Summary Basis for Regulatory Action

Date	February 23, 2016
From	Mikhail V. Ovanesov, PhD, Committee Chair
BLA STN	125582/0
Applicant	CSL Behring Recombinant Facility AG
Date of Submission	December 5, 2014
PDUFA Goal Date	March 4, 2016 after extension by a Major Amendment
Proprietary Name / Established Name	IDELVION / Coagulation Factor IX (Recombinant), Albumin Fusion Protein
Dosage Form	Lyophilized powder with nominal potencies: 250 IU, 500 IU, 1000 IU and 2000 IU per vial
Indications	To treat children and adults with hemophilia B (congenital Factor IX deficiency) for: • Routine prophylaxis to prevent or reduce the frequency of bleeding episodes • On-demand control and prevention of bleeding episodes • Perioperative management of bleeding
Recommended Action	Approval
Signatory Authority Action	Jay Epstein, MD_____ *Offices Signatory Authority* ☐ *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a separate review or addendum* Mary Anne Malarkey_____ *Offices Signatory Authority* ☐ *I concur with the summary review* ☐ *I concur with the summary review and include a separate review or addendum to add further analysis* ☐ *I do not concur with the summary review and include a separate review or addendum*

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1. Introduction

STN 125582/0 is an original biologics license application (BLA) submitted by CSL Behring Recombinant Facility AG (CSLB) for Coagulation Factor IX (Recombinant), Albumin Fusion Protein with the proprietary name IDELVION. The active ingredient of IDELVION is a recombinant fusion protein linking human coagulation Factor (F) IX with human serum albumin by recombinant DNA technology. The fusion protein is expressed in a Chinese Hamster Ovary (CHO) cell line, and purified using traditional manufacturing processes. The product is supplied as a sterile, freeze-dried concentrate in single-use vials containing nominal potencies of 250 International Units (IU), 500 IU, 1000 IU and 2000 IU of FIX activity. After reconstitution with sterile Water for Injection (sWFI), the product is administered intravenously. Both the nominal and actual FIX potencies are provided on the vial and carton labels.

IDELVION is indicated to treat children and adults with hemophilia B (congenital FIX deficiency) for: (1) on-demand control and prevention of bleeding episodes, (2) perioperative management of bleeding, and (3) routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

STN 125582/0 is reviewed under the standard review schedule of the PDUFA V Program. CSLB submitted the BLA on December 5, 2014. In response to an FDA information request for chemistry, manufacturing and controls (CMC) information, CSLB submitted an amendment with new method validation data on August 31, 2015. This submission was designated as a *Major Amendment*, thereby extending the goal date from December 4, 2015 to March 4, 2016. This amendment was part of a series of 16 CMC amendments submitted by CSLB between June and October of 2015, in which CSLB provided considerable new data to address deficiencies in the validation of analytical methods, deficiencies in the establishment of release specifications, and deficiencies in the studies to demonstrate comparability of processes.

2. Background

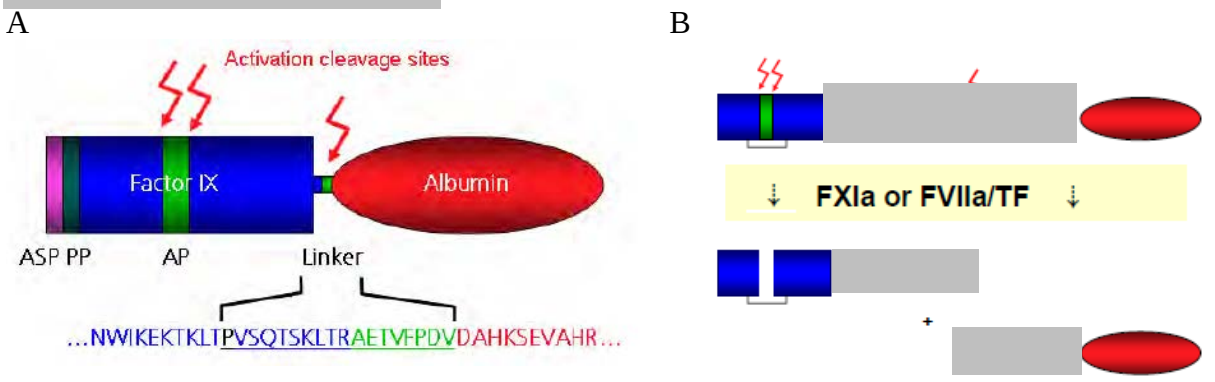
IDELVION was developed for the U.S. market under IND 14978 for the control and prevention of bleeding episodes, peri-operative management of bleeding, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes in children and adults with hemophilia B. There are approximately 20,000 people with hemophilia B in the U.S. Several FIX-containing products are licensed in the U.S. for the treatment of patients with hemophilia B. These products include three recombinant FIX products, one recombinant FIX-Fc Fusion Protein product, and several plasma-derived FIX concentrates and complexes.

IDELVION is a recombinant protein comprised of a human FIX molecule which is genetically linked to a human serum albumin molecule by a short cleavable peptide derived from the activation peptide of native FIX (Figure 1). The structure and function of the recombinant FIX and albumin moieties of IDELVION are shown to be similar to those of the naturally occurring FIX and albumin molecules in human plasma. Human serum albumin is a carrier protein with a circulatory half-life of 20 days, and genetic fusion of albumin with therapeutic

proteins has been shown to improve the half-life and bioavailability of the therapeutic proteins. In clinical trials, IDELVION demonstrated a 3-5 fold prolongation of the half-life of FIX activity in circulation when compared to the typical half-lives reported for licensed unmodified FIX products, leading to a less frequent dosing regimen for prophylactic treatment.

IDELVION remains intact in the circulation until the FIX moiety is activated and the albumin moiety is cleaved off by the physiological activators of FIX – either coagulation FXIa or a complex of FVIIa with tissue factor. Since the albumin moiety and linker partially interfere with the function of FIX in IDELVION, the activity of FIX in IDELVION is approximately of that of plasma-derived or recombinant FIX. *In vitro* studies demonstrated an . In addition, although the rate of cleavage of the activation peptide is similar to that of licensed plasma-derived and recombinant products, the time required for the full activation and release of activated FIX from albumin is . Upon the release of the albumin moiety, the resultant activated FIX behaves similarly to native activated FIX in the correction of prolonged clotting time of hemophilia B plasma. Therefore, IDELVION shares the same mechanism of action with the licensed FIX products in hemostasis.

Figure 1: IDELVION structure (A) and schematic outline of IDELVION activation (B). During activation, the activation peptide (green) is cleaved (red arrows) by either Factor XIa (FXIa) or Factor VIIa-tissue factor (FVIIa/TF) complex resulting in its liberation from activated FIX (blue); concomitantly the linker is cleaved releasing the albumin moiety (red oval) from FIXa. Abbreviations: ASP, albumin signal peptide; PP, FIX propeptide; and AP, activation peptide. Purified IDELVION lacks



IDELVION is labeled with the actual FIX potency as measured by a one-stage clotting assay in units traceable to the World Health Organization (WHO) International Standard for Factor IX concentrate, which is a plasma-derived preparation. However, variations in the biochemistry and instrumentation in FIX activity assay systems (e.g., composition of phospholipids, coagulation activators, reagent concentrations or instrument settings) may lead to differences of up to 30% in the potency assignment of IDELVION against plasma-derived reference standards. As a result, under- or over-estimation of FIX activity in post-infusion

patient plasma samples is expected in different clinical laboratories because plasma reference standards of FIX activity are customarily used to calibrate assays in clinical laboratories. The effect of assay differences on product manufacturing is essentially mitigated because CSLB has established a product-specific reference standard, which ensures consistent potency assignment and dosage throughout the product life-cycle of IDELVION.

3. Chemistry, Manufacturing and Controls

a) Product Quality

Manufacturing Process

The manufacture of IDELVION is divided into [redacted] main stages (see Figure 2) conducted at two FDA-licensed manufacturing facilities. Production of unprocessed bulk and Bulk Drug Intermediate (BDI) takes place at contract manufacturer [redacted], and production of Bulk Drug Substance (BDS) and Final Drug Product (FDP) are conducted by CSLB's subsidiary CSL Behring GmbH in Marburg, Germany.

[redacted]

(b) (4)

Table 1: Nominal composition of reconstituted IDELVION

Ingredient	Nominal composition after reconstitution with sWFI				Function
	250 IU vial	500 IU vial	1000 IU vial	2000 IU vial	
IDELVION fusion protein	100 IU/mL	200 IU/mL	400 IU/mL	400 IU/mL	Active Substance
Tri-sodium citrate					
Polysorbate 80					
Mannitol					
Sucrose					

Final Drug Product

is used to manufacture batches of FDP. FDP batch size varies between approximately vials, depending on which dose presentation is manufactured. The FDP is provided as a lyophilized powder in single-use glass vials containing nominally 250, 500, 1000 or 2000 IU of FIX activity (Table 1). The FDP is reconstituted with sWFI using a needleless *Mix2vial* device. There are no overages in the filling of IDELVION, but appropriate are incorporated in the formulations to account for losses after reconstitution with sWFI.

Evaluation of Safety Regarding Adventitious Agents

For non-viral adventitious agents including bacteria, fungi, and mycoplasma, the potential of contamination of these agents is well controlled through the use of: (1) appropriate

environmental control monitoring in the manufacturing process; (2) in-process controls, e.g., testing for endotoxins and mycoplasma ; and (3) filtration steps including sterile filtration. The potential of IDELVION to be contaminated with non-viral adventitious agents is further reduced by testing the FDP for sterility and endotoxins. CSLB manufactures IDELVION according to cGMP regulations.

No human or animal derived raw materials are used in the manufacture of IDELVION. No raw materials or ingredients of human or animal origin are used in the formulation of IDELVION FDP. Thus, the potential risk of contamination with adventitious viruses or transmissible spongiform encephalopathy agents is minimized.

The potential of contamination by viruses in cell culture is well controlled in the manufacture of IDELVION, which is produced in a genetically modified CHO cell line. CSLB performed viral tests on the Master Cell Bank (MCB) for IDELVION that are consistent with the International Conference on Harmonization (ICH) Q5A(R1) guideline. All results of viral tests were negative except for the presence of , which are considered to be non-pathogenic. Moreover, all viral tests were negative except for that were at the limit of their established used for production. CSLB routinely tests cell cultures used in the manufacturing process for adventitious viruses to ensure that viruses are below their detectable levels.

Additionally, the potential risk of viral contamination of IDELVION is further mitigated through two dedicated, orthogonal viral clearance steps: Solvent/Detergent (S/D) treatment step in the manufacturing process also contributes to virus removal. CSLB has evaluated these viral clearance steps in relevant down-scale studies using model viruses. The viruses selected for the studies include The wide range of physico-chemical properties of these model viruses demonstrates the ability of the manufacturing process to reduce potential viral contamination in IDELVION. Down-scale studies on relevant steps resulted in the following overall log reduction factors, in parenthesis, for these viruses: The results support the assertion that viral clearance is effective in the manufacture of IDELVION.

Process Validation and Qualification

CSLB applied multiple elements of a Quality by Design (QbD) approach to the development and validation of the BDI, BDS and FDP manufacturing processes. However, CSLB did not propose a design space. The release specifications and in-process controls are as extensive as those found in traditional BLAs.

Process Performance Qualification (PPQ) was accomplished in three separate parts, corresponding to the three major stages of production, BDI [redacted] PPQ batches), BDS [redacted] PPQ batches) and FDP [redacted] PPQ batches). PPQ for FDP consisted of the manufacture of [redacted] consecutive batches covering each of the filling sizes. The PPQ data demonstrated that the manufacturing processes for IDELVION BDI, BDS and FDP were successfully qualified.

In addition to the PPQ studies, several ancillary validation studies were performed to support the consistency of the manufacture of IDELVION BDI and BDS. The studies included *Impurity Clearance Validation, In-Process Hold Time Validation,* [redacted] *Validation, Mixing Validation,* [redacted] and *Shipping Qualification*.

CSLB developed Continued Process Verification (CPV) plans at both [redacted] and CSL Behring GmbH to ensure the validated state of the IDELVION manufacturing process throughout the product lifecycle. The CPV program is designed to collect process data and perform statistical evaluation of the dataset in order to routinely confirm the validated state and to identify and evaluate planned and unplanned changes in the manufacturing process.

In-Process Controls

The process control strategy was developed using a risk-based and science-based QbD approach that ensures the consistency of the manufacturing process and product quality.

Potency

The potency of IDELVION is expressed in international units of FIX activity and determined using an *in vitro* activated partial thromboplastin time (aPTT)-based one-stage clotting assay. A single primary product-specific potency standard calibrated against the WHO International Standard for Factor IX concentrate was used for the duration of clinical development of IDELVION. To ensure the consistency of the unitage, stability and integrity of this primary product-specific potency standard, it is monitored in ongoing stability studies utilizing the WHO International Standard as control. In addition, [redacted]

Elucidation of Structure and Other Characteristics

The structure and function of the FIX and albumin moieties in IDELVION were characterized in a series of studies, which also examined the comparability of IDELVION batches manufactured at different sites and scales of the manufacturing process during product development. [redacted], and are not expected to interfere with the hemostatic effect of IDELVION in hemophilia B patients.

Minimal API lot-to-lot variability was observed between IDELVION batches produced at different scales or process iterations. However, comparison of IDELVION batches manufactured at commercial scale with the lots produced at pilot scale (used in preclinical

studies and Phase 1/2 clinical trials) revealed differences in process-related impurities [redacted] Impurities in Polysorbate 80, a component in [redacted] were attributable to the difference in the [redacted]. The presence of [redacted] Polysorbate 80 impurities did not affect any other parameters tested regarding the structure and function of IDELVION. These impurities are now controlled to acceptable levels by dedicated assays at the release of the FDP.

Release specifications

The specifications of BDI, BDS and FDP are summarized in tables 2-4 below. The methods and established specifications are based on manufacturing experience and available safety and efficacy data.

Table 2: BDI Specifications

(b) (4)

1 Page determined to be not releasable: (b)(4)

Table 4: **FDP Specifications**

Test	**Parameter Monitored**	**Specification**
(b) (4)	Quantity	
FIX coagulation activity	Potency Identity	
Albumin by (b) (4)	Identity	
	Identity	
	Identity	
	Purity	
	Purity	
Factor IXa Assay	Purity	
	Purity	
Factor IX activity	Purity	
	Purity	
-visible particles by	Purity	

Test	Parameter Monitored	Specification
[redacted]		[redacted]
Endotoxin	Purity, Safety	
Sterility	Safety	Pass if no contamination detected
Appearance by visual inspection (Lyophilized cake)	Quality	Pass if pale yellow to white [redacted] cake
Residual water [redacted]	Quality	[redacted]
[redacted]	Quality	[redacted]
Appearance by visual inspection (Dissolution time)	Quality	[redacted]
Appearance by visual inspection (Appearance after reconstitution)	Quality	Pass if yellow to colorless clear liquid and free of visible particles
[redacted]	Quality	[redacted]
[redacted])	Quality	
Polysorbate 80 [redacted]	Quality	
Mannitol [redacted]	Quality	
Sucrose [redacted]	Quality	
Trisodium Citrate [g]	Quality	

[redacted]

Analytical Methods

The release methods were validated for their suitability for the intended use. The respective reference standards and their maintenance program were established. The results of in-support testing for potency and purity of the FDP were within the proposed specifications.

Facilities Review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Coagulation Factor IX (Recombinant), Albumin Fusion Protein are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 5: Manufacturing Facilities for Coagulation Factor IX (Recombinant), Albumin Fusion Protein

Name/Address	FEI number	DUNS number	Inspection/ waiver	Justification / Results
Drug Substance				Team Biologics NAI
Drug Substance Manufacturing and Testing *Drug Product* Formulation, Fill/Finish, Labeling & Packaging, Testing CSL Behring GmbH (CSLB) Emil-von-Behring-Strasse 76 D-35041 Marburg Germany	3003098680	326530474	Pre-License Inspection	CBER DMPQ May 28-June 5, 2015 VAI

Team Biologics performed a surveillance inspection of the drug substance and testing facility from . No Form FDA 483 was issued and the inspection was classified as no action indicated (NAI).

CBER conducted a pre-license inspection (PLI) of CSLB from May 28 - June 5, 2015 of the quality, facilities & equipment, materials, production, packaging & labeling, and laboratory systems. At the end of the inspection, a Form FDA 483 with 19 observations was issued. Deficiencies were related to the quality and manufacturing systems. The firm responded to the observations on July 1, 2015 and the corrective actions were reviewed and found to be adequate. All inspectional issues were considered to be satisfactorily resolved and the inspection was classified as voluntary action indicated (VAI).

Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment

Container/ Closure

The drug product is filled into 6 & 10 mL glass vials ( ) closed with bromobutyl rubber stoppers

(b) (4)). The stoppers are secured by combination caps consisting of an aluminum crimp cap with a concentric hole and an integrated polypropylene plastic disc. CSLB performed the container closure integrity testing at the Marburg, Germany facility, employing a test method; all acceptance criteria were met.

With the exception of the color of the overseal, the container closure system is identical for the presentations of 250, 500, and 1000 IU, which are all filled in 6-mL vials. The 2000 IU fill size uses a 10-mL vial to allow for reconstitution with 5 mL of sterile WFI, instead of 2.5 mL for the smaller fill sizes.

Stability

The stability data support that BDS can be stored at The FDP can be stored at +5°C to +25°C for 24 months for the 250 IU and 500 IU dosage strengths and for 36 months for the 1000 IU and 2000 IU dosage strengths.

Exemption from CBER Lot Release

Under the provision described in Federal Register (FR) 58:38771-38773 and the 60 FR 63048-63049 publication (December 8, 1995), routine lot-by-lot CBER release is not required for IDELVION because it is a well-characterized recombinant product. Thus, exemption of IDELVION from CBER Lot Release is justified. CBER has performed in-support testing of commercial scale IDELVION product lots of 250 IU and 2000 IU nominal potencies. Test results were deemed consistent with the proposed commercial release specifications.

SIGNIFICANT ISSUES RESOLVED DURING THE BLA REVIEW

The following substantive issues were resolved during the review of the IDELVION BLA:

a. Deficiencies in method validations

Review of method validation found multiple deficiencies, including incomplete validation of some parameters, validation of incorrect assay ranges, and acceptance criteria inappropriate for assessing method performance. Some of these deficiencies could be traced back to deficiencies in the standard operating procedures (SOPs) identified during the facility inspection. CSLB satisfactorily addressed these review concerns by conducting additional validation studies, and preparing new SOPs and test instructions. These newly developed validation data were used to confirm the validity of the data associated with process development, qualification and verification, and comparability studies.

b. Deficiencies in specifications

Multiple deficiencies were found in the specifications of the BDS and FDP. The acceptance criteria in the original application were established arbitrarily. The justifications of specifications were not supported by statistical analysis of manufacturing data, so the specifications did not allow for adequate control of the manufacturing process. Additionally, as verified during the pre-license inspection, CSLB did not have in place a procedure to establish BDS and FDP specifications. CSLB successfully addressed these concerns by re-assessing the manufacturing data, revising, and justifying the specifications. CSLB also committed to re-assess the acceptance criteria for some parameters when more data are

available from the commercial manufacturing process for statistical analysis. Procedures are now established to ensure that specifications will be set based on scientifically sound principles in the future.

c. Insufficient control of the albumin moiety

The proposed release assays and specifications were not sufficient to control the quality of the albumin moiety. CSLB conducted additional method qualification studies to demonstrate that the analysis of the albumin moiety by

d. Deficiencies in comparability studies

Results from the studies by indicated qualitative differences between product lots manufactured at the pilot vs. commercial scales. CSLB found the probable cause to be due to different impurities in the Polysorbate 80 used in the manufacture of the product batches. The Polysorbate 80 used for the pilot scale batches contained impurities which, Based on the results of *in vitro* characterization studies and nonclinical animal studies, the Polysorbate 80 impurities did not appear to affect the structural and functional properties of IDELVION. Furthermore, to ensure consistent quality of IDELVION, a method was added as a temporary release assay for the FDP. CSLB is in the process of

Chemistry, Manufacturing and Controls - Conclusion

The CMC data support the quality and safety of IDELVION to be used in the treatment of children and adults with hemophilia B.

4. Nonclinical Pharmacology/Toxicology

General Considerations

Single and repeat-dose toxicity, pharmacokinetic and pharmacodynamics studies were conducted in animals using the pilot scale IDELVION product. Manufacturing process changes during commercial development resulted in increased levels of in the final

commercial grade IDELVION product, compared to the pilot scale product. Additional nonclinical toxicity testing was completed to compare the safety of the pilot scale product to the proposed commercial scale IDELVION product. A risk assessment of product-derived impurities, [redacted] was also completed.

Nonclinical Findings

Pharmacology

Nonclinical pharmacology studies with IDELVION were conducted in a canine model of Hemophilia B (i.e. dogs with a naturally occurring mutation and/or deletion of FIX function) and in FIX knock-out (i.e. deletion of FIX function) mice. Hemophilic dogs were dosed intravenously with 2.5 to 4 times the recommended clinical dose of IDELVION or another, approved recombinant FIX product. At a dose that represents the upper end of the clinical dose range, the aPTT and *ex vivo* whole blood clotting time activity were restored to levels within the normal limits, and the results were comparable to those obtained following equivalent dosing (on an IU/kg basis) with the approved recombinant FIX product. There was no evidence of thrombogenicity and no serious adverse effects were reported.

Pharmacology studies with IDELVION in FIX knock-out mice showed a significant improvement in hemostatic parameters (i.e. blood loss and time to hemostasis) with increasing doses of IDELVION in the tail clip bleeding model. At doses 2 to 4-fold greater than the recommended clinical dose, the time to hemostasis and the amount of blood loss for IDEVLION-dosed FIX knock-out mice were slightly greater than those reported in mice dosed with the approved, comparator FIX product. However, at equal doses of 8-fold greater than the recommended clinical starting dose, the approved FIX product was slightly less effective in reducing the time to hemostasis and blood loss in hemophilic mice than IDELVION. The differences in the time to hemostasis and blood loss with IDELVION and the approved FIX product were neither statistically nor biologically meaningful, due to significant variability in the amount of blood loss with the tail clip model in FIX knock-out mice. Dosing of FIX knock-out mice with IDELVION or the approved FIX product showed significant decreases in aPTT at all dose levels compared to the control group, with similar magnitude of effect for both products at doses approximately 2 to 8-fold over the recommended clinical doses of 25 to 40 IU/kg of IDELVION.

In summary, animal studies with IDELVION showed the expected pharmacologic, i.e. pro-coagulant activity in both canine and mouse models of Hemophilia B, and the results were similar to those obtained with another, approved recombinant FIX product. There was no evidence of thrombogenesis or any other serious adverse effects. The data from these pharmacology studies were used as proof-of-concept to support the initiation of clinical trials, and are reflected in the pharmacology section of the IDELVION BLA package insert.

Pharmacokinetics

Pharmacokinetic studies with IDELVION were conducted in [redacted] monkeys, and the recombinant human FIX antigen levels were determined by [redacted]. The pharmacokinetic profile of IDELVION in [redacted] monkeys showed a dose-dependent increase in the parameters measured (i.e. C_{max}, AUC_{last} and V_{ss}). In the rats administered IDELVION, there

was a linear, dose-proportional increase in C_{max} and AUC with increasing doses of IDELVION.

Toxicology

Nonclinical toxicity studies conducted with IDELVION in rats and [redacted] monkeys did not identify any unexpected findings or significant safety concerns. FIX-replete [redacted] rats dosed with a single intravenous injection of up to 10-fold greater than the clinical starting dose of IDELVION demonstrated no systemic toxicities or tissue pathologies. A repeat-dose toxicity study was conducted in [redacted] rats; animals were injected with doses of IDELVION at up to 10-fold greater than the clinical starting dose daily for 14 days. Statistically significant differences in some hematological parameters (i.e. prothrombin time, serum chemistry) were reported; however, the findings were not consistent or dose-related between the IDELVION dose groups. A repeat-dose toxicity study with IDELVION was conducted in [redacted] monkeys with daily intravenous dosing of up to 10 times the clinical starting dose for 28 days. Based on the results of this study IDELVION was well tolerated, with no findings indicative of systemic toxicity, pro-thrombogenic properties or adverse local tolerance.

No animal studies evaluating the carcinogenicity, in vitro or in vivo mutagenicity, or effects on fertility, reproductive toxicity, or teratogenicity were conducted with IDELVION. IDELVION is a recombinant, human protein; animals receiving repeated doses of the product developed antibodies against FIX that both accelerated clearance of the protein and in some cases, neutralized its pro-coagulant activity. Therefore, long-term, repeat-dose toxicity studies as well as the standard carcinogenicity bioassay (i.e., 2 years of daily IDELVION dosing in both rats and mice) were not feasible to conduct.

The standard battery of genotoxicity testing as recommended in the International Conference on Harmonization (ICH) S2 guidance documents was not conducted for IDELVION, because it is a protein and as per the ICH S6 guidance on biotechnology-derived protein therapeutics these studies were not required. The lack of carcinogenicity, mutagenicity and chronic toxicity data are addressed in the appropriate section of the package insert.

Nonclinical reproductive or developmental toxicity studies were not conducted in support of this submission. The IDELVION label states that are no animal reproductive or developmental toxicity data available, and there are no data with IDELVION use in pregnant or lactating women to inform on drug-associated risk. The label is consistent with prescribing information for other approved recombinant human coagulation factors for the treatment of Hemophilia A or B.

A single dose toxicity study including toxicokinetic analysis was conducted in rats to compare the safety and exposures of the commercial grade IDELVION planned for marketing with the pilot grade material used in the nonclinical program. After dosing rats with approximately 10-fold the maximum recommended clinical dose of IDELVION produced by either the pilot or commercial process, there were no differences in the toxicokinetic parameters (i.e., half-life, volume of distribution or clearance). The in vivo exposures (i.e. AUC and C_{max}) for the commercial grade IDELVION and the pilot grade IDELVION were similar and without statistically meaningful differences. The commercial grade IDELVION dose group showed a

statistically significant increase in albumin concentration when compared to the group of rats dosed with the pilot grade IDELVION; however, this finding did not have any clinical significance. Despite the higher concentrations of [redacted] within the commercial grade IDELVION, there were no significant toxicities observed at 10-fold the maximum recommended clinical dose, and its safety is considered to be qualified. Based on the results of this study the commercial grade IDELVION was well tolerated and comparable to the pilot grade IDELVION, with no findings indicative of toxicity or adverse local tolerance.

The data from the nonclinical program suggest that the safety profile of IDELVION supports its use for the proposed indications of on-demand control and prevention of bleeding episodes, routine prophylaxis to prevent or reduce the frequency of bleeding episodes and perioperative management of bleeding, in adults and children with Hemophilia B.

5. Clinical Pharmacology

The clinical pharmacokinetics and efficacy of IDELVION have been assessed in four clinical studies described below.

Study #1: An open-label, multi-center, dose-escalation safety and pharmacokinetic study of a recombinant coagulation FIX albumin fusion protein in subjects with hemophilia B (CSL654-2001).

This study was a phase 1 prospective, multicenter, open-label, dose escalation (25, 50 and 75 international units (IU) per kilogram (kg) body weight) safety and PK study. For PK study, there were 6 subjects for 25 IU/kg dose, 13 subjects for 50 IU/kg dose, and 8 subjects for 75 IU/kg dose. The PK study of 50 IU/kg IDELVION was performed in 13 previously treated patients (>150 exposures days (EDs)), diagnosed with severe hemophilia B (FIX activity ≤ 2%). Males aged 12 to 65 years with a body weight ≥ 30 kg and ≤ 120 kg were included in the study.

Blood samples for PK study were taken at time 0, 5 and 30 minutes, 3, 6, 9, 24, 48, 72 hours and 5, 7, 10, and 14 days. PK parameters were estimated individually for baseline-corrected and uncorrected FIX activity in plasma by non-compartmental analysis. The half-life and clearance (baseline corrected) of IDELVION ranged from 99 to 105 hours and 0.73 to 0.87 mL/hr per kg, respectively. The incremental recovery (at 30 min) ranged from 1.08 to 1.65 IU/dL/IU/kg. Based on C_{max}, AUC, and clearance the PK of IDELVION was not linear over the dose range of 25 to 75 IU/kg.

Study #2: A phase 1/2 open-label, multi-center, safety and efficacy study of a recombinant coagulation FIX albumin fusion protein in subjects with hemophilia B (CSL654-2004).

This phase 1/2 study evaluated the safety, PK and efficacy of IDELVION for both weekly prophylaxis (15 to 35 IU/kg, adjusted up to a maximum of 75 IU/kg) and on-demand treatment of bleeding episodes (≥25 IU/kg) in subjects with hemophilia B (FIX activity ≤2%) aged 13 to 46 years.

For the PK assessment, subjects received 25 IU/kg IDELVION as a single IV injection. Plasma FIX activity was measured before dosing and then at 30 minutes, and at 3, 24, 48, 72, 120, 168, 240 and 336 hours after injection of IDELVION. There were 13 subjects (10 for prophylaxis and 3 on demand treatment) who received at least 1 dose of IDELVION and had a sufficient number of blood samples for evaluation of IDELVION PK. The plasma concentrations of IDELVION were measured as FIX activity using a validated one-stage assay in a central laboratory. PK parameters were estimated individually for baseline-corrected and uncorrected FIX activity in plasma by non-compartmental analysis.

Following 25 IU/kg IDELVION administration to patients with hemophilia B (prophylaxis treatment group, n = 10), the clearance and half-life of IDELVION (baseline corrected) were 1.04 mL/hr per kg and 48 hours, respectively. In patients with hemophilia B (on-demand treatment group, n = 3), the clearance and half-life of IDELVION were 0.73 mL/hr per kg and 139 hours, respectively. The clearance and half-life of IDELVION of 25 IU/kg dose observed in this study (on-demand treatment group) were comparable with the previous study at the same dose (study #1; CSL654-2001) in patients with hemophilia B. The clearance and half-life of IDELVION were faster (1.4-fold) and shorter (2.9-fold) in prophylaxis treatment group than on-demand treatment group. This difference in PK parameters in this study may be due to unbalanced sample size between the two patient groups (in study #3, a balanced sample size between the two groups indicated no difference in the PK of IDELVION between these two groups).

Study #3: A phase 2/3 open-label, multi-center, safety and efficacy study of a recombinant coagulation FIX albumin fusion protein in subjects with hemophilia B (CSL654-3001).

This prospective, open-label, phase 2/3 study evaluated the efficacy, pharmacokinetics (PK), and safety profile of IDELVION for routine prophylaxis and for the treatment of bleeding episodes in subjects with severe hemophilia B (FIX activity of $\leq$2%). For the PK study, there were 6 subjects for 25 IU/kg dose, 46 subjects for 50 IU/kg dose, and 5 subjects for 75 IU/kg dose (12 to 65 years of age). Blood samples were collected for PK analysis prior to injection, and at 30 minutes, 3, 24, 48, 72, 120, 168, 240 hours after injection for both 25 and 50 IU/kg IDELVION. For the 50 IU/kg IDELVION dose, blood samples were also collected at 336 hours. For repeat PK study with 50 IU/kg IDELVION at week 26, blood samples were collected at the same time points as described previously for the first dose. PK parameters were estimated by non-compartmental analysis using FIX activity levels. The limited number of blood samples for 75 IU/kg dose did not allow the characterization of the full PK of IDELVION.

The half-lives of IDELVION at 25 and 50 IU/kg were 60 and 86 hours, respectively, and clearances were 0.99 and 0.88 mL/hr per kg, respectively. Following 50 IU/kg repeat dose at week 26, AUC was 18% higher than single dose, whereas C_{max} was comparable between single and repeat dosing. There were 28 and 18 subjects in the prophylaxis group and in the on-demand group (50 IU/kg dose), respectively. No difference in PK was observed between these two groups.

Study #4: A phase 3 open-label, multi-center, pharmacokinetics, safety, and efficacy study of a recombinant fusion protein linking coagulation FIX with albumin in previously treated children with hemophilia B (CSL654-3002).

This was a prospective, open-label study of IDELVION in subjects <12 years of age. Male subjects, younger than 12 years of age (prior to their 12th birthday at day 1), and body weight ≥10 kg at the time of the screening, were included in the study. Twelve subjects were <6 years (1-5 years) of age and 15 subjects were 6 to <12 years (6-10 years) of age.

A single dose of 50 IU/kg IDELVION was administered by IV infusion (in approximately 5 to 15 minutes). Blood samples for the PK assessment were collected at time 0, 30 minutes, 48 hours, 168 hours, 240 hours, and 336 hours following 50 IU/kg of IDELVION dose. The PK parameters were calculated with and without correction for baseline (pre-dose) FIX levels. A non-compartmental analysis was used for the estimation of PK parameters.

The results (baseline corrected) of this study indicated that the clearance of IDELVION in children <6 years (1.59 mL/hr per kg) and 6 to <12 years (1.37 mL/hr per kg) of age is higher by 2.2-fold and 1.9-fold, respectively, as compared to adults (0.73 mL/hr per kg). The half-life of IDELVION is shorter by 47 hours in children <6 years of age (half-life = 57 hours) and 35 hours in children 6 to <12 years of age (half-life = 69 hours) when compared to adults (half-life = 104 hours). In adolescents (>12 -<18 years), the clearance was 1.5-fold higher and half-life was 17 hours shorter than the adults.

Comments: Considering a substantial difference in clearance and half-life of IDELVION between children and adults, dose adjustment is required in the pediatric population.

Conclusions:

- The PK of IDELVION indicates a long half-life and slow clearance in adult subjects.
- There was no difference in the PK of IDELVION following single and repeat dosing in patients 12 years and older.
- No difference in the PK of IDELVION was observed between prophylaxis and on-demand groups.
- Children (0-12 years of age) have substantially higher clearance and shorter half-life of IDELVION than adults. As a result, dose adjustments are required in the pediatric population.

6. Clinical/ Statistical

a) Clinical Program

To support licensure of IDELVION, CSLB performed 5 prospective, open label clinical studies of 111 unique subjects with FIX deficiency/hemophilia B (FIX<2%) to evaluate PK, safety and efficacy of IDELVION. Although the number of subjects in the five studies sum totaled to 195, only 111 unique subjects were enrolled into five studies as some of these unique subjects were enrolled in more than one study. The clinical development program is

summarized in the table below. Studies 3001 and 3003 were performed under IND 14978. Studies 2001, 2004, and 3002 were not conducted under IND.

Table 6: Summary of Clinical Studies

Trial ID (Type of Study)	Objectives	Dosage Regimen	Subjects (n);Age	Treatment Regimen/ Duration	Study status
2001 (Phase 1, single ascending dose study)	PK, safety, inhibitor development	PK: 25, 50, or 75 IU/kg	25 PTPs; 15-58 years of age	14 days	Completed
2004 (Phase 1 /2, safety, PK and efficacy study)	PK, safety and efficacy, inhibitor development	PK: 25 or 50 IU/kg Prophylaxis: 15-35 IU/kg weekly max 75 IU/kg On-demand: 25 IU/kg max 75 IU/kg	17 PTPs; 13-46 years of age	20 weeks	Completed
3001 (Phase 2/3, open label safety and efficacy study)	PK, safety and efficacy, inhibitor development; surgery sub-study	PK: 50 IU/kg Arm 1: Routine prophylaxis, 15-35 IU/kg (subjects from study 2004) or 35-50 IU/kg; max 75 IU/kg Arm 2: On-demand up to 75 IU/kg Surgery: 50 to 75 IU/kg	63 PTPs; 12-61 years of age Arm 1 N=40 Arm 2 N=23 Surgery Substudy from Arms 1 and 2; N=4	Arm 1: 7, 10 or 14 day regimens, up to 30 weeks Arm 2: 26 weeks followed by 12-30 weeks of prophylaxis	Completed
3002 (Phase 3; pediatric)	PK, inhibitor development	PK: 50 IU/kg On demand or	27 PTPs; <12 years of age	Weekly (7-day) routine prophylaxis; 12 months	Completed

		Prophylaxis: 35-50 IU/kg, max 75 IU/kg			
3003 (Phase 3b) Extension of 3001 and 3002	Safety, inhibitor development		115 targeted including 20 PUPs Actual: 9 surgery	3 years	Ongoing

PTPs=previously treated patients, PUPs=previously untreated patients

Study 3001 was a non-randomized, prospective, open-label, phase 2/3 safety and efficacy study to assess the PK, clinical efficacy and safety of IDELVION when used for on-demand treatment, routine prophylaxis and perioperative management in 63 PTPs with severe hemophilia B (<2% FIX activity) aged 12 to 61 years of age. The study was designed to evaluate the safety of IDELVION with respect to the development of inhibitors to FIX and to compare on-demand treatment of IDELVION to weekly routine prophylaxis and every 10 to 14 day routine prophylaxis.

Forty subjects were enrolled in Arm 1 to receive 7-day prophylaxis treatment with IDELVION for 26-30 weeks; 23 subjects were enrolled in Arm 2 to receive 26 weeks of on-demand treatment, followed by 26 weeks (minimum of 12 weeks) of weekly prophylaxis therapy with IDELVION. Subjects treated on the 10 to 14 day regimen (n=26) were a selected subgroup from Arm 1 that met pre-specified switching criteria of: 1) no dose adjustment in the previous month on study, 2) no spontaneous bleeding events in the previous month, and 3) a weekly prophylaxis dose of ≤ 40 IU/kg of IDELVION. The primary objective of efficacy was evaluated on subjects in Arm 2 only. Secondary objectives included the evaluation of the clinical response to IDELVION for the treatment and prevention of bleeding episodes on subjects from both arms.

The overall clinical assessment of hemostatic efficacy for the treatment of minor to moderate bleeding episodes and major bleeding episodes was based on two different 4-point ordinal scales (refer to Appendix I). Success for each infusion was defined as a rating of “excellent” or “good.” The criteria for evaluation of the effectiveness were number of infusions required to treat a bleed (primary factor), relief of pain or other objective signs of bleeding. Hemostasis was assessed post-operatively using a four-point scale of excellent, good, moderate, and poor/no response (refer to Appendix II).

All subjects were males with severe hemophilia B (<2% FIX activity). The median age was 33 years (range 12 to 61 years). The majority of the subjects were White (83%); the second-largest group was Asian (16%).

Eight of 63 subjects discontinued the study. Three subjects were in arm 1 (prophylaxis; (3/40 = 7.5%), and five were in arm 2 (on-demand; 5/23 = 21.7%). Of the three subjects who discontinued from arm 1, one subject experienced an adverse event (AE) of infusion reaction; the other two subjects chose to withdraw from the study in the context of having experienced multiple AEs:

- Subject [redacted] was a 26 year old White male who experienced five occurrences of rash (reported term "exanthem") and subsequently withdrew from the study.
- Subject [redacted] was a 58 year old African-American male who reported continued hip pain after treatment of a spontaneous muscle bleed in his right thigh/groin area. Clinical evaluations, which included a CT scan of the hip, did not reveal any active bleeding or source for the hip pain.

Four of the five subjects in arm 2 discontinued before the start of the follow on prophylaxis regimen. Two of the four were lost to follow-up [redacted]), one had a protocol deviation (subject [redacted] failed to start prophylaxis, but continued on-demand), and one discontinued the study as a result of AEs of headache and eczena [redacted]).The other subject was lost to follow-up after only two prophylaxis doses.

Efficacy Analyses

Bioresearch Monitoring

CBER conducted Bioresearch Monitoring inspections at three clinical study sites that enrolled subjects in support of this BLA. The three clinical sites selected for inspection represented 30% of the total treated subjects (19 out of 63). The inspections of three clinical investigators did not reveal substantive problems that impact the data submitted in the application.

Efficacy Results

The efficacy results presented below summarize the analyses and conclusions of the clinical and statistical reviewers.

Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
The primary efficacy endpoint, annualized spontaneous bleeding rate (AsBR) during different treatment regimens, was compared on the 19 subjects in Arm 2 who switched from the on-demand treatment to weekly prophylaxis using the Wilcoxon signed-rank test. This study met the success criteria (> 50% reduction of AsBR after treatment switching): the median AsBR was 15.4 for on-demand treatment and 0.7 for the prophylaxis treatment. The result was robust to sensitivity analyses.

Of the 40 subjects in Arm 1 that were treated with a weekly routine prophylaxis regimen, 14 subjects remained on a 7-day regimen, 7 subjects switched to a 10-day regimen and 21 switched to a 14-day regimen. Two subjects were treated with both 10- and then 14-day regimens. Among the 14 subjects who did not switch to any extended prophylaxis treatment regimen, 2 of them had AsBR missing data. The median AsBRs for the remaining 12 subjects was 0.9 (range: 0 to 3.59). The AsBRs for the 7 subjects treated with weekly and then on a 10-day prophylaxis dosing regimen was zero (range: 0 to 0) and zero (range: 0 to 0.9), respectively. In addition, the median AsBRs for the 21 subjects that was treated with weekly and 14-day prophylaxis was zero (range: 0 to 4.5) and zero (range 0 to 7.3) respectively.

CSLB requested a labeling claim for both 7-day and 14-day dosing regimens; however, FDA concluded that the:

1. Population and observed pharmacokinetic (PK) data did not support a claim for a 14-day dosing regimen for the general hemophilia population because unselected patients would not be able to maintain FIX activity levels above 1%, which FDA considers a clinically relevant threshold.
2. Clinical trial data did not support a claim for a 14-day dosing regimen for the general population because the subjects treated with the extended (10 or 14-day) regimens were a select population who were maintained on a 7-day regimen and met pre-specified switching criteria. Because of this selection bias, any observed efficacy may not be generalizable to the hemophilia population at large.
3. Clinical trial and observed PK data supported a 14-day regimen for patients initially maintained on the 7-day regimen, who met the same switching criteria as was used in clinical trial 3001.

On-demand control and prevention of bleeding episodes

The indication, on demand control and prevention of bleeding episodes, had a pre-specified success criterion: > 80% of mild or moderate bleeding events will be treated with two or fewer infusions. A total of 358 bleeding episodes were treated with IDELVION, including 353 (98.6%) that required one (335; 94%) or two (18; 5%) infusions. The investigator's overall clinical assessment of hemostatic efficacy was excellent or good for 337 (94%) of bleeding episodes. One bleeding episode in the lower right leg of a 21 year old White was rated as poor/no response after a single infusion (no additional treatment was administered for the bleed) and eleven ratings were missing. Across all studies > 98% of bleeds were treated with 1 or 2 doses.

Perioperative management of bleeding

Data from 15 surgeries in 13 subjects (10 adults, 3 children < 12 years) were assessed from Studies 3001, 3002 and extension Study 3003, including nine that were considered major. The nine surgical procedures included a double mastectomy, two total knee replacements, a hemorrhoidectomy, a rhinoplasty, and three complicated and one uncomplicated dental surgeries. Two of the 4 four dental surgeries were performed in children <12 years of age. For all the 15 surgeries, hemostatic efficacy of IDELVION was rated either excellent or good by the investigators at all available time points (wound closure, 72 hours after surgery or at hospital discharge, and at the end of the surgical sub-study).

b) Pediatrics

This product received orphan designation for treatment of patients with congenital FIX deficiency (hemophilia B) on April 27, 2012; therefore pediatric studies were not required. However, the safety and efficacy of IDELVION in pediatric subjects was evaluated in Study 3002, a multicenter, prospective, open-label phase 3 trial of 27 male (26 White, 1 African American) pediatric subjects <12 years of age who received IDELVION for PK assessment, on-demand treatment or routine prophylaxis. Subjects received weekly routine prophylaxis with 35-50 IU/kg, and the same dose was used for treatment of bleeding episodes. PK assessments were performed using single doses of IDELVION of 50 IU/kg. The primary objective was the safety indicator of inhibitor development.

Results
There were no confirmed neutralizing antibodies to FIX. The median AsBR for the efficacy subpopulations was zero for those children <6 years and 0.78 for children 6 to<12 years of age during routine prophylaxis with weekly 35-50 IU/kg; and 52% (14/27) of subjects had no spontaneous bleeds during the study period. The mean (SD) AsBR for the 6 to < 12 year old subjects was 0.96 (1.1), and the AsBR for the <6 year was 0.08 (0.29).

One hundred and six total bleeding episodes (e.g., traumatic, spontaneous) were treated during the study. Most bleeding episodes (103/106, 97.2%) were successfully treated with either one or two injections of IDELVION. The investigator's assessment of hemostatic efficacy was excellent (78/104, 75.0%) or good (22/104; 21.2%) for 96% (100/104) of bleeding episodes.

c) Other Special Populations
There is no information regarding the presence of IDELVION in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IDELVION and any potential adverse effects on the breast-fed infant from IDELVION or from the underlying maternal condition. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when IDELVION is administered to a nursing woman. IDELVION was not assessed in women or in elderly subjects older than 65 years of age.

d) Overall Comparability Assessment

Not applicable to this BLA

7. Safety

The labeled safety concerns for IDELVION (based on previous experience with FIX products) are: hypersensitivity/anaphylactic reactions, thromboembolic events, development of FIX inhibitors and development of antibodies against CHO host cell proteins. All safety analyses were based on the safety population, which included all subjects who received at least one dose of IDELVION as part of either PK evaluation, on-demand treatment of bleeding episodes, routine prophylaxis, or perioperative management of bleeding episodes. FIX inhibitors and non-neutralizing antibodies to IDELVION were assessed in all studies, and antibodies to CHO host cell proteins were assessed in Trials 3001, 3002, and 3003.

Of the 111 subjects treated (January 9, 2015 cutoff date), two were reported to have experienced hypersensitivity reactions; however, the Independent Data Monitoring Committee assessed one of the two reported reactions to be more likely a reaction to the infusion and less likely a hypersensitivity reaction" as classic signs of hypersensitivity (e.g., urticaria, edema, chest tightness, shortness of breath, hypotension, etc.) were not evident during the event. The infusion related-reaction is detailed in the following narrative, reproduced from the clinical review.

Subject [redacted], a 22 year old male in the prophylaxis arm of Study 3001 developed a reaction that manifested during his 4th infusion (day 50) and it was interpreted as a hypersensitivity reaction. The subjective report was nausea, "sweet taste at the back of the throat and tachycardia". The objective report was heart rate increased from 51 to 60, and blood pressure change was 110/69 to 134/78 mmHg. The infusion was stopped after less than 1 ml had been delivered, and IV saline was infused. The event was declared moderate but resolved after 23 minutes with no intervention except for the IV fluid.

No thromboembolic events, FIX inhibitors or antibodies against either IDELVION or CHO host cell proteins were noted in any of the patients who received at least one dose of IDELVION. The most common adverse reaction (incidence ≥1%) reported in clinical trials was headache.

Four subjects (4/63; 6%) enrolled in Study 3001, who had negative urinalyses at baseline, developed proteinuria after treatment with IDELVION. These findings were reviewed by the study's IDMC and no action was taken by the Committee. None of the cases were reported as adverse events. Follow-up data from three of the four subjects enrolled in the extension study did not show persistent proteinuria and serum chemistry values for kidney function (albumin, blood urea nitrogen, creatinine, and serum protein) were within normal range. One subject was lost to follow-up.

8. Advisory Committee Meeting

The *Division of Hematology Research and Review* and the *Division of Hematology Clinical Review* in the *Office of Blood Research and Review* reviewed the information in this application and determined that referral to the *Blood Products Advisory Committee* prior to product approval was not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]):

- The FIX portion of IDELVION has a primary amino acid sequence that is comparable to the most prevalent Thr 148 allelic form of human plasma-derived FIX. IDELVION was generated by the genetic fusion of human albumin to human FIX by a FIX-derived cleavable linker sequence [redacted]. At this time, FDA has licensed one recombinant albumin fusion protein product, a glucagon-like peptide-1-albumin fusion protein (TANZEUM®, GlaxoSmithKline LLC). *In vitro* and *in vivo* biochemical and functional characterization of IDELVION has demonstrated that its hemostatic activities are comparable to those of licensed recombinant FIX products. Currently, three recombinant FIX, one recombinant FIX-Fc Fusion Protein, and several plasma-derived FIX-containing products are licensed in the U.S.

- Whereas the product is a new molecular entity (NME), there is precedent in the FDA for the approval of recombinant albumin fusion proteins. As such, OBRR does not need external scientific advice on safety issues that might be associated with an albumin fusion protein *per se*.

- The mechanism of action and function of FIX in the blood coagulation cascade are well studied and understood. When infused into a FIX-deficient patient, IDELVION temporarily replaces the missing endogenous FIX.

- The design of the pivotal clinical study to evaluate the safety and efficacy of IDELVION was adequate, was generally similar to those of licensed FIX products, and the results of the study did not raise any concerns related to its safety and efficacy. The size of the safety database for IDELVION was considered adequate. In the study, no FIX inhibitors were detected and no events of anaphylaxis were reported.

- Monitoring of potential immunogenic responses to IDELVION will continue after the approval of the BLA in PMC extension studies.

- The measures taken by CSLB to control adventitious agents in the manufacture of IDELVION are acceptable. The manufacturing process includes two steps specific for viral clearance: solvent/detergent treatment [redacted] filter.

- Review of information submitted in the BLA for IDELVION did not raise any controversial issues or pose unanswered scientific questions which would have benefited from Advisory Committee discussion and recommendations.

9. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of STN BLA 125582/0.

10. Labeling

a) Proprietary Name

The proposed proprietary name for the product, IDELVION, was reviewed by the Advertising and Promotional Labeling Branch (APLB), and found to be acceptable on February 10, 2015. The sponsor was notified that IDELVION was acceptable as the proprietary name for the product on March 3, 2015.

b) Conclusion of APLB and Committee Review of Draft Prescribing Information and Other Labeling

The product labeling (i.e., prescribing information, patient package insert, and instructions for use) and the product package and container labels were reviewed, commented, and/or revised by the appropriate discipline reviewers. APLB provided its review from a promotional and comprehension perspective on December 2, 2015. FDA comments and recommendations regarding the product labeling and carton/vial labels were initially conveyed to CSLB on July 16, 2015, and negotiated throughout the months of February and March of 2016.

Final versions of the product labeling (PI) and labels submitted to the BLA on March 4, 2016 were considered acceptable. A copy of the PI is attached.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The review committee recommends the approval of the BLA for Coagulation Factor IX (Recombinant), Albumin Fusion Protein, under the proprietary name of IDELVION, for the following indications to treat children and adults with hemophilia B (congenital FIX deficiency) for:

- On-demand control and prevention of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

b) Benefit/Risk Assessment

Hemophilia B is a potentially life threatening disorder that requires FIX replacement for survival, and for normal function. Patients with hemophilia B are at risk for acute bleeding episodes predominantly into joints, muscles, mucosa, and body cavities. Repeated bleeding into a joint can lead to disabling joint disease. Treatment regimens for hemophilia have shifted from on-demand treatment of bleeding episodes to routine prophylaxis because of observed improvement in long-term clinical outcomes, such as joint damage. However, compliance is a barrier in implementing prophylactic therapy because frequent infusions are required. IDELVION replaces the missing clotting FIX that is needed to achieve hemostasis in bleeding patients with hemophilia B. It is designed to enable less frequent dosing in routine prophylaxis regimens for hemophilia B patients.

Benefits

The efficacy of IDELVION has been established for on-demand treatment and control of bleeding episodes, perioperative management of bleeding and routine prophylaxis to prevent or reduce the frequency of bleeding episodes, in clinical studies that enrolled 111 subjects. The terminal half-life of IDELVION is longer and allows for dosing every 7 to 14 days to maintain a plasma level of FIX level above 1%, a level that has been shown to prevent or reduce the frequency of bleeding. A dosing schedule of every 7 days, or greater, is considered a major contribution to the improvement of patient care.

Risks

The principal identified risks of hemophilia replacement products are inhibitor development, hypersensitivity reactions, and thromboembolic events. No thromboembolic events, FIX inhibitors or antibodies against CHO host cell proteins were noted as of January 9, 2015. Hypersensitivity reactions were reported for two subjects; however, one subject experienced nausea, a sweet taste at the back of the throat and increased heart rate that was likely related to the infusion of the product, rather than a hypersensitivity reaction. An important limitation of the available data is that the group with the greatest risk for inhibitor development and hypersensitivity reactions, previously untreated patients, has yet to be fully evaluated. The potential for developing inhibitors is discussed in the Warnings and Precautions section of the Package Insert (PI).

Overall Benefit/Risk Profile

The benefit/risk profile of IDELVION is favorable. Clinical studies demonstrated the efficacy of the drug for its labeled indications. No serious adverse events were attributable to the drug. As of the data lock point, there were no reports of FIX inhibitor development, hypersensitivity reactions or reports of thrombosis.

c) Recommendation for Postmarketing Risk Management Activities

The safety evaluation did not substantiate a need for a post-marketing requirement or Risk Evaluation and Mitigation Strategy.

d) Recommendation for Postmarketing Activities

Based on the review of the pre-licensure safety data and CSLB's proposed pharmacovigilance plan, routine pharmacovigilance is recommended for post-licensure safety surveillance activities of IDELVION.

CSLB made post-marketing CMC commitments to i) develop a assay for .

Appendix I: Efficacy Evaluation of On-Demand Treatment by Investigator

Minor to Moderate Bleeding Episodes

Excellent	Pain relief and/or unequivocal improvement in objective signs of bleeding (i.e., swelling, tenderness, and/or decreased range of motion in the case of musculoskeletal hemorrhage) at approximately 24 hours after the first FIX infusion and no additional infusion required in order to achieve hemostasis.
Good	Definite pain relief and/or improvement in signs of bleeding at approximately 24 hours after the first infusion, but required a second infusion in order to achieve hemostasis.
Moderate	Probable or slight beneficial effect at approximately 24 hours after the first infusion, and required more than 2 infusions to achieve hemostasis.
Poor/No Response	No improvement at all or condition worsened (ie, signs of bleeding) at approximately 24 hours after the first infusion and additional hemostatic intervention was required with other FIX product or plasma to achieve hemostasis.

Major Trauma or Life-Threatening Bleeding Episodes

Excellent	Hemostasis clinically not significantly different from normal (e.g., achieved hemostasis comparable to that expected for a similar bleed in a nonfactor deficient patient) and actual blood loss was not more than 20% higher than the estimated predicted blood loss for the type of injury or problem.
Good	Normal or mildly abnormal hemostasis in terms of quantity and/or quality (e.g., slight oozing, prolonged time to hemostasis with somewhat increased bleeding compared to a nonfactor deficient patient) or estimated actual blood loss was >20% but less than or equal to 30% higher than the estimated predicted blood loss for this type of injury or problem.
Moderate	Moderately abnormal hemostasis in terms of quantity and/or quality (e.g., moderate hemorrhage that was difficult to control) with estimated blood loss greater than what is defined as Good.
Poor/No Response	Severely abnormal hemostasis in terms of quantity and/or quality (e.g., severe hemorrhage that was difficult to control) and/or additional hemostatic intervention required with other FIX product, cryoprecipitate, or plasma more than expected for the type of injury or problem.

Appendix II: Efficacy Evaluation of Surgical Treatment by Investigator

Excellent	Hemostasis clinically not significantly different from normal (e.g., achieved hemostasis comparable to that expected during similar surgery in a nonfactor deficient patient in the absence of other hemostasis intervention) or estimated actual blood loss was not more than 20% higher than the estimated predicted blood loss for the intended surgery.
Good	Normal or mildly abnormal hemostasis in terms of quantity and/or quality (e.g., slight oozing, prolonged time to hemostasis with somewhat increased bleeding compared to a nonfactor deficient patient in the absence of other hemostatic intervention) or estimated actual blood loss was >20% but less than or equal to 30% higher than the estimated predicted blood loss for the intended surgery.
Moderate	Moderately abnormal hemostasis in terms of quantity and/or quality (e.g., moderate hemorrhage that was difficult to control) with estimated blood loss greater than what is defined as Good.
Poor/No Response	Severely abnormal hemostasis in terms of quantity and/or quality (e.g., severe hemorrhage that was difficult to control) and/or additional hemostatic intervention required with other FIX product or plasma for complete resolution.