 15 year old White male who is physically active and exercises regularly, which can cause proteinuria. Due to multiple trauma-induced severe bleeding episodes (requiring hospitalization) during the screening period, he received his first dose of rIX-FP 8 months after his initial screening urine dipstick test, making it difficult to ascertain whether the proteinuria might have developed prior to rIX-FP exposure. The

sponsor notes that the subject's urine specific gravity was 1.011 upon initial screening, but close to or greater than 1.020 on all subsequent dipsticks (all of which were positive for protein). Follow-up urinalysis and spot urine protein/creatinine ratio 58 weeks after the end of study 3001 were both negative, demonstrating the transient nature of the previously detected proteinuria.

Subject (b) (6) is a 43 year old male with hepatitis C who tested positive for proteinuria at Week 44 and at EOS (Week 80). The subject had 2 urinary tract infections (during weeks 16-40), one treated with a fluoroquinolone and one treated with a penicillin, and an episode of syphilis (weeks 56-68), treated with a parenteral carbapenem; both diseases and medications to treat them can increase protein in the urine. Follow-up urinalysis 62 weeks after the end of study 3001 was negative, with urine protein too low to perform a spot urine protein/creatinine ratio test; this, coupled with a normal serum protein and a low serum creatinine, also suggests the transient nature of the previously detected proteinuria.

Subject (b) (6) is a 26 year old male with no chronic diseases that are potentially causative of proteinuria; he did report receipt of concomitant medications amoxicillin and acetaminophen, which can cause proteinuria. Leukocytes were detected on 2 of the 3 positive dipsticks, which might indicate sample contamination or pyuria.

4.4 Proposed Pharmacovigilance Plan

The sponsor-identified safety concerns and planned pharmacovigilance actions are listed in Table 7.

Table 7. Summary of Safety Concerns & Action Plan for Safety Issues Proposed by CSL Behring

Important Identified Risks	Planned Risk Management / Pharmacovigilance Actions
None	–
Important Potential Risks	Planned Risk Management / Pharmacovigilance Actions
Hypersensitivity / anaphylactic reactions	<ul style="list-style-type: none"> • Product labeling that includes: <ul style="list-style-type: none"> ○ A contraindication for individuals with known hypersensitivity to rIX-FP or its excipients, including hamster protein ○ Warnings/precautions for the possibility of allergic reactions and a recommendation regarding hypersensitivity ○ Patient counseling information to report any adverse reaction or issues following rIX-FP administration to their physician or healthcare provider; advice regarding the early signs of hypersensitivity reactions; advice on what to do if a hypersensitivity reaction should occur • CSL654-3003 Phase IIIb including PUPs • Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including specific follow-up questionnaire
Development of inhibitors to FIX	<ul style="list-style-type: none"> • Product labeling that includes recommendations to evaluate patients regularly for FIX inhibitors • CSL654-3003 Phase IIIb including PUPs • Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up and specific follow-up questionnaire
Development of antibodies to product (rIX-FP)	<ul style="list-style-type: none"> • Product labeling that includes recommendations to evaluate patients regularly for inhibitors to the product • CSL654-3003 Phase IIIb including PUPs • Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up and target questionnaire
Development of antibodies to CHO host cell proteins	<ul style="list-style-type: none"> • A (b) (4) step is used in the production process to purify rIX-FP from process- and product-related impurities. • CSL654-3003 Phase IIIb including PUPs • Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up and target questionnaire
Dosing errors based on variability in the assays used during treatment monitoring of FIX levels	<ul style="list-style-type: none"> • Product labeling that includes a statement in the Warnings/Precautions section to inform of the variability of reagent results • CSL654-3003 Phase IIIb including PUPs • Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up and target questionnaire

Important Missing Information	Planned Risk Management / Pharmacovigilance Actions
Experience in patients with a history of thrombosis	<ul style="list-style-type: none"> • CSL654-3003 Phase IIIb including PUPs • Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up and specific follow-up questionnaire
Experience of inhibitor formation in PUPs	<ul style="list-style-type: none"> • CSL654-3003 Phase IIIb including PUPs • Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up and specific follow-up questionnaire
Experience in pregnancy and lactation, including labor and delivery	<ul style="list-style-type: none"> • Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up and pregnancy follow-up questionnaire
Experience in elderly patients (65 years and above)	<ul style="list-style-type: none"> • Routine Pharmacovigilance (AE reporting in accordance with 21 CFR 600.80) including additional follow-up

Abbreviations: CFR=Code of Federal Regulations; CHO = Chinese hamster ovary; FIX = coagulation factor IX; PUPs = previously untreated patients; rIX-FP: recombinant fusion protein linking coagulation FIX with albumin

5 ADDITIONAL COMPONENTS OF BLA REVIEW

5.1 Pharmacological Class Effects – Recombinant Factor IX Products

There are currently four recombinant factor IX products licensed in the US: BeneFIX®(1997), Alprolix®(2014), Rixubis®(2013), and Ixinity®(2015). Three of them (BeneFIX, Rixubis and Ixinity) are derived from CHO proteins, similar to Idelvion, and one (Alprolix) is derived from human embryonic kidney cells. The following adverse reactions have been observed among FIX product recipients and are listed in the Warnings and Precautions section of the package insert (PI) for all four products:

- **Hypersensitivity reactions**

Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with FIX replacement products, including BeneFIX and Rixubis. Allergic manifestations include pruritis, rash, urticaria/hives, facial swelling, dizziness, hypotension, nausea, chest discomfort, cough, dyspnea, wheezing, flushing, generalized discomfort and fatigue. These reactions have frequently been associated with the development of FIX inhibitors.^{15,16} A retrospective chart review of FIX recipients (both plasma-derived and recombinant) detected a total of 7/180 (3.9%) subjects with a moderate to severe allergic reaction to a FIX product. Of these 7, 5 (71%) also had FIX inhibitors.¹⁷ In an examination of a 2005 FIX registry, 51 (58%) of the 88 FIX inhibitor cases were associated with an allergic manifestation.¹⁸ Groups at risk of hypersensitivity reactions to Idelvion include people with known hypersensitivity to rIX-FP or its excipients, including hamster protein.

- **Neutralizing antibodies (inhibitors) to FIX**

Formation of neutralizing antibodies (inhibitors) to FIX has been reported during factor replacement therapy in the treatment of hemophilia B. Although no cases have been reported among recipients of Alprolix, Ixinity and Rixubis, inhibitors were detected in 1/65 (1.5%) previously treated patients (PTPs) and high-titer inhibitor formation was seen in 2/63 (3.2%) pediatric previously untreated patients (PUPs) who received BeneFIX. The published incidence of FIX inhibitors among all patients with hemophilia B is between 1.5% and 5%.^{18,19} The biggest risk factor for FIX inhibitor formation is considered to be major deletions or nonsense mutations of the FIX gene resulting in the absence of FIX, resulting in exogenous FIX being detected as foreign and thus triggering antibody formation.⁹ Inhibitor formation reduces the activity of coagulating factors, thus decreasing their efficacy. Inhibitors in some patients are transient and resolve without treatment. The most effective approach for eradicating inhibitors is immune tolerance induction (ITI), which entails a desensitization process through a gradual progression of FIX dosing with or without adjunctive immunosuppressant or immunomodulator administration. ITI has a success rate of 15-30% for hemophilia B.¹⁹ All 4 recombinant FIX products contain warnings about the development of FIX inhibitors. The PI for all 4 products recommends that all FIX recipients should be monitored regularly for inhibitor development, and if expected FIX levels are not achieved, or bleeding is not controlled, or an allergic reaction occurs, an assay that measures FIX inhibitor concentration should be performed.

- **Risk of thromboembolic events (TEE)**

FIX products are coagulation factors and the use of FIX products has been associated with the development of thromboembolic complications, especially in individuals receiving continuous infusion through a central venous catheter. Although no TEE have been reported among recipients of Ixinity and

Rixubis, post-marketing reports of TEE with receipt of BeneFIX have occurred, including life-threatening superior vena cava syndrome in critically ill neonates while receiving BeneFIX through a central venous catheter. In an Alprolix clinical study, 1 patient developed an obstructive uropathy due to a clot that resolved with hydration. Cases of peripheral thrombophlebitis and deep venous thrombosis have also been reported. Of note, Idelvion will not be recommended for use via continuous infusion.

- **Nephrotic syndrome after immune tolerance induction (ITI)**

Nephrotic syndrome has been reported following ITI with FIX products in hemophilia B patients with FIX inhibitors.²⁰ The mechanism behind the development of nephrotic syndrome among those undergoing ITI is believed to be similar to immune dysregulation seen in autoimmune diseases, such as systemic lupus erythematosus and Crohn's disease. Despite ITI not being an indication for any of the recombinant FIX products currently licensed, this general warning is included in the PI for BeneFIX, Ixinity and Rixubis.

Other possible adverse event risks among FIX product recipients include:

- **Development of non-inhibitory antibodies to product (rIX-FP)**

While the development of inhibitory antibodies to rIX-FP can reduce the efficacy of the product or cause allergic reactions, non-inhibitory antibodies may have no impact on efficacy or safety. The development of non-inhibitory antibodies could still result in hypersensitivity reactions, although no safety issues regarding non-inhibitory antibodies have been identified in the 4 licensed recombinant FIX products.

- **Development of antibodies against CHO host cell proteins (for products derived from CHO proteins)**

Host cell protein impurities are a known risk for biological products. CHO host cell proteins may not be completely removed during purification, which may then induce a hypersensitivity response.²¹ Of the 4 recombinant FIX products already licensed, 3 are derived from CHO proteins (BeneFIX, Ixinity and Rixubis). In a clinical study of 91 Rixubis recipients, 13 (14.3%) developed antibodies against a CHO protein, although 4 of these subjects had antibodies prior to treatment and 2 had antibodies that were only transient. No adverse clinical findings were observed in any of these subjects. Additionally, in a study of 500 healthy volunteers using the same assay as in the Rixubis clinical trial, 7% had titers of 1:20 or 1:40 and 1.2% had titers from 1:80 to 1:320. These antibodies are thought to be part of a natural immune response and have not been associated with any adverse clinical findings. Despite this, a warning for the potential for development of antibodies to CHO proteins is included in the PI for BeneFIX, Ixinity and Rixubis. Of note, a (b) (4) step is used in the production process to purify rIX-FP from process- and product-related impurities.

- **Dosing errors based on variability in the assays used during treatment monitoring of FIX levels**

The frequency of this type of error for the 4 currently-licensed FIX products is not known; however, detailed guidance on dosing and monitoring of FIX levels is included in the PIs for all 4 products.

- **Dosing frequency errors due to longer half-life (for fusion products)**

Alprolix is a FIX fusion product similar to Idelvion, except that it is linked to the Fc domain of human immunoglobulin G1 instead of albumin. For both products, this fusion results in a longer half-life, often allowing less frequent dosing regimens (e.g., every 7-14 days). Because of this, dosing errors may occur in patients who are accustomed to more frequent dosing with other non-fusion FIX products. Alprolix notes this as a precaution in the dosing section of its PI.

One advantage to recombinant FIX products, particularly those derived from CHO proteins, is the lack of infectious disease transmission risk. The CHO cell line is extensively characterized and known to be free of infectious agents. The cell line secretes recombinant FIX into a defined cell culture medium that does not contain any proteins derived from animal or human sources, and the recombinant FIX is purified by a (b) (4) purification process that does not require a monoclonal antibody step and yields a high-purity, active product. It is inherently free from the risk of transmission of human blood-borne pathogens, such as HIV, hepatitis viruses and parvovirus.

5.2 Clinical Reviewer Assessment

(See Clinical Review BLA for individual study details and pertinent case narratives.)

Safety Conclusions of the clinical reviewer:

The clinical trials provided an adequate exposure to characterize the safety concerns with the exception of the previously untreated patients (PUPs) and surgical subjects (as of 1/9/2015). None of the events of special interest (i.e., hypersensitivity reactions, inhibitor development, thromboembolic events) were reported for subjects. There were a large number of adverse events, as is expected for a trial conducted with a median participation time of 600 days. The number of serious adverse events was small, and none of them were attributed to Idelvion. The sponsor proposed a limited list of events in the Adverse Reactions section of the PI (not including proteinuria). The approach is consistent with the FDA Guidance for Industry, Adverse Reactions Section for Labeling, and with recent approvals of hemophilia products. The identified adverse events are similar in type and severity to the events associated with other hemophilia products and, more specifically, recombinant Factor IX products. One safety issue, abnormal urinalyses/proteinuria, is still being investigated, but it appears mild.

5.3 Renal Consult and Evaluation of Patients with Proteinuria

The FDA Renal Consultant requested clarification of urine protein scoring as well as a possible explanation for the abnormal urine protein findings in Subject (b) (6) (26 year old). She noted that in 1 of the 4 cases ((b) (6)), the finding was intermittent and the patient also had underlying conditions that can cause proteinuria. In a second case ((b) (6)), there was a significant time lag between the screening measurement and the 12-week measurement (when the abnormal finding was first noticed), making it possible that the proteinuria was present prior to treatment. It was concluded that a signal for proteinuria was not obvious. A recommendation was made to obtain screening urinalyses on all new subjects and follow-up urinalyses on already-enrolled subjects in ongoing extension study 3003, and to follow-up any proteinuria with a spot protein/creatinine ratio to quantify the proteinuria and assess whether it warrants further work-up. The sponsor agreed only to follow-up 3 of the 4 subjects who had treatment-emergent proteinuria (1, Subject (b) (6) was lost to follow-up in March 2015) with routine follow-up urinalyses and, if positive for protein, spot urine protein/creatinine tests, as well as corresponding serum chemistries.

In August/September 2015, follow-up of the 3 subjects with proteinuria in study 3001 who were still enrolled in study 3003 revealed normal urinalyses and spot urine protein/creatinine ratios (in those who had adequate urine protein to test). This indicated no persistent proteinuria despite continued rIX-FP exposure and no other physiological manifestations suggestive of renal damage.

6 EPIDEMIOLOGY REVIEW / RISK ASSESSMENT

Among the 662 TEAEs experienced by the 111 subjects enrolled in the 5 BLA studies, only 16 (2.4%) were deemed related and 10 (1.5%) were deemed serious (with none of these considered to be related to rIX-FP). As noted in the Clinical Reviewer assessment, none of the health outcomes of interest for FIX products (hypersensitivity reactions, inhibitor or antibody formation, TEE) occurred following rIX-FP in any of the clinical trials subjects. These data are consistent with the acceptable safety profile of several currently-licensed FIX products for patients with Hemophilia B.

The development of inhibitors among hemophilia B patients receiving FIX replacement products is a serious concern in that it can result in a reduction of product effectiveness, as well as an elevated risk of hypersensitivity reactions.^{15,16} Inhibitor development is more likely to occur among patients who have not received coagulation products previously (PUPs).²² The clinical trials data as of January 9, 2015 did not include any PUPs and therefore cannot yet assess the rate of inhibitor formation (or corresponding hypersensitivity reactions) among PUPs. However, Study 3003 includes a treatment arm for PUPs, with the goal of enrolling at least 20 during the study period.² It is worth noting that inhibitor formation is less frequent among hemophilia B patients (FIX recipients) compared with hemophilia A patients (Factor VIII recipients). Because of this, this safety outcome can be measured in the course of completion of study 3003 without requiring additional study or monitoring activities for safety reasons. Regulatory actions and/or changes can be made to the product label if an elevated risk of inhibitor formation or other corresponding outcomes of interest are observed in this subpopulation.

Women comprise only a very small proportion (2.6%) of patients with hemophilia B⁵ and no women were enrolled in the clinical trials for Idelvion. Additionally, no animal reproduction studies were conducted with rIX-FP. Therefore, no data is available regarding the use of rIX-FP during pregnancy and subsequent breastfeeding. Because of this, the label will advise to use rIX-FP during pregnancy and lactation only if clearly indicated, and any adverse events occurring in the small subpopulation will be identified via routine pharmacovigilance and further specified with a pregnancy follow-up questionnaire.

To date, the clinical trials data do not include information on Idelvion exposure in the elderly (>65 years of age). Any adverse events occurring in this subpopulation will be identified via routine pharmacovigilance, including additional follow-up.

One additional safety issue identified by FDA among rIX-FP recipients was treatment-emergent proteinuria on more than one measurement, observed in 4 subjects enrolled in Study 3001 (and ongoing extension study 3003). One subject (b) (6) had two underlying disease conditions (hepatitis C and HIV) and exposure to a drug class (NSAIDs) that can cause proteinuria,²³⁻²⁵ as well as a history of proteinuria prior to rIX-FP exposure. This subject also had a history of hypertension, which can cause proteinuria; while he had a few elevated blood pressure measurements during Study 3001, 3 of 7 (43%) occurred prior to his first rIX-FP exposure. Additionally, the positive protein tests occurred when his urine specific gravity was >1.030, making the urine dipstick results of “trace” and “1+” less predictive of significant proteinuria, and he had subsequent urine dipstick tests that were negative for protein when he was still receiving rIX-FP, making a causal association less likely. Negative follow-up urinalysis and spot urine protein/creatinine ratio testing, along with normal renal function throughout rIX-FP exposure, suggests the proteinuria was mild, transient, and not causally related to rIX-FP.

A second subject (b) (6) is very physically active, which might explain the proteinuria observed at his follow-up visits. Because he received his first dose of rIX-FP 8 months after his initial screening urine dipstick test, it is difficult to ascertain whether the proteinuria might have developed prior to rIX-FP exposure. It is still possible the proteinuria occurred only after exposure to rIX-FP. However, negative follow-up urinalysis and spot urine protein/creatinine ratio testing, along with normal renal function throughout rIX-FP exposure, suggests the proteinuria was mild, transient, and not causally related to rIX-FP.

A third subject ((b) (6) had several potential alternate explanations for his proteinuria. He has chronic hepatitis C, which can cause proteinuria, although he did not develop proteinuria until Week 44 post-rIX-FP exposure. However, prior to the first positive urine dipstick test for protein, he had 2 urinary tract infections that were treated with a fluoroquinolone and penicillin. Urinary tract infections, as well as both of these antibiotics, can cause proteinuria. Prior to the end of his study participation, this patient was also diagnosed with syphilis, for which he received a carbapenem antibiotic. Both this disease and its treatment can cause proteinuria. This subject also had a negative follow-up urinalysis and urine protein was too low to perform a spot protein/creatinine ratio test, again suggesting the proteinuria was mild, transient, and not causally related to rIX-FP.

The fourth subject (b) (6) had no chronic diseases that can cause proteinuria; however he did report receipt of concomitant medications amoxicillin and acetaminophen, both of which can cause proteinuria. Regardless of these potential alternate explanations, rIX-FP exposure might still have been a possible cause of this subject’s proteinuria in study 3001. However, serum creatinine remained normal throughout his exposure to rIX-FP and he demonstrated no clinical manifestations of renal damage.

Despite a lack of quantifiable lab data for this fourth subject, all 4 cases suggest the proteinuria observed was mild, transient, and not causally related to rIX-FP. This reviewer agrees with the sponsor’s assessment that proteinuria is not a safety signal that warrants a post-marketing safety study or notation in the label.

Overall, the results of the BLA nonclinical and clinical studies suggest an acceptable safety profile for Idelvion. The benefits and risks of Idelvion are outlined below.

Idelvion Benefits:

- Demonstrated efficacy for bleeding prevention using an on-demand or routine prophylaxis regimen
- Control and prevention of recurrence of bleeding at a site of injury
- Recombinant product confers no infection risk
- Fusion with albumin results in longer half-life and provides longer dosing regimens, increasing convenience and compliance and correspondingly improving quality of life

Idelvion Risks:

- Hypersensitivity reactions
- Inhibitor (neutralizing antibody) development, resulting in lack of effectiveness and potential for increased morbidity
- Thromboembolic events

None of the above events occurred in the clinical development program, although assessment of the first two events among PUPs, who carry the greatest risk for hypersensitivity reactions and inhibitor development, has yet to be studied. Given that none of the above-listed risks were observed and the above-listed benefits were demonstrated during the clinical development program, it can be concluded that the benefits of Idelvion outweigh the risks. The Risk Management Plan proposed by the sponsor appropriately addresses the known areas of concern; the ongoing extension study (3003) will assess safety among PUPs.

7 RECOMMENDATIONS

Based on the review of the pre-licensure safety data and the sponsor's proposed pharmacovigilance plan, OBE/DE agrees with the Risk Management Plan as proposed by CSL Behring with the following actions for post-licensure safety surveillance activities of Idelvion:

- Routine pharmacovigilance to monitor AEs among Idelvion recipients in accordance with 21 CFR 600.80
- Completion and review of safety data for ongoing study 3003 (target number of subjects: 115; 85 from previous studies, 20 PUPs, 10 surgeries)
- Labeling to include: a contraindication for individuals with known hypersensitivity to rIX-FP or its excipients, including hamster protein; warnings/precautions for the possibility of allergic reactions and a recommendation regarding hypersensitivity; patient counseling information to report any adverse reaction or issues following rIX-FP administration to one's physician or healthcare provider; advice regarding the early signs of hypersensitivity reactions; advice on what to do if a hypersensitivity reaction should occur

The reviewed safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS).

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