



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Pharmacology/Toxicology Primary Discipline Review
Division of Hematology Clinical Review
Office of Blood Research & Review

To: The file (Original BLA STN 125582/0)
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(DHCR)/Office of Blood Research and Review (OBRR)
Through : Anne M. Pilaro, PhD, Supervisory Toxicologist, DHCR/OBRR/CBER
BLA#: 125582/0
Applicant: CSL Behring
Product: IDELVION, Factor IX albumin fusion protein (rIX-FP) product
Subject: Final Review Memo for the Pharmacology/Toxicology Data in STN 125582/0

This memorandum is the final primary pharmacology/toxicology review of the nonclinical program for the biologics licensing application (BLA) for Idelvion[™].

Executive Summary

CSL Behring has submitted an original BLA for their recombinant fusion protein product Idelvion, a human recombinant Factor (F) IX albumin fusion protein (rIX-FP) product. The proposed indication for Idelvion is prophylaxis and treatment of bleeding in patients with FIX deficiency, including the control and prevention of bleeding in surgical settings. The completed nonclinical program for the characterization of the safety of IDELVION consisted of acute and repeat-dose toxicity studies in both monkeys and rats, and local tolerance and thrombogenicity studies in rabbits. Based on the nonclinical results, IDELVION appears to be well tolerated for the intended route of administration and effective for the proposed use of the product. From the pharmacology/toxicology standpoint, the nonclinical data submitted in the original BLA are acceptable to support licensure of IDELVION. There are no outstanding issues from the nonclinical discipline that would prevent the approval of this BLA.

Background

Hemophilia B, or Christmas disease, is a sex-linked (X chromosome) recessive genetic disease caused by deletion or mutation of the FIX gene, leading to deficiency in coagulation which results in spontaneous bleeding. Hemophilia B is the second most common form of hemophilia, and is usually treated with FIX replacement therapy. FIX is a serine protease that plays a central role in the clotting cascade. Factor IX is normally found circulating in the bloodstream as an inactive zymogen, which is converted to activated FIX (FIXa) in response to stimuli through the intrinsic or extrinsic pathways, by activated FXI (FXIa) or activated FVII complexed with lipidated tissue factor (FVIIa/TF), respectively. FIXa, in the presence of FVIIIa, calcium, and a phospholipid surface, catalyzes the conversion of FX to activated FXa, which ultimately leads to the generation of thrombin and the formation of the fibrin clot and cessation of bleeding events.

CSL Behring, Inc. has manufactured a novel product called recombinant FIX fusion protein or rIX-FP that was generated by fusion of the DNA sequence for albumin to that of human-derived coagulation FIX, and subsequent transfection and expression of the FIX-albumin fusion protein in Chinese Hamster Ovary (CHO) cells in (b) (4). The Applicant claims that rFIX-FP has a longer half-life (extended according to (b) (4) assay) compared to currently marketed products, and that the advantage of albumin fusion technology over other methods of extending protein half-life in vivo is that it allows a full length FIX protein to be expressed as a fusion to recombinant human albumin. This product is intended to improve the quality of life for Hemophilia B patients by reducing the frequency of treatments of FIX replacement therapy.

Proposed Use and Doses

The intended clinical doses are 25, 50, or 75 IU/kg by intravenous bolus administration. The proposed indication is “Prophylaxis and treatment of bleeding in patients with factor IX deficiency including control and prevention of bleeding in surgical settings”. Specifically, the proposed indications are:

1. Routine prophylaxis treatment in patients with congenital Factor IX deficiency
2. Control and prevention of bleeding episodes in patients with congenital Factor IX deficiency
3. Prevention and control of bleeding in perioperative (surgical) settings in patients with congenital Factor IX deficiency

Recommendation

There were no nonclinical deficiencies identified in this submission, based on review of the pharmacological and toxicological data presented in BLA 125582/0. There are no requests for any further nonclinical testing of IDELVION at this time. Based on the review of the submitted toxicology and pharmacology data, this original biological application BLA 125582/0 is recommended for approval.

Summary Basis for Regulatory Action for Nonclinical Idelvion™ Data**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 (b) (4) 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, (b) (4) 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 IDELVION-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 (b) (4) monkeys, and the recombinant human FIX antigen levels were determined by (b) (4). The pharmacokinetic profile of IDELVION in (b) (4) 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 (b) (4) monkeys did not identify any unexpected findings or significant safety concerns. FIX-replete (b) (4) 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 (b) (4) 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 (b) (4) 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 there 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 (b) (4) 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.

Nonclinical Label for Package Insert (PI) for BLA 125582/0

The label was revised to reflect current labeling guidelines and the relevant information for prescribing data based on nonclinical and clinical experience using Idelvion™.

Reviewer Comment: The language in the label is currently being negotiated with the Sponsor, therefore the language may be subject to further revisions.

Clean Revised Version of Label for Nonclinical**8.1 Pregnancy****Risk Summary**

There are no data with IDELVION use in pregnant women to inform on drug-associated risk. Animal reproduction studies have not been conducted using IDELVION. It is not known whether IDELVION can cause fetal harm or affect reproduction capacity when administered to a pregnant woman. IDELVION should be given to a pregnant woman only if clearly needed. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation**Risk Summary**

There is no information regarding the excretion of IDELVION in human milk, the effect 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 breastfed infant from IDELVION or from the underlying maternal condition.

13 Nonclinical Toxicology**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Nonclinical studies evaluating the carcinogenic potential of IDELVION have not been conducted. A bacterial reverse mutation test ((b) (4) test) and a chromosome aberration test in human lymphocytes demonstrated no evidence of mutagenic activity using IDELVION.

No macroscopic or microscopic pathologies in reproductive organs were observed in repeat dose toxicity studies of IDELVION in animals dosed every day with 6.6 times the maximum recommended clinical dose of 75 IU/kg IDEVLION for 28 days. No animal studies regarding impairment of fertility following IDELVION dosing were conducted.

Pharmacology and Toxicology Study Review**I. New Studies Included in the BLA Submission*****Study APQ0002: rIX-FP Single Dose PK Study in (b) (4) Monkeys***

Study Objective: to assess the pharmacokinetics of rIX-FP following intravenous administration.

Study Design: Single IV doses of rIX-FP and BeneFIX® were administered to (b) (4) monkeys as shown in the table below:

Phase	Treatment	Dose (IU/kg)	Number of animals		Animal numbers	
			Male	Female	Male	Female
A	rIX-FP	50	1	1	501	502
B	rIX-FP	100	1	1	503	504
C	BeneFIX®	50	1	1	505	506
D	BeneFIX®	100	1	1	507	508

Over a 19 day period, blood samples were taken from each monkey at the following time points: pre-dose and 5 minutes, 15 minutes, 1, 3, 8, 23, 47, 72, 96, 120, 216, 312 and 456 hours post-dose. In addition, blood samples were taken pre-dose, on Day 6 (i.e. 120 h post-dose), Day 14 (i.e. 312 h post-dose) and at Day 20 (i.e. 456 h post-dose) for immunogenicity analysis. Immunogenicity and human factor IX concentrations in monkey plasma were analyzed using a validated (b) (4) method.

Results:

Mean Pharmacokinetic parameters

Phase	Dose level (IU/kg)	C _{max} (mIU/mL)	AUC _t (mIU.h/mL)	AUC (mIU.h/mL)	t½ (h)
A	50	1030	35700	38200	41.9
B	100	1930	72100	73400	42.4

Phase	Dose level (IU/kg)	C _{max} (mIU/mL)	AUC _t (mIU.h/mL)
C	50	649	14400
D	100	1800	42200

The mean half-life for rIX-FP in the monkeys ranged from 39.8 to 44.4 hrs. The C_{max} and AUC values for rIX-FP increased dose-proportionally in the monkeys. The C_{max} and AUC values following rIX-FP dosing were markedly higher than the C_{max} and AUC values after administration of BeneFIX®. In addition, the half-life of rIX-FP was considerably longer than the half-life of BeneFIX®, or to published t_{1/2} data of another recombinant human factor IX product.

None of the samples tested positive for antibodies against human factor IX at pre-dose, and after treatment on days 6, 14 and 20 had antibody titers against human factor IX above the threshold for antibody confirmation.

II. Qualification of Safety of Process-Related Impurities

Based on the toxicologic risk assessment analysis provided in the BLA submission, there is no unreasonable risk of (b) (4) toxicity following treatment with Idelvion™. It was determined that at the maximum dose of 100 IU/kg Idelvion™, the levels of (b) (4) (b) (4) are an order of magnitude less than the permissible daily exposure (PDE). Furthermore, in genotoxicity testing (b) (4) was reported to be non-mutagenic, as there were no indications of chromosomal or genetic damage in the appropriate nonclinical assays.

During development, the Applicant made manufacturing changes which resulted in increased levels of (b) (4) in the final product, compared to the levels present in product from the pilot scale production. A compound known as (b) (4) was also identified, which is a (b) (4). A risk assessment of the specific exposure to these chemicals was conducted; the absence of specific toxicity testing data for (b) (4) resulted in the Applicant using an alternative approach to ascertain the potential toxic risk for the chemical. The chemical structure was compared to that of (b) (4), and

was also classified by the (b) (4) computational toxicology program for potential mutagenic or carcinogenic structures. (b) (4) analysis tool identified one structural alert for genotoxicity in the (b) (4) but this same structural alert was also present in the parent compound (b) (4). There were no novel alerts identified in the (b) (4). Therefore, (b) (4) can be considered non-mutagenic since the same alert is seen in the parent compound (b) (4) which is an endogenous substance and is not associated with mutagenicity concerns as per the ICH M7 guidance.

III. Nonclinical Studies Previously Reviewed under IND 14978

Reviewer comment: The following nonclinical studies were reviewed for the original IND 14978, and the reviewer's findings and conclusions are summarized in the IND memorandum. A synopsis of these data is provided in the Executive Summary, above and based on the nonclinical findings, rIX-FP does not pose an unreasonable safety risk for its intended use.

Study Report IVX 01/09 – Effects on Coagulation Parameter aPTT Following Spiking of rFIX-FP and (b) (4) into Plasma of Various Species

Study Report 040200011 - rFIX-FP: Single Dose Pharmacokinetic and Pharmacodynamic Study in Intravenous (Bolus) Administration to Hemophilia B Dogs

Study Report NBM04/09 (or Study 040200012) - Correction of Hemostasis in FIX Knock-out (KO) Mice Following Treatment with rFIX-FP

Study Report NBM 05/09 (or Study 040200013) - Correction of Coagulation (aPTT) in FIX Knock-Out (KO) Mice Following Treatment with rFIX-FP

Study Report APQ0003 - rIX-FP: Evaluation of Respiratory Parameters in the Conscious Rat Using Whole Body Bias Flow Plethysmography (Intravenous Bolus Administration)

Study Report APQ0003 - rIX-FP: Single Dose Pharmacokinetic Study by Intravenous (Bolus) Administration to (b) (4) Monkeys

Study Report APQ0005 – rIX-FP: Single Dose Toxicity Study by Intravenous (bolus Administration to (b) (4) Rats

Study Report 8244656 - rIX-FP and rIX-FP-B: Single Dose Intravenous (Bolus) Administration Toxicity Study in the Rat Followed by a 5 Day Treatment-free Period

Study Report APQ0007 - rIX-FP: Single Dose toxicity Study by Intravenous (Bolus) Administration to (b) (4) Monkeys

Study Report APQ0009 – rIX-FP: Toxicity Study by Intravenous (Bolus) Administration to (b) (4) Rats for 4 Weeks Followed by a 2 Weeks Recovery Period

Study Report APQ0001 - rIX-FP: Single Dose Intravenous (Bolus) Administration to (b) (4) Monkeys for 4 weeks

Study Report APQ0004 - rIX-FP Bacterial Reverse Mutation Test

Study Report APQ0006 - rIX-FP *In Vitro* Mammalian Chromosome Aberration Test in Human Lymphocytes

Study Report APQ0008 - rIX-FP: Local Tolerance Study in Rabbits Following Intravenous, Intra-arterial or Perivenous Injection

Study Report S22456 - *In Vivo* Thrombogenicity Test in the Rabbit