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Division / Office	DHRR /OBRR
Priority Review	No
Reviewers Name(s)	Peter E. Waldron, MD; Lisa Faulcon, MD; Howard Chazin, MD CDER CardioRenal Consultant - Aliza Thompson, MD
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	CSL Behring Recombinant Facility AG
Established Name	Coagulation Factor IX (Recombinant), Albumin Fusion Protein
(Proposed) Trade Name	IDELVION
Pharmacologic Class	Coagulation Factor IX recombinant, human
Formulation(s), including Adjuvants, etc.	<No Formulations>
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder for Injectable Solution, Intravenous
Dosing Regimen	25-40 IU/kg
Indication(s) and Intended Population(s)	On demand treatment and control of bleeding episodes Routine prophylaxis to reduce the frequency of bleeding episodes Perioperative management of bleeding
Orphan Designated (Yes/No)	Yes

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GLOSSARY

ABR	annualized bleeding rate
AE	adverse event
AsBR	annualized spontaneous bleeding rating
AUC	area under the curve
BLA	Biologics License Application
BU	Bethesda units
CHO	Chinese Hamster Ovary
CI	confidence interval
Cl	clearance
CJD	Creutzfeldt-Jakob disease
CSLB	CSL Behring
CSP	complete study protocol
CSR	complete study report
DIC	disseminated intravascular coagulation
EBL	estimated blood loss
ED	exposure days
EMA	European Medicines Agency
FIX	coagulation factor IX
IR	incremental recovery (in PK context), also information request
IU	international units
MRT	mean residual time
NS	nephrotic syndrome
PT	preferred term
PTPs	Previously treated patients
PUPs	Previously untreated patients
rFIX	recombinant coagulation factor IX
rIX-FP	coagulation Factor IX (Recombinant), albumin fusion protein; IDELVION
SAE	serious adverse events
SOC	system organ class
$t_{1/2}$	half-life
TEAE	treatment emergent adverse event
V _z	volume of distribution
WFH	World Federation of Hemophilia

1. EXECUTIVE SUMMARY

Note to the reader: During the IDELVION BLA review cycle, the clinical review was initially assigned to and worked on by Peter Waldron, MD, CDER medical officer on detail to OBRR/Division of Hematology Clinical Review (DHCR) and continued by Lisa Faulcon, MD, CBER medical officer/Acting Team Leader in DHCR. Integration of both reviews including reviewer comments, further clarifications, Risk Benefit considerations and final recommendations were added by Howard Chazin, MD, Deputy Director, DHCR. Dr. Faulcon will provide her own addendum to this review for the file.

CSL Behring (CSLB) submitted a Biologics License Application (BLA) for recombinant Coagulation Factor IX (FIX), albumin fusion protein (rIX-FP) for the indications of routine prophylaxis to reduce the frequency of bleeding episodes, on-demand treatment and control of bleeding episodes and perioperative management of bleeding in adults and children with congenital FIX deficiency. The proprietary name is IDELVION. The product is a purified protein derived from a Chinese Hamster Ovary (CHO) cell line and produced by recombinant DNA technology. It is produced by the genetic fusion of recombinant albumin to recombinant coagulation FIX.

The recombinant FIX portion is identical to the Thr148 allelic form of human plasma-derived FIX. The cleavable linker between the recombinant FIX and albumin molecules is derived from the endogenous “activation peptide” in native FIX. IDELVION remains intact in the circulation until FIX is activated and upon activation of FIX, albumin is cleaved off and activated FIX (FIXa) is released.

The final drug product is provided as a lyophilized powder in single-use glass vials containing 250, 500, 1000 or 2000 international units (IU) of the active ingredient. The potency in IU is determined using an in vitro thromboplastin time (aPTT)-based one-stage clotting assay calibrated against the World Health Organization International Standard for FIX concentrate. For intravenous injection, the lyophilized drug product is reconstituted using 2.5 mL or 5 mL (for 2000 IU) of sterile water for injection, using a needleless Mix2vial device.

Efficacy

To support licensure of IDELVION, CSLB performed five prospective, open label clinical studies of 111 unique subjects with FIX deficiency/hemophilia B (FIX<2%) to evaluate safety and efficacy of IDELVION. Studies 3001 and 3003 were studies under IND 14978. Studies 2001, 2004, and 3002 were not conducted under IND.

Study 2001 was a phase 1, single ascending dose study of IDELVION in 25 previously treated patients (PTPs); 15-58 years of age. This was the first use of IDELVION in humans with the main objectives to study safety by evaluating adverse events (AEs) and laboratory changes over time. In addition, pharmacokinetic testing was performed using a single infusion dose of 50 IU/kg. The mean half-life was 92 hours suggesting the potential for less frequent dosing compared to plasma derived and recombinant FIX. The

safety profile demonstrated AEs similar to those expected for approved FIX replacement products.

Study 2004 was a phase 1 / 2 safety, pharmacokinetic, and efficacy study in 17 PTPs; 13-46 years of age who received IDELVION for on-demand and/or routine prophylaxis treatment. This study was used as a pilot study for the phase 3 Study 3001. The IDELVION dose used for PK was either 25 or 50 IU/kg. For routine prophylaxis subjects, treatment was initiated at a starting dose of IDELVION between 15 to 35 IU/kg. For subjects on the on-demand regimen, the dose was determined by the subjects PK data, but was at least 25 IU/kg. Both groups could have doses adjusted to a maximum dose of 75 IU/kg.

In addition, PK analysis was performed on 15 subjects following a single infusion of 25 IU/kg. Results noted that the mean half-life was slightly shorter at 69 hours. The 7-day interval of prophylactic administration yielded an Annualized Bleeding Rate (ABR) and an Annualized Spontaneous Bleeding Rate (AsBR) similar to findings in other studies of prophylaxis with similar or more frequent administration. All treated bleeds (N=85) were managed with 1 or 2 infusions, consistent with effective treatment of the bleeds. No SAE and no AEs of interest occurred. There was no inhibitor or antibody development against IDELVION during the study.

Study 3001 was an open label, phase 2/3 safety and efficacy study comparing on-demand treatment of IDELVION to weekly routine prophylaxis and every 10 to 14 day routine prophylaxis and/or perioperative management (surgery substudy) in 63 PTPs; 12 to 61 years of age.

Subjects (N=40) in Arm 1 were treated with **routine weekly (7-day) prophylaxis** during the duration of the study.

- Subjects in Block A continued on the same weekly study dose as that used in Study 2004. After completion of once weekly dosing for 26 weeks, subjects could switch to another dosing regimen (either a 10-day or 14-day interval) at a dose of 75 IU/kg.
- Subjects in Block B, all of whom had not received IDELVION previously underwent a two week PK evaluation of their previous FIX product and began a two week PK assessment of 60 IU/kg IDELVION as the initial dose. Following that, subjects remained on routine weekly prophylaxis at a dose of 35-50 IU/kg. After completion of once weekly treatment for 30 weeks, subjects could switch to a 10-day or 14 day regimen at a dose of 75 IU/kg.
- Subjects in Block C completed a PK assessment of 50 IU/kg as the first IDELVION dose; subjects were then treated with routine prophylaxis at a dose of 35-50 IU/kg. After completion of once weekly treatment for 30 weeks, subjects could switch to a 10-day or 14 day regimen at a dose of 75 IU/kg.

Subjects (N=23) in Arm 2 were treated with an **on-demand** regimen for approximately 26 weeks, using a treatment dose calculated from the subject's own PK data from Arm 2 followed by approximately 26 weeks of prophylactic weekly therapy.

Subjects in the surgery substudy (N=4) were enrolled from the two arms above, three from the prophylaxis arm and one from the on demand arm.

The primary efficacy endpoint analysis was based on the AsBR for the 7-day prophylaxis regimen compared with the on demand regimen. The primary efficacy analysis set was defined as all subjects assigned to the on demand treatment (Arm 2) who received at least one dose of on-demand treatment, crossed over, and received at least one dose of routine prophylaxis treatment. The primary efficacy analysis resulted in a mean reduction in AsBR of 93.5%; SD 8.0; $p < 0.0001$.

Study 3002 was a phase 3 pediatric study in 27 children; <12 years of age who received IDELVION for on-demand treatment or routine prophylaxis. Participants received weekly routine prophylaxis with 35-50 IU/kg, and the same dose was used for treatment of bleeding episodes. The protocol permitted a dose modification of 5-15 IU/kg to a maximum dose of 75 IU/kg, for subjects who developed a spontaneous bleeding episode. Descriptive statistics were performed for bleeding rates as an indicator of efficacy. The primary objective was the safety indicator of inhibitor development and no subject developed an inhibitor during the study. PK assessments were performed using single doses of IDELVION of 50 IU/kg and PK results were similar to those in Study 2001, with a mean half-life 91.4 hours.

Study 3003 is an ongoing extension study for Studies 3001 and 3002 and consisted of approximately 80 subjects (target=115) who were either previously enrolled or were previously untreated but undergoing major, nonemergency surgery. Additional surgery subjects were enrolled increasing the evaluable surgeries to 15 surgeries in 13 subjects with 9 major surgeries including 4 total knee replacements. Hemostasis was assessed as good to excellent and therefore effective in all surgeries performed.

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 Studies 3001, 3002, and 3003.

Of the 111 subjects treated (09 January 2015 cutoff date), two experienced hypersensitivity reactions, with one likely to be an infusion-related reaction, rather than a

hypersensitivity reaction. No thromboembolic events, FIX inhibitors or antibodies against CHO host cell proteins were noted.

An identified potential safety concern of proteinuria in four subjects (4/63; 6%) enrolled in the Study 3001 who had negative urinalyses at baseline and positive urinalyses during the study were explored to further address this concern. A consult from the Center for Drug Evaluation and Research, Division of Cardiovascular and Renal Products, Aliza Thompson, MD was obtained (hereafter CDER CardioRenal Consult).

Per the CDER CardioRenal consultant, “In each of the four cases a causal relationship between the use of IDELVION and abnormal proteinuria by urinalysis could be established. The first three cases would be considered at least possibly related (event or laboratory test abnormality with reasonable time relationship to intake of the investigational product but could also be explained by disease or other drugs). However, the fourth case (subject (b) (6)) had unexplained observations and could be considered probably related.”

However, Dr. Lisa Faulcon, who further details this issue in her separate review memo, noted that, “ In terms of ascertaining a safety signal or considerations of pharmacovigilance, these findings alone are not sufficient to support a request for a PMR study, and would not support a REMS as there was no clear biologically plausible reason why this product should cause proteinuria (the albumin load and clearance should not result in proteinuria), none of the cases were reported as adverse events and no associated clinical sequelae have been documented. Based on expert opinion and consultation with the Office of Biostatistics and Epidemiology, there is insufficient evidence to suggest that this is a safety signal. There are limitations to the safety database, namely it was derived from observational studies of patients with confounding comorbidities that could make interpretation of a possible clinically significant signal difficult.”

The review team recommended that these findings should be included in the label and additional data should be collected to assess the risk and to further inform the label. FDA advised CSLB to revise the protocol for the ongoing extension Study 3003 to include urinalysis and spot urine protein/creatinine ratio testing in a pre-specified number of naively treated subjects. CSLB was also advised that testing should be done every 6 months, and at the end of the study. The protocol should also be revised to specify a clinical workup for subjects with increased protein creatinine ratios including a threshold of >0.2 mg protein/mg creatinine in children greater than two years of age and ≥ 500 mg/g in adults should trigger further evaluation. The revised extension study would then be considered a PMC study.

Benefit-Risk

The overall risk benefit was perceived as favorable and the clinical reviewer recommended approval for this application for the on demand and routine prophylaxis indications. However, at the time of his review, Dr. Waldron did not feel that there had been enough subjects enrolled to assess efficacy of perioperative bleeding in major

surgeries and therefore did not recommend approval for the indication of control of perioperative bleeding. This reviewer (Chazin) disagreed and noted that as of the January 9, 2015 data lock, there was efficacy evidence in a wide variety of surgeries in enough subjects to proceed with recommending approval for the perioperative indication.

No other post marketing recommendations other than routine pharmacovigilance were suggested. IDELVION is an orphan designated product and therefore further pediatric studies are not required.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Enrollment of subjects in the phase 3 Study 3001 was unique in that the underlying disease, severe factor IX deficiency ($\leq 2\%$ FIX activity), is an x-linked disorder that is almost exclusively seen in males. Most of the 63 subjects in Study 3001 were young, white males with a small cohort of Asians and only a single African-American subject. Almost all of the white patients identified themselves as non-Hispanics. The numbers of patients and racial breakdown are too small to make any meaningful conclusions as to the role of age or race in the treatment of FIX deficiency with IDELVION. Since this disease is very rare, difficulty recruiting patients may be the reason for a lack of racial diversity.

Demographics for Study 3001 are summarized in the table below.

Demographics of Phase 3 Study 3001	
N	63
Age (yr.)	
Mean	33(14)
Sex	
Males	63
Females	0
Race	
White	52
Asian	10
African-American	1
Ethnicity	
Not Hispanic/Latino	62
Hispanic/Latino	1

Pediatric Study 3002 enrolled 26 white and 1 African American male subjects 1-10 years of age. Consistent with the adults above, the numbers of subjects are too small to make any meaningful conclusions about the effect of sex, age, or race on treatment of FIX

deficiency with IDELVION. Demographics of the pediatric population are summarized in the table below.

Demographics of Phase 3 Pediatric Study 3002		
	< 6 yo N=12	6- < 12 yo N=15
Age (yr.)		
Median	3.5	8.0
Range	1, 5	6, 10
Race		
White	11	15
African American	1	0

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Factor IX deficiency/Hemophilia B/Christmas Disease

Factor IX (FIX) deficiency (hemophilia B, Christmas disease) is the second most common coagulation factor deficiency. Most FIX deficiency occurs in males (86%) as expected for an X-linked disease, but females comprise 3% of affected persons and 11% of FIX deficient persons were of unknown gender in the World Federation of Hemophilia (WFH) Annual Global Survey, 2013¹. The U.S. incidence is 1.3 per 100,000 individuals and the WFH Global Survey, 2013 identified 28,430 worldwide including 4,022 U.S. subjects with a diagnosis of FIX deficiency, consistent with a rare disease.

Hemophilia B is often divided into groups by factor level correlating with the disease pattern. Patients with FIX activity level <1% of normal are called **severe**, and have bleeds with no identified trauma, at least monthly, most frequently in joints. A FIX activity level of 1-5% is designated as **moderate**. These patients have bleeds associated with mild trauma, and their bleeding frequency is less often than severe patients. Patients with **mild** deficiency FIX activity levels of ≥5-40% will have prolonged bleeding with worse than mild trauma as well as with surgery and since females are almost exclusively in this group, with menstruation. Results of a North American survey showed that approximately 37% of hemophilia B patients have severe hemophilia; 33% have moderate disease and 30% have mild disease. Of these only 1.5% had FIX inhibitors. (Katz, 1996²).

A goal of modern hemophilia management is to prevent spontaneous (no identified trauma) bleeds, by supplying replacement factor that will maintain FIX (or FVIII)

1 Report on the Annual Global Survey, 2013, retrieved from: www1.wfh.org/publications/files/pdf-1591.pdf

2 Katz, J. Prevalence of Factor IX inhibitors among patients with hemophilia B: results of a large-scale North American survey. *Haemophilia* 2 (1) 28-31 January 1996.

activity levels to a value of ≥ 1 -5%, i.e., in the range of patients with the moderate form of the disease. This approach is known as routine prophylaxis.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

The currently approved products for FIX replacement are shown in the table below.

Product	Category	IR	Half-life (hr)	Year approved
Alphanine SD	Plasma derived	0.48	21	1990
Mononine	Plasma derived	0.57-1.11	23-31	1992
BENEFIX	Recombinant	0.96	18	1997
Rixubis	Recombinant	0.87	26.7	2013
Alprolix	Recombinant fusion protein	1.02	86.5	2014

All approved products are approved for the indications, control and prevention of bleeding episodes, and perioperative management. Only Rixubis and Alprolix are approved with the additional indication of routine prophylaxis. The goal of maintaining FIX activity levels of at least 1% (routine prophylaxis) requires regularly scheduled FIX infusions. For routine prophylaxis, the labeled dosing frequency is twice a week for Rixubis, and once every 7 to 10 days for Alprolix.

2.3 Safety and Efficacy of Pharmacologically Related Products

The safety issues that are identified in all the Warnings Sections of the FIX replacement products include: inhibitor formation, anaphylaxis, thrombosis and nephrotic syndrome. For the plasma derived products (Alphanine SD and Mononine) there are additional Warnings of infection from viruses, Creutzfeldt-Jakob Syndrome, and disseminated intravascular coagulation. There is no apparent difference in efficacy among the available products in terms of stopping or preventing bleeding, or for management of hemostasis in a perioperative context, when FIX products are given at doses and schedules that provide equal plasma FIX activities.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

There is no previous human experience with IDELVION. The application for marketing was submitted to the European Medicines Authority at the same time as it was submitted to the FDA. The Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP) molecule is produced in a Chinese Hamster Ovary (CHO) cell line, which is well characterized. The excipients are Tri-sodium citrate, polysorbate 80, mannitol (b) (4) in 250

IU vial and (b) (4) in the 500 IU to 2000 IU vials) and sucrose (b) (4) in the 250 IU vial and (b) (4) in the 500 IU to 2000 IU vials). Sucrose has been associated with acute kidney injury in intravenous immune globulin products, necessitating a boxed warning however, the sucrose dose in those implicated products was more than 100 fold greater than the concentration in IDELVION.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Primary Efficacy Analysis

In written responses on June 3, 2013 the Statistician reviewer, C. Cheng, agreed to the proposals for the primary efficacy analysis made in the meeting request dated May 7, 2013. “The primary efficacy endpoint analysis for CSL654_3001 will be based on the annualized spontaneous bleeding rate (AsBR) for 7-day prophylaxis treatment compared with on demand treatment. This is a within-subject, matched-pairs comparison.” In addition, the primary analysis set was defined: “all subjects assigned to the on demand treatment (Arm 2) who receive at least one dose of on-demand treatment, crossover and receive at least one dose of routine prophylaxis treatment.”

Primary Safety Analysis

An agreement was reached on Dec 6, 2011 that the incidence of inhibitory antibodies against FIX, defined as any level > 0.6 BU by (b) (4) assay, would be the primary safety endpoint.

WALDRON comment: It seems that ED for PTPs and PUPs should have been included as part of this agreement, but I did not see it in the file.

Surgical Sub-study of Protocol 3001

Sep 27, 2010

An agreement was reached that favorable safety and efficacy data from at least 5 subjects in 10 elective major surgical procedures would be sufficient to support the proposed surgical indication.

Nov 10, 2011

FDA sent the following to the applicant, “If the prophylaxis (Arm 1) and on-demand treatment (Arm 2) arms in Study CSL654_3001 are completed prior to completing 10 major surgeries with at least 5 subjects (surgical sub-study), then the Sponsor may close study 3001, and submit the BLA. Enrollment of surgical subjects may continue in another study.”

Amendments to Protocol 3001

There were 3 amendments to this phase 3 protocol. Most of the changes were not structural changes to the conduct or analysis of the trial, but were for clarification. Changes that did represent alterations of the structure include:

- Amendment 1 date Nov 30, 2011

The finding, “number of subjects with FIX inhibitors”, was changed from a secondary endpoint to the primary safety endpoint.

- Amendment 2 date October 18, 2012

The period of dose adjustment for the on demand group (Arm 2) was limited to the first 4 weeks during the prophylaxis treatment.

A comparison of mean annual bleeding rates was added as a secondary endpoint to the analysis of prophylaxis regimens.

- Amendment 3 Feb 27, 2014

The bleeding events for Arm 2 (on-demand) subjects during the first 4 weeks (run-in period) of the prophylaxis phase will now be included. Previously these events were excluded. Also, the duration of the prophylaxis phase for Arm 2 was reduced to 26 weeks from 30 weeks.

Changes to the statistical section included a plan to handle missing data, definitions of analysis populations, and an analysis plan for comparisons of the 7, 10 and 14 day prophylaxis regimens.

Additional relevant correspondence to Protocol 3001

- May 12, 2014 written response to a request for a pre-BLA meeting (CRMTS #9332).

In response to the sponsor’s question, “Does the FDA have any comments on the draft SAP for the pivotal study?” FDA responded in part: For the second efficacy endpoint “number of infusions of rIX-FP to achieve hemostasis”, please revise the acceptance criterion for the number of bleeding episodes treated with one or two infusions so that it is based on the lower limit of a two-sided 95% confidence interval, rather than the point estimate of 85%.

Amendments to Protocol 3002

There were no substantial amendments to this protocol.

Amendments to Protocol 3003

- Amendment 1 May 14, 2013

A third arm was added comprising “subjects who have not previously completed a CSLB-sponsored rIX-FP lead-in study and who are scheduled to have a major non-emergency surgery within 8 weeks from the start of the initial pharmacokinetic rIX-FP (100 IU/kg) evaluation period”. The sample size was increased to 95 from 85. A clarifying statement, regarding the limitation of the quality of life exploratory objective to subjects who were enrolled on 3002, was added.

- Amendment 2 applied only to subjects enrolled in France.

- Amendment 3 June 3, 2014

Previously untreated patients (PUPs n=20) were added to the protocol, with an associated increase in sample size (from 95 to 115), and an independent data monitoring committee for the PUPs.

2.6 Other Relevant Background Information

None

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

WALDRON comment: The submission is well organized and easily navigated. The submission was largely complete with few requests for additional information.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The application complied with Good Clinical Practices and there are no identified data integrity issues. The following minor exceptions to GCP are noted:

- Research facilities were not described. A list of audited investigative sites and vendors was provided.
- The names and addresses of IRBs are provided, but there is no statement that the IRBs met regulatory requirements. This missing information was supplied in response to an information request, and it was acceptable.
- No summaries of IRBs' decisions to approve or modify the trials were provided. This missing information was supplied in response to an information request. No IRB requested any modification among approved sites. The IRBs' decisions were reported simply as approved.
- The consent form had a section which described compensation to include: costs incurred as a direct result of participation, and the possibility of payment for participation in PK studies. The CSLB-provided consent form did not include payment details, since it was intended for use across all clinical sites, and specific country regulations frequently control what compensation can be offered. No country or institution-specific compensation information (costs as a direct result of participation or payment for participation in PK studies) was provided. This missing information was supplied in response to an information request.

WALDRON comment: The applicant supplied the requested information in a timely manner. The financial compensation varied, but it was in proportion to numbers of visits, and it did not appear economically coercive.

3.3 Financial Disclosures

Investigators with disclosable financial interests/arrangements:

Site #0400001 - Dr. Ingrid Pabinger-Fasching (b) (4), (b) (6) USD, conversion date 29-Aug-14) received from CSLB for an unrestricted research grant in 2014.

Site #2760034 - Dr. Johannes Oldenburg reimbursement for attending symposia /congresses, honoraria for speaking, honoraria for consulting, and/or research funds received from CSLB since 2005. Dr. Oldenburg has received between (b) (4), (b) (6) (b) (4), (b) (6) USD, conversion date 29Aug2014) per year from CSLB for these purposes.

Site #2760065 - Dr. Martina Buehrle funding received from CSLB in the amount of (b) (4), (b) (6) USD, conversion date 29-Aug-14). The funding is support of an investigator initiated trial being conducted at the institution from 01Feb 2014 – 31 Jan2016.

WALDRON comment: The disclosure of financial conflict of interest seems appropriate and adequate. Three investigators disclosed financial conflicts among the 34 principal investigators in Study 3001. Together these 3 investigators enrolled 5 of 63 subjects in the study. The small number of principal investigators with financial conflicts, and the small proportion of patients enrolled by investigators with financial conflicts, minimizes the risk for a financial conflict influencing the trial outcome.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Coagulation Factor IX (Recombinant), Albumin Fusion Protein (hereafter rIX-FP) is a purified fusion protein that has 1018 amino acids. It is produced by the genetic fusion of recombinant albumin to recombinant coagulation FIX (Thr148 allelic form). The cleavable linker between the recombinant FIX and the albumin molecules is derived from the endogenous activation peptide in native FIX. rIX-FP remains intact in the circulation until FIX is activated, whereupon albumin is cleaved off, releasing activated FIX (FIXa). rIX-FP is secreted by a genetically engineered Chinese Hamster Ovary (CHO) cell line. The CHO cell line secretes rIX-FP into a defined cell culture medium, and the rIX-FP is purified by a (b) (4) purification process that does not require a monoclonal antibody step. The final product is a preservative-free, sterile, non-pyrogenic, lyophilized powder to be reconstituted with water for intravenous injection.

4.2 Assay Validation

See the Chemistry, Manufacturing and Controls review for more details. There are no issues with assay validation.

4.3 Nonclinical Pharmacology/Toxicology

See the full Nonclinical Pharmacology/Toxicology review. There were no findings from the animal models that affected the human safety evaluation.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action of IDELVION is replacement of the deficient FIX in the reactions which ultimately generate thrombin. IDELVION has a longer half-life than plasma derived FIX. The prolonged half-life is attributed to the increased size, which decreases renal clearance, and to prevention of digestion in lysosomes by binding to the neonatal Fc receptor (FcRn), which normally prevents degradation of albumin.

4.4.2 Human Pharmacodynamics (PD)

The product infusion increases FIX levels. No other important PD findings were identified.

4.4.3 Human Pharmacokinetics (PK)

See individual review of PK studies 2001 and 2004 from the Clinical Pharmacologist review.

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data.

4.6 Pharmacovigilance

Not applicable

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The primary clinical reviewer for this BLA, Peter Waldron, MD reviewed the primary clinical data from the phase 3 study, CSL654-**3001**, and four additional individual studies CSL654-**2001**, CSL654-**2004**, CSL654-**3002**, and **3003** contained in the BLA. Each individual clinical study is discussed separately in section 6. There are some limited pooled efficacy analyses presented in section 7. Pooled safety data is discussed in section 8. The BLA was transferred to Lisa Faulcon, MD, after the departure of Peter Waldron. Since the majority of the review was completed during the first review cycle after submission, Dr. Faulcon was assigned follow up of outstanding IR requests (related to potential renal safety signals), and labeling. Dr. Faulcon will provide a separate addendum memo related to these issues to the file. Howard Chazin, MD, Deputy Director, DHCR reviewed this BLA, integrated work done by Lisa Faulcon into the review, wrote the executive summary and risk benefit sections, corrected errors and finalized the review for signoff.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The documents used for this review were included in BLA 125582/0 and include documents in Modules 1, 2, and 5 of the eCTD.

5.3 Table of Studies/Clinical Trials

Phase	Trial	Objectives	Efficacy endpoint(s)	N	Subjects	Duration	Study status
Phase 1	2001	Inhibitor development, PK	NA	25	PTP with FIX activity $\leq 2\%$	14 days	Completed
Phase 1/2	2004	PK, safety, and inhibitor development	2°:breakthrough bleeds on prophylaxis	17	PTP with FIX activity $\leq 2\%$	20 weeks	Completed
Phase 2/3	3001	Safety and efficacy, inhibitor development, PK at start and 6 mo.; surgery sub-study hemostatic efficacy	AsBR prophylaxis vs on-demand; treatments per bleed; hemostatic efficacy in surgery	63	PTP with FIX activity $\leq 2\%$ Surgery = 4 subjects with 6 surgeries (2 major, 4 minor)	Variable, up to 28 months	Completed
Phase 3	3002	PK and inhibitor development	ABR, response to bleeding, hemostatic efficacy in surgery	27	< 12 yo PTP with FIX activity < 2%	12 months	Completed
Phase 3b	3003	Extension of 3001, 3002 Safety (inhibitor development); previously enrolled subjects scheduled to have major non-emergency surgery; PUPs	ABR, inhibitor development, response to bleeds; hemostatic efficacy in surgery	115	Extension 85 Surgery = 15 PUPs = 20	3 years	Ongoing

PK=pharmacokinetics, PTP=previously treated patients, PUP=previously untreated patients, ABR=annualized bleeding rate, AsBR=annualized spontaneous bleeding rate

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

An advisory committee meeting was not applicable to this BLA. The review team felt that although this product was the first FIX fusion protein to albumin, it did not offer a unique method of action and did not raise any questions for the committee.

5.4.2 External Consults/Collaborations

A consult to the Division of Cardiovascular and Renal Products/CDER was initiated to address concerns in four subjects in study CSL654-3001 with observed increased protein in urinalysis.

Four subjects (of a 63 subject safety population) had normal screening urinalysis, and then developed one or more positive tests for protein in urine, without blood on subsequent urinalysis. None of the four subjects had a pattern of increasing serum creatinine, or hypertension. Of the five studies submitted, only Study 2004 included urinalysis. Study 2004 included a smaller number of subjects (14), and a shorter (20 week) observation time. No subjects in Study 2004 fit the urine protein selection criteria. Due to the nature of the product tested in this clinical trial, overflow proteinuria was a possible explanation.

Consult question:

What additional steps are recommended to characterize (a) the observed proteinuria including the cause of proteinuria and (b) any effect on renal function over time? If the available data allow any conclusions on this issue, then please provide specific concepts that should be conveyed in the prescribing information.

The CDER CardioRenalconsultant recommended requesting additional information from CSLB as noted below

FDA - The results in the laboratory data set for Study 3001 for urine protein were positive or negative. The typical result of a urine dip stick for protein is negative or a graded result from 1+ to 4+. What were the actual test results in these subjects?

Regarding Subject (b) (6) .

In the applicant's laboratory dataset, the end-of-study value for urine protein is given as "1". Please clarify what "1" means. CSLB should also provide additional information on the medications that were taken (names and dates of administration). It seems likely that the proteinuria seen in this subject was caused by other factors, but the applicant should provide the requested information.

There is no apparent cause for urine protein findings in Subject (b) (6). Please provide a possible explanation for this finding, and additional information on the subject's course.

An information request was made to the RPM at COB May 23, 2015. A second request was made on June 9, 2015 and a response is requested by COB June 16. Please see the separate addendum to this clinical review written by Dr. Lisa Faulcon and section 8.4.5 Clinical Laboratory Tests for a follow up of the data requested related to this consultation.

5.5 Literature Reviewed (if applicable)

None

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Phase 3 Study - CSL654_3001

6.1.1 Objectives (Primary, Secondary, etc.)

Primary Objectives

The primary objectives were to evaluate the efficacy of IDELVION in preventing bleeding episodes (prophylaxis) and the safety of IDELVION with respect to the development of inhibitors against FIX in subjects with severe hemophilia B (consistently defined hereafter as FIX activity of $\leq 2\%$).

Secondary Objectives

The secondary objectives of the study were to evaluate:

- The PK of a single dose of IDELVION
- The clinical response to IDELVION for the prevention and treatment of bleeding episodes in subjects with severe hemophilia B
- The safety of IDELVION, based on adverse events (AEs) and the development of antibodies to rIX-FP

Surgical sub-study

Primary Objective

The primary objective of the surgical sub-study was to evaluate the efficacy of IDELVION in the prevention and control of bleeding in subjects with severe hemophilia B during surgical procedures.

Secondary Objectives

The secondary objectives of the surgical sub-study were to evaluate the efficacy of IDELVION in surgical prophylaxis as well as to evaluate the safety of IDELVION during the intraoperative and postoperative periods.

6.1.2 Design Overview

The efficacy component of the study was an open label, within-subject, matched-pairs comparison. The safety study was an open-label, prospective, observational study using electronic subject diaries and scheduled in-person and laboratory assessments.

In addition, the surgical sub-study was also an open label study, along with a single dose PK study.

WALDRON comment: The within subject comparison is an effective means to control for the variation in individuals disease severity and disease management (when to treat).

6.1.3 Population

Eligibility criteria:

- Male subjects, 12 to 65 years of age
- Documented severe hemophilia B (FIX activity of $\leq 2\%$), or confirmed at Screening by the central laboratory
- Received FIX products (plasma-derived and/or recombinant FIX) for >150 exposure days (EDs), confirmed by their treating physician
- No confirmed prior history of FIX inhibitor formation (defined as 2 consecutive positive tests, i.e., requiring a confirmatory test on a second separately drawn blood sample shortly after the previous positive test), no confirmed detectable inhibitors (defined as <0.6 Bethesda Units [BU]) at screening by the central laboratory, and no family history of inhibitor formation against FIX
- Written informed consent for study participation obtained before undergoing any study specific procedures

Additional inclusion criteria for on-demand (Arm 2) subjects only:

- Experienced a minimum average of 2 spontaneous (non-trauma-induced) bleeding episodes per month over the past 3 to 6 months, which required FIX replacement therapy and were documented in their medical records
- Were willing to switch to a prophylaxis regimen

Additional inclusion criteria for the surgical sub-study:

- Required non-emergency surgery
- Written informed consent for sub-study participation obtained before undergoing any sub-study-specific procedures

Exclusion criteria

- Known hypersensitivity (allergic reaction or anaphylaxis) to any FIX product or hamster Protein
- Known congenital or acquired coagulation disorder other than congenital FIX deficiency
- Currently (i.e., at study entry) receiving IV immunomodulating agents such as Immuno- globulin or chronic systemic corticosteroid treatment
- Platelet count $<100,000/\mu\text{L}$ at screening

- HIV positive subjects with a CD4 (lymphocyte) count $<200/\text{mm}^3$. A HIV-positive subject could participate in the study and receive antiviral therapy at the discretion of the Investigator.
- Serum aspartate aminotransferase (AST) or serum alanine aminotransferase (ALT) concentration $>5 \times$ upper limit of normal (ULN) at screening
- Serum creatinine concentration $>2 \times$ ULN at screening
- Evidence of thrombosis, including deep vein thrombosis, stroke, myocardial infarction, or arterial embolus within 4 months prior to dosing on Day 1
- Experienced a life-threatening bleeding episode, including bleeding in the central nervous system, gastrointestinal tract, neck/throat, or severe trauma-induced bleeding episode, or had major surgical intervention within 4 months prior to dosing on Day 1
- Use of any investigational medical product (IMP) other than IDELVION within 4 weeks prior to the first IDELVION administration on Day 1
- Concurrent non-hemophiliac inflammatory joint disease or other medical condition that, in the Investigator's judgment, could confound study results
- Suspected inability (e.g., language problem or mental condition) or unwillingness to comply with study procedures or history of noncompliance

Additional exclusion criteria for on-demand subjects only:

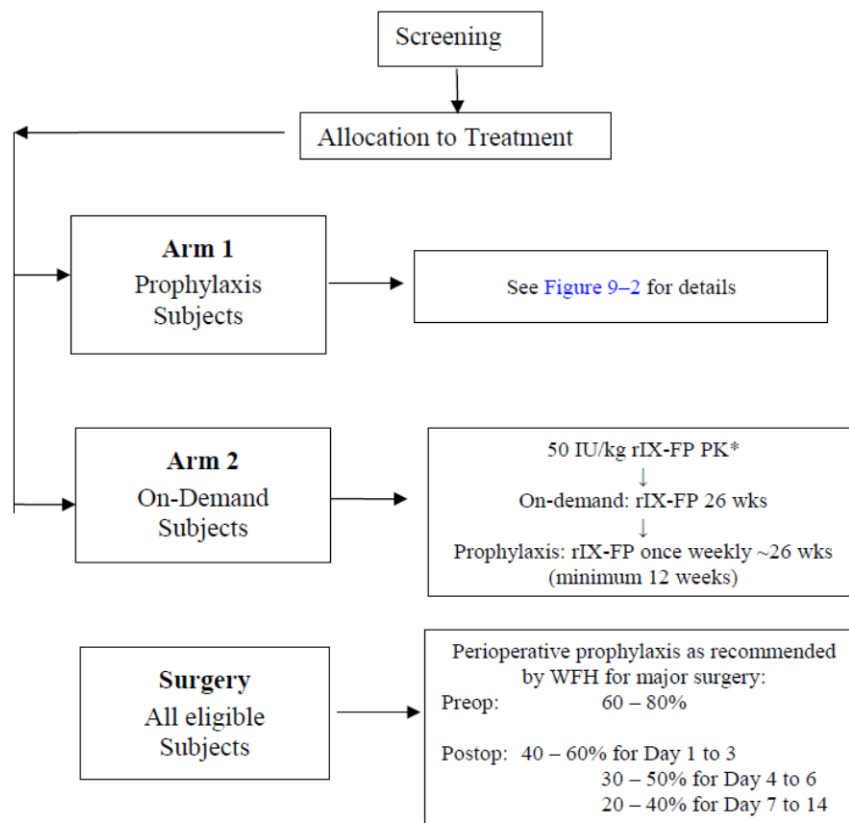
- Active synovitis
- Routinely received FIX infusion prior to activity (e.g., sports) as a preventative measure more than 2 times per month

WALDRON comment: The inclusion and exclusion criteria are appropriate for developing a population that is representative of the target population, and for minimizing known confounding conditions.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study treatment flow diagram is reproduced from the study report for Study 3001 below (p.23):

Figure 9–1 Treatment Flow Diagram



*except the on-demand subjects who had PK performed in Study 2004
Abbreviations: WFH World Federation of Hemophilia.

rIX-FP – IDELVION

Arm 1 (prophylaxis) subjects were divided into 3 groups (blocks A to C)

- Block A subjects had completed Study 2004. Subjects continued on the every 7 day IDELVION prophylaxis dose that they received at the end of Study 2004.
- Block B and block C subjects received weekly doses of 35 to 50 IU/kg IDELVION.

All Bleeding episodes in arm 1 were treated with the same dose of IDELVION as was used for the on-demand (arm 2) group.

Arm 2 (on-demand) subjects had PK data which included FIX recovery data. The target FIX activity level was based on the WFH recommendations and the following formula was used to calculate the IDELVION dose:

FIX (IU) required = Body weight (kg) × target FIX (% or IU/dl) increase × Reciprocal of
observed
recovery
(IU/kg per IU/dL)

Subjects who enrolled in the **surgery sub-study** received a dose of IDELVION in the range of 50 to 75 IU/kg, based on the subject's PK parameters, in order to increase the FIX levels to 60% - 80%. The dose was delivered as a bolus approximately one hour before the start of the surgical procedure. An intra-operative dose could be given based on results of FIX activity assay with a goal of maintaining a FIX level of "at least 60-80%" during the procedure. The subjects received postoperative doses of IDELVION from 1 to 14 days, depending on the FIX activity levels, type of surgery, and as recommended by WFH. The cited WFH recommendation was to maintain FIX activity levels at 40-60% post-operative days 1-3, 30-50% days 4-6, and 20-40% days 7-14.

6.1.5 Directions for Use

The draft label includes illustrated reconstitution instructions.

6.1.6 Sites and Centers

Numbers of enrollees by Country and Study Site are noted in the table below.

Country	Site	Number
Austria	0400001	1
Bulgaria	1000008	6
Germany	2760001	1
	2760034	3
	2760065	1
	2760066	2
	2760067	1
Spain	7240007	2
	7240008	1
	7240009	2
France	2500001	2
	2500001	4
	2500015	1
	2500017	1
Israel	3760001	11
Italy	3800015	2

	3800023	4
	3800025	1
Japan	3920025	1
	3920026	1
	3920027	1
	3920028	1
	3920029	2
	3920030	3
	3920031	1
Russian Federation	6430014	1
USA	8400154	1
	8400160	1
	8400184	3
	8400191	1
Total		63

WALDRON comment: Distribution by region: 34 Europe, 11 Middle East, 10 Asia, 6 N. America. This distribution leaves a likely under-representation of people with African, Native American, and Oceanic ancestry.

6.1.7 Surveillance/Monitoring

The schedule of assessments is reproduced from the study report from Study 3001 (p. 41 and 42) below.

WALDRON comment: These appeared to be reasonable and there were no issues related to the planned study assessments.

Table 9–5 Schedule of Assessments: Prophylaxis Subjects (Arm 1)

Assessments	Wk1-2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 60
Time Window		±4 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	or EoS
Concomitant therapy	On an ongoing basis															
Vital signs and weight	50 IU/kg rIX-FP PK	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical examination		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Social/physical activity		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Serum chemistry/hematology				✓				✓				✓				✓
Urinalysis				✓				✓				✓				✓
Inhibitor against FIX (CL)				✓				✓				✓				✓
Antibodies (rIX-FP ^a and CHO)(CL)				✓				✓				✓				✓
Plasma FIX level ^b (CL, optional local lab)		✓	✓	✓ ^b	✓	✓	✓	✓ ^b	✓	✓	✓	✓ ^b	✓	✓	✓	✓ ^b
Retained samples (CL)																✓
Training of self-administration	✓															
Investigator assessment		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Review subject eDiary		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adjust treatment regimen								✓ ^c	✓ ^d							
rIX-FP PK	✓ ^e							✓ ^c	✓ ^d							
AE observation period	On an ongoing basis															

Abbreviations: AE=adverse event; CHO=Chinese hamster ovary; CL=central laboratory; ED=exposure day; eDiary=electronic diary; EoS=end-of-study; FIX=factor IX; PK=pharmacokinetic; rFIX=recombinant factor IX; rIX-FP=recombinant fusion protein linking coagulation factor IX with albumin.

^a A sample positive for antibodies against rIX-FP was retested to discriminate between plasma-derived FIX, rFIX, and albumin antibodies.

^b Site visit was to occur within 24 hours prior to the next prophylaxis rIX-FP administration in order to test for trough level of FIX. All FIX activity level during monthly visits could be tested at the central lab (batched/shipped together with inhibitor sample) and could also be tested at the local laboratory.

^c Block A subjects who had 26 weeks of rIX-FP (7-day treatment interval) and 50 EDs (including previous studies) could switch to a 10-day or 14-day treatment interval at this visit, after PK assessment.

^d Block B subjects who had 30 weeks of rIX-FP (7-day treatment interval) could switch to a 10-day or 14-day treatment interval at this visit after repeating PK of 50 IU/kg rIX-FP. Block C subjects could switch to a 10-day or 14-day treatment interval without repeating the PK.

^e All non-Study 2004 study subjects.

Table 9–6 Schedule of Assessments: On-Demand Subjects Receiving On-Demand and Prophylaxis Treatment (Arm 2)

Assessments	Wk 1-2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 60
Time Window		±4 d	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	or EoS
Concomitant therapy	On an ongoing basis															
Vital signs and weight	50 IU/kg rIX-FP PK ^c	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical examination		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Social/physical activity		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Serum chemistry/hematology				✓			✓				✓					✓
Urinalysis				✓			✓				✓					✓
Inhibitor against FIX (CL)				✓			✓				✓					✓
Antibodies (rIX-FP ^a and CHO) (CL)				✓			✓				✓					✓
Plasma FIX level ^b (CL, optional LL)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Retained samples (CL)																✓
Training of self-administration	✓															
Investigator assessment		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Review subject eDiary		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Start prophylaxis regimen							✓									
AE observation period	On an ongoing basis															

Abbreviations: LL local laboratory

^a All FIX activity level time points were tested at the central lab, and could also be tested at the local laboratory after local laboratory qualification.

^b rIX-FP was to be administered at least 4 days after previous FIX infusion or 14 days after previous rIX-FP infusion.

The primary efficacy endpoint was spontaneous bleeding. The subjects recorded these events in the electronic subject diary (ediary), which was used as the source for data analysis of spontaneous bleeds. The data source was identical for both periods (on-demand and routine prophylaxis) of the primary efficacy analysis.

6.1.8 Endpoints and Criteria for Study Success

The **primary efficacy endpoint analysis** was based on the annualized spontaneous bleeding rate (AsBR) for the 7-day prophylaxis regimen compared with the on demand regimen. This was a within-subject, matched-pairs comparison. The primary efficacy analysis set was defined as all subjects assigned to the on demand treatment (arm 2) who received at least one dose of on-demand treatment, crossed over, and received at least one dose of routine prophylaxis treatment.

The AsBR was derived for each subject as follows: (number of spontaneous bleeding episodes) / (observed treatment period of interest) * 365.25. Only spontaneous bleeding episodes requiring treatment were included. Data during a surgical period were excluded. Data during the PK period were counted only if the bleeding episode was treated with IDELVION. If a subject completed at least 12 weeks of treatment, the AsBR was estimated using the subject's observed data for that treatment period. However, if a subject had at least 12 bleeding episodes with on-demand treatment, then the observed data was used regardless of the observation time. Otherwise, the AsBR was considered missing.

Missing data for the Primary Efficacy data set were handled as follows:

Missing on-demand AsBR was imputed using the mean AsBR observed among on-demand subjects who had at least 12 weeks of treatment or had at least 12 bleeding episodes during the on-demand treatment period. Missing prophylaxis AsBR was imputed according to the reason for not completing at least 12 weeks of prophylaxis treatment. If the reason for withdrawal was not for lack of efficacy, then the mean observed AsBR with prophylaxis treatment was used. If the reason for withdrawal was lack of efficacy, then the highest observed AsBR with prophylaxis treatment was used.

The **secondary efficacy analyses** were:

- Sensitivity analyses of the primary efficacy endpoint. Three sensitivity analyses were performed for the AsBR of arm 2:
 - Any missing prophylaxis AsBR were imputed using the mean observed AsBR with prophylaxis treatment
 - Any missing prophylaxis AsBR were imputed using the highest observed AsBR with prophylaxis treatment
 - Any missing prophylaxis AsBR were imputed using the subjects on-demand AsBR
- Number of spontaneous bleeding episodes per year in Arm 2
- Annualized bleeding rate for total bleeding episodes in Arm 2
- Number of infusions of IDELVION to achieve hemostasis in the treatment of minor/moderate bleeding episodes
- Investigator's overall clinical assessment of hemostatic efficacy for the treatment of bleeding episodes
- IDELVION consumption during routine prophylaxis
- Comparison of annualized spontaneous bleeding rate between the 7-day and >7-day prophylaxis regimens (arm 1)

Other efficacy analyses included:

- Time from last dose of IDELVION to onset of a spontaneous bleeding episode
- Annualized bleeding rates, by cause (traumatic and non-traumatic) and by site (total and joint)
- Bleeding episodes (additional information, including untreated bleeding episodes)
- Monthly consumption of IDELVION versus previous FIX for routine prophylaxis

WALDRON comment: The primary efficacy analysis evaluates the effect of IDELVION on a standard measure of effectiveness of bleeding prevention (AsBR) when used as routine prophylaxis. This measure (AsBR), and the comparison with an on demand regimen, represent an accepted basis for demonstration of effectiveness of factor replacement for hemophilia subjects.

6.1.9 Statistical Consideration

The null hypothesis was: the on-demand treatment arm will have a median difference in the annualized spontaneous bleeding rates, between the on-demand treatment period and the routine prophylaxis treatment period, equal to zero. This analysis will be performed on the Primary Efficacy population.

The sample size calculation for arm 2 (on demand and Primary Efficacy population) used the assumptions that the mean AsBR during on demand treatment is 24 (24 events per year), and that the mean AsBR for prophylaxis is 12. This yields an assumption that the AsBR will be reduced by 50% when subjects are switched from on-demand to prophylaxis. A sample size of 21 will provide a 95% power to detect a mean AsBR difference of 12 (50% reduction) between the on-demand treatment period and the prophylaxis treatment period. This assumes a standard deviation of differences of 14 and a two-sided alpha level of 0.05. The study planned to enroll approximately 25 subjects in the on-demand treatment arm to ensure that there are at least 21 evaluable subjects, while accounting for potential dropouts.

WALDRON comment: Below is a table of literature reports of trials which compared ABRs of an on-demand regimen with a routine prophylaxis regimen. Since the mean reduction in ABRs for this set was 95.1%, this suggests that the assumption of difference of 50% for Study 3001 was an underestimate. The effect of the choice of a 50% reduction was a calculation that indicated a need for a larger sample size than was required to detect the expected difference based on published results for the planned power.

Reference	Age	ABR On demand	ABR Routine prophylaxis
Manco-Johnson 2007	<6	17.1	1.15
Manco-Johnson 2013	12-50	28	0
Collinson 2010	30-45	40	0
Lalezari 2014	13-64	NA	2.2
Powell 2013*#	12-65	17.7	1.4

Windyga 2013*	12-65	16.9	1.99
Collins PW 2014*40	13-70	15.6	1.04
Collins PW 2014*10§	“	“	2.93

* Factor IX deficient patients. #These are the same data that appear in the Alprolix PI.

WALDRON Comment The mean of these 6 O-D is 22.55; mean of 7 RP is 1.11.

Mean reduction in ABR with prophylaxis = $[1 - (1.11/22.55)] = 95.1\%$

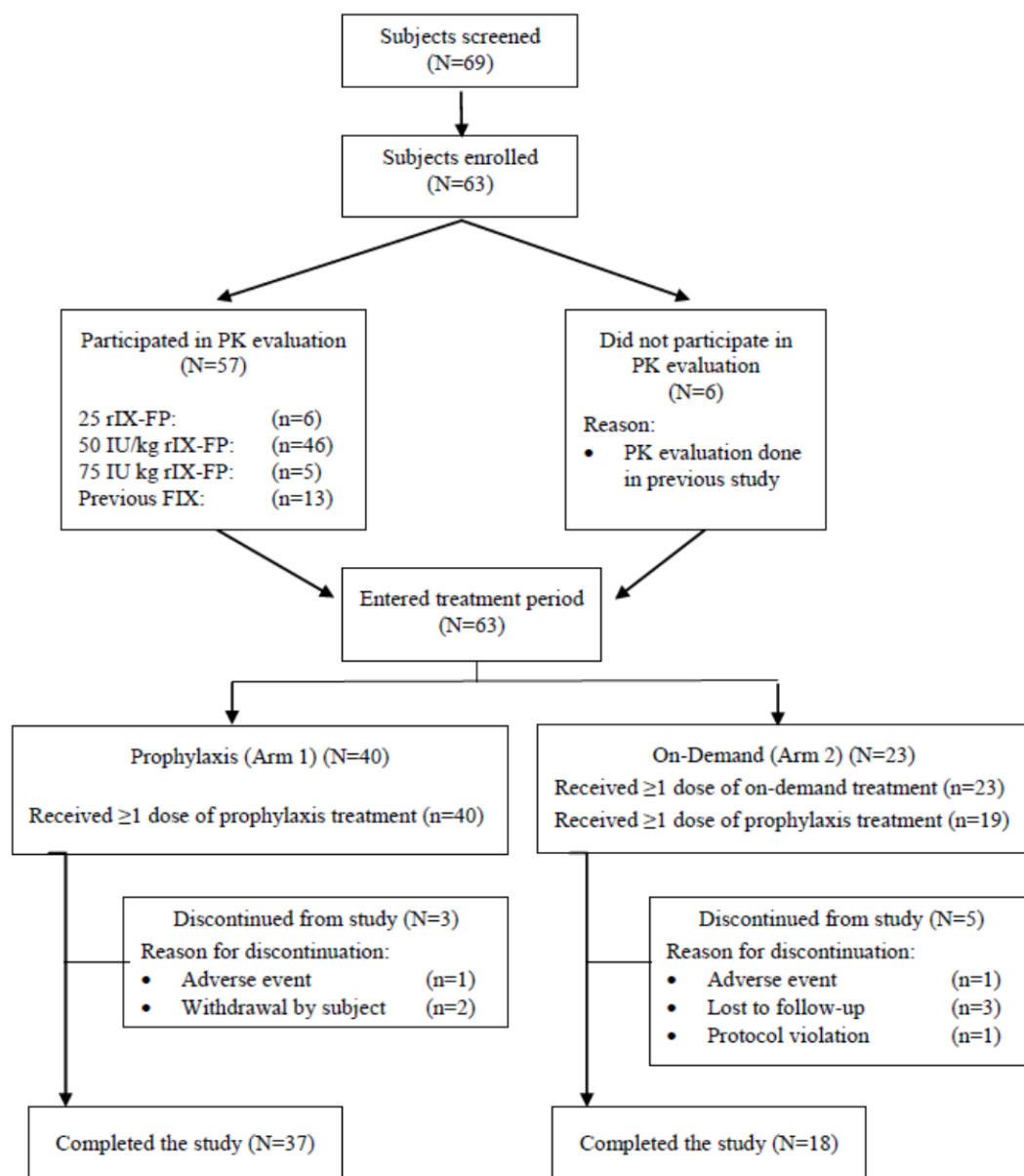
§These data were not used in the calculation of the means, since the dose was not optimal.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Refer to the table below for number of subjects in each defined enrolled/analyzed population and Subject disposition for Study 3001 is reproduced from the report from Study 3001 (p. 70 and Table 14.1.1.1) below. Sixty nine subjects were screened for an enrollment of 63 subjects. Of these 57 participated in the PK evaluation, 40 began the prophylaxis (arm 1) and 23 entered the on demand (arm 2). Of these 37 completed the prophylaxis study and 18 of 23 subjects completed the study in the on demand arm. The associated AEs that led to withdrawal of the product by the applicant (one in each treatment arm) were Subject (b) (6) a 55 year old male with acquired epileptic aphasia and Subject (b) (6), an 18 year old male with left knee synovitis, both of which were not considered associated with IDELVION and resolved approximately one month from onset. See section 6.1.11.4 for further discussion on dropouts and discontinuations.

Figure 10–1 Subject Disposition



Abbreviations: FIX factor IX; PK pharmacokinetic; rIX-FP recombinant fusion protein linking coagulation factor IX with albumin.

Source: [Table 14.1.1.1](#) and [Listings 16.2.5.1](#) and [16.2.5.7](#).

Safety population

The safety population consists of all subjects who received at least one dose of IDELVION during the study. All safety analyses were performed on the safety population.

Pharmacokinetic population

The formal PK population is comprised of the subjects who have received at least one dose of IDELVION for PK assessment and for whom a sufficient number of analyzable PK samples were obtained to permit the evaluation of the PK profile of IDELVION, and who did not receive a dose of IDELVION or any other FIX product for the treatment of a bleed during the PK sampling period.

Efficacy population

The Efficacy population consists of all subjects who participated in the non-surgical efficacy portion of the study and received at least one dose of IDELVION.

Primary Efficacy population

The Primary Efficacy population includes all subjects in the Efficacy population assigned to the on-demand treatment arm (Arm 2), who crossed over, and receive at least one dose of routine prophylaxis treatment.

Per Protocol population

The Per Protocol (PP) population consists of all subjects in the Efficacy population who did not have any inclusion or exclusion criteria deviations, and who incurred no protocol deviations that pertain to the assessment of treatment efficacy. If a subject did not treat a bleed per the protocol, the PP analysis may exclude the bleed in question, rather than all of the subject's data. Accordingly, the following bleeding events were assessed for exclusion from the PP analysis, including but not limited to: use of a FIX product other than IMP to treat a bleed; treatment more than 4 hours after the start of the bleed or a bleed that occurred after a time interval greater than the subject's prophylaxis dose regimen. A full review of the bleeding data was performed to identify other bleeds that should be removed from the analysis. Rationale for the reason these bleeds are being excluded will be provided.

WALDRON comment: The per protocol population was not used for any regulatory purpose.

Surgical population

The Surgical population included all subjects who received at least one dose of IDELVION for a major or minor surgical procedure. See section 7.1.7 for all surgery subjects.

* Four subjects in the on-demand arm discontinued the study after receiving at least one dose during the on-demand phase, but none during the prophylaxis phase. These 4 subjects are included in the safety and efficacy populations, but they were excluded from the primary efficacy population due to failure to initiate routine prophylaxis. One subject ((b) (6)) from the primary efficacy population discontinued after only 2 prophylaxis doses. The approach to imputing this subject's data was pre-specified, and the possible choices of imputed data were a subject of a sensitivity analysis.

The demographics of the Study 3001 safety population is summarized in the table below. All patients were male and most were white. Meaningful differences in subpopulations cannot be ascertained.

Demographics of Study 3001 Safety Population	
N	63
Age (yr.)	
Mean (SD)	33 (14)
Geographic Region (%)	
Europe	36 (57)
Middle East	11 (17.5)
Asia	10 (16)
N America	6 (9.5)
Race (%)	
White	52 (82)
Asian	10 (16)
African-American	1 (2)
Ethnicity (%)	
Not Hispanic/Latino	62 (98)
Hispanic/Latino	1 (2)
Weight (kg)	
Mean (SD)	72 (17)
BMI (kg/m ²)	
Mean (SD)	24 (6)
BMI distribution (%)	
< 30 kg/m ²	57 (91)
>30 kg/m ²	6 (9)

WALDRON comment: The demographic profile of Study 3001 was notable for under representation of subjects with African, Native American, and Oceanic ancestry. The role of race in hemophilia B is of uncertain significance. Female subjects were not included, since they rarely if ever have severe ($\leq 2\%$ FIX activity) FIX deficiency.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Medical history of special interest ongoing at screening of safety population is summarized in the table below.

Medical History	N (%)
------------------------	--------------

Musculoskeletal and connective tissue disorders	36 (57.1)
Hepatitis C	23 (36.5)
HIV infection	12 (19.0)
Hepatitis B	2 (3.2)

Hemophilia B History (safety population N=63)

Cumulative ED	
Median	621
Q1, Q3	220, 1000
Range	151 – 4000
In the preceding 12 months:	
Total bleeding episodes	
Median	5.5
Q1, Q3	1, 22
Range	0 – 50
Spontaneous bleeds	
Median	2.0
Q1, Q3	0, 12.0
Range	0 – 29
Trauma bleeds	
Median	1.0
Q1, Q3	0, 4.0
Range	0 – 38

Chronic hemarthrosis

Of the 6 joints reported (left and right ankle, knee, and elbow) and the 60-62 subjects, for whom this history was reported, a total of 79 joints had chronic hemarthrosis.

WALDRON comment: The representation of the broad, intended population among the enrolled population is well supported by section 6.1.10.1.2 (medical history), which describes the enrolled population's bleeding, joint, and chronic infection histories.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Primary Efficacy Population

The primary efficacy analysis was performed on the Primary Efficacy Analysis set (N=19) and included subjects in the on demand treatment arm who received on demand

treatment during the first half of the study followed by prophylaxis treatment. Subjects had to receive at least one dose of IDELVION in each treatment period to be included in the analysis. This analysis compared the AsBR between on demand and prophylaxis treatment arms. The mean AsBR was significantly reduced when subjects switched from on-demand to weekly prophylaxis treatment 96% reduction ($p < 0.0001$). Results comparing the On-demand to the routine prophylaxis regimen are summarized in the tables below.

Annualized Spontaneous Bleeding Rate (AsBR) – Study 3001		
	On-demand	Routine prophylaxis
N	19	19
Median days on treatment	187	316
Mean (SD)	14.6 (8.4)	0.9 (1.2)
Median	15.4	0.7
Q1, Q3	8, 18	0, 1.6
Range	2 – 39.5	0 – 4.2
Subjects with no treated bleeds	0	10

NOTE: These data were revised from the initial submission using the March 3, 2015 addendum 1 data (data cut-off Jan 9, 2015).

Reduction (%) within subject of AsBR by the prophylaxis regimen compared to the AsBR during the on-demand regimen	
N	19
Mean (SD)	93.5 (8.0)
Median	95.9
Q1, Q3	89.0, 100.0
Min, Max	75.2, 100.0
p-value	<0.0001

The p-value is based on Wilcoxon Signed-rank test of the null hypothesis: AsBR ratio (routine prophylaxis/on-demand) ≥ 0.50

WALDRON comment: This finding overturns the null hypothesis, and supports efficacy for the routine prophylaxis indication.

6.1.11.2 Analyses of Secondary Endpoints

All secondary efficacy analyses in this section were specified in the protocol:

- Sensitivity analyses of the primary efficacy endpoint. Three sensitivity analyses were performed for the AsBR of arm 2:
 - Any missing prophylaxis AsBR were imputed using the mean observed AsBR with prophylaxis treatment

- Any missing prophylaxis AsBR were imputed using the highest observed AsBR with prophylaxis treatment
- Any missing prophylaxis AsBR were imputed using the subjects on-demand AsBR

One subject ((b) (6)) from the primary efficacy analysis population had missing AsBR data (Clinical Study Report (CSR) p. 108). Since he was lost to follow up 12 days after start of routine prophylaxis, his AsBR was imputed to be the mean AsBR for the routine prophylaxis regimen.

The planned secondary efficacy analyses included three sensitivity analyses to evaluate the effect on the reduction in AsBR of the choice of imputed data used in place of the missing data: sensitivity analysis (SA)1, uses the mean AsBR from arm 2 prophylactic regimen; SA2 replaces the missing AsBR with the AsBR of the subject from arm 2 with the highest observed AsBR during the prophylactic regimen, and SA3 uses the AsBR during the on-demand regimen of the subject whose data is missing.

Percent Reduction in AsBR with prophylaxis treatment (%)				
	Primary	SA1	SA2	SA3
Mean* (SD)	93.5 (8.03)	same	92.4 (9.1)	88.5 (22.87)
Median	95.9	same	same	same
Min	75.2	same	74.6	0
p-value	<0.0001	same	same	same

*The mean, median, and min (minimum) are the respective values for the within subject percent reductions

The p-value is based on Wilcoxon Signed-rank test of the null hypothesis.

WALDRON NOTE: These data were revised from the initial submission using the March 3, 2015 addendum 1 data (data cut-off Jan 9, 2015). The sensitivity analyses are robust and support the finding that the null hypothesis (AsBR RP/OD > 0.5) is false.

Number of spontaneous bleeding episodes per year in Arm 2			
	On-demand	Prophylaxis	Prophylaxis/on-demand
N	19	19	
Mean (SD)	13.8 (11.0, 17.2)	0.7 (0.4, 1.3)	0.0 (0.0, 0.0)
Annualized Bleeding Rate for Total Bleeding Episodes in Arm 2			

	On-demand	Prophylaxis	% reduction in ABR with prophylaxis
N	19	19	
Mean (SD)	20.8 (9.2)	2.9 (4.8)	88% (14.1)
Median	19.2	1.6	90.9%
Min	2	0	54.3%
p-value			<0.0001

WALDRON NOTE: These data were revised from the initial submission using the March 3, 2015 addendum 1 data (Table 2) (data cut-off Jan 9, 2015)

Number of Infusions of IDELVION to Achieve Hemostasis in the Treatment of Minor/Moderate Bleeding Episodes	
	Efficacy population N=63
Bleeding episodes requiring treatment	358
Infusions to achieve hemostasis	N (%)
1 (%)	335 (93.6)
2 (%)	18 (5)
>2 (%)	5 (1.4)
≤ 2 % (95% CI)	98.6 (96.2, 99.5)

WALDRON comment: The prespecified level for success of effectiveness of achieving control of bleeding was that the lower limit of the 95% CI of proportion of bleeds requiring 2 or fewer infusions would be > 80%. These findings meet that goal.

There were no reported major bleeds. Iliopsoas bleeds are a deep tissue bleed that typically require a prolonged period of factor replacement to treat adequately. As such they provide some assessment of the efficacy of treating bleeds, which are at the severe end of the moderate severity category. This small series of subjects from Study 3001 (below) is consistent with the overall findings from the minor and moderate bleeding events.

Iliopsoas bleeds on Study 3001

Subject ID	Doses to achieve hemostasis	Maintenance doses	Investigator rating*	Pain rating at 24 hrs.
(b) (6)	1	2	M	P
(b) (6)	1	0	G	P
(b) (6)	1	3	E	D
Same pt. L side	3	4	M	D
(b) (6)	1	0	E	D

*Investigator rating of IDELVION treatment: E=Excellent, G=Good, M=Moderate,
P=Poor/No Response

#Pain Assessment: A=Abupt, D=Definite, P=Probable, N=No Improvement

WALDRON comment: The next two evaluations (clinical assessment and IDELVION consumption) have no regulatory value in my opinion.

Investigator's overall clinical assessment of hemostatic efficacy for the treatment of bleeding episodes

Efficacy population

Bleeding Severity Assessment	Prophylaxis (Arm 1) (N=40) n (%)	On-demand (Arm 2) (N=23) n (%)	Total (N=63) n (%)
Minor/moderate bleeding episodes			
Number of bleeding episodes requiring treatment	101	257	358
Excellent	72 (71.3)	225 (87.5)	297 (83.0)
Good	21 (20.8)	19 (7.4)	40 (11.2)
Moderate	3 (3.0)	6 (2.3)	9 (2.5)
Poor/no response	0	1 (0.4)	1 (0.3)
Missing	5 (5.0)	6 (2.3)	11 (3.1)

- rIX-FP consumption during routine prophylaxis

Efficacy population

	Prophylaxis (Arm 1)			On-demand (Arm 2)	Total 7-day prophylaxis
	7-day regimen (N=40)	10-day regimen (N=7)	14-day regimen (N=21)	Prophylaxis regimen (N=19)	(N=59)
Number of subjects on routine prophylaxis treatment, n (%)	40 (100.0)	7 (100.0)	21 (100.0)	19 (100.0)	59 (100.0)
Total number of prophylaxis infusions during study	1955	180	537	849	2804
Number of prophylaxis infusions per month					
n	40	7	21	19	59
Mean (SD)	4.23 (0.128)	2.84 (0.379)	2.19 (0.057)	4.30 (0.190)	4.25 (0.152)
Median	4.24	3.02	2.19	4.34	4.32
Q1, Q3	4.18, 4.34	2.67, 3.04	2.17, 2.23	4.30, 4.36	4.20, 4.35
Min,	3.8, 4.4	2.0, 3.1	2.1, 2.3	3.7, 4.5	3.7, 4.5
Total prophylaxis dose per month (IU/kg)					
n	40	7	21	19	59
Mean (SD)	202.679 (47.922)	201.499 (42.557)	157.439 (16.344)	191.687 (36.331)	199.139 (44.505)
Median	194.693	222.483	162.280	173.254	192.688
Q1, Q3	167.412, 215.043	149.029, 224.733	158.642, 164.214	164.091, 223.447	166.201, 219.297
Min, Max	139.86, 321.52	131.57, 238.86	111.76, 179.12	147.44, 263.10	139.86, 321.52

Comparison of annualized spontaneous bleeding rate between the 7-day and >7-day prophylaxis regimens (arm 1)

Annualized spontaneous bleeding rate (efficacy population arm 1)

	7 day regimen	10 day regimen	7 day regimen	14 day regimen
N	7	7	21	21
Mean (SD)	0.0 (0.00)	0.1	0.3 (1.0)	1.1 (2.1)
Median	0.00	0.00	0.00	0.00
Q1, Q3	0.00, 0.00	0.00, 0.00	0.0, 0.0	0.0, 1.00
Min, Max	0.0, 0.0	0.0, 0.9	0.0, 4.5	0.0, 7.3
no bleeds n(%)	7 (100)	6 (86)	16 (76)	9 (43)
Mean days of treatment (DoT)	284.4 (117.2)	267.1 (132.8)	265.7 (82.7)	354 (130.7)
Median DoT	238	240	225	386
Min, Max DoT	197, 521	114, 413	195, 507	98, 575

Waldron comment: The table only includes subjects with at least 12 weeks of treatment on more than one regimen. The text is not explicit, but it seems a reasonable assumption that the data for the 7 day and 10 day regimens were from identical groups, who switched to the longer interval. (The same appears true for the 14 day set.)

WALDRON comment: (Source CSR 3001 Tables 14.2.6.2, 14.2.6.3) The subjects who received routine prophylaxis on a > 7 day regimen were a selected sub-group who met the following criteria as reproduced from the submission:

- no dose adjustment in the preceding month
- no spontaneous bleeds in the previous month
- a weekly prophylaxis dose of ≤ 50 IU/kg

These rules make the >7 d population a selected group with a lower on-study bleeding rate, and different PK parameters, than those subjects who remained on the 7 day interval. Therefore, comparisons of the AsBR, between groups defined by the interval of dosing, are not comparisons of similar groups, and are not appropriate.

The clinical study protocol (p. 90) describes a test of non-inferiority for the 10 and 14 day routine prophylaxis:

“In order to demonstrate that a similar treatment effect also exists for the 10-day or 14-day prophylaxis regimen (i.e., extended), the mean annualized spontaneous bleeding rate will be compared between the two prophylaxis regimens to evaluate non-inferiority.”

“In order to show noninferiority, 50% of this treatment effect [reduction of mean annualized spontaneous bleeding rate from the assumed 24 bleeds per year, during the arm 2 on-demand phase, to 12 bleeds per year, during the every 7 day routine prophylaxis stage] should be maintained when comparing the [arm 1] mean annualized 10 or 14-day regimen bleeding rate and the mean annualized 7-day regimen bleeding rate in the prophylaxis treatment arm (6 bleeds per /year). The null and alternative hypotheses are as follows:

H0: $\mu_{7\text{-day}} - \mu_{\text{extended}} \leq -6$

H1: $\mu_{7\text{-day}} - \mu_{\text{extended}} > -6$

The lower confidence limit of the 95% confidence interval for the difference between the two means must be greater than -6 bleeds/year.”

NOTE: The material in brackets [] was added by the reviewer.

WALDRON comment: This test of efficacy of the extended (10 or 14 day) routine prophylaxis schedules is not well defined. The treatment effect was demonstrated in the arm 2 subjects, but the subjects for the extended interval trial are from arm 1. Thus, the statement, 50% of this treatment effect should be maintained... has an undefined meaning, since the arm 1 subjects had no treatment effect evaluated. In addition the non-inferiority margin (50%) is of questionable clinical meaning, since this AsBR (=18, preserving 50% of the reduction of 12, from 24 to 12) is far in excess of the expectations for AsBR with current hemophilia management. See below, also.

The clinical study report (p. 113) appears to use an approach that is different from the pre-specified (above) approach to evaluate non-inferiority of the > 7 day prophylaxis regimens. It ignores the above "...50% of this treatment effect should be maintained" and defines the population for evaluation as the efficacy population of the prophylaxis treatment arm (Arm 1) with at least 12 weeks of treatment on both a 7 day regimen and a > 7 day regimen (n=26). This population underwent a matched pair analysis.

14 day (Table 14.2.6.3 from the submission)			
	7 day	14 day	(7 d – 14 d)
N	21	21	
Median duration (d)	225	386	
AsBR mean	0.28	1.07	
AsBR median	0.0	0.0	
AsBR mean difference (95% CI)			-0.8 (-1.8, 0.2)
Subj 0 bleeds	16	9	
ABR Mean	0.7	2.0	
ABR Median	0.0	0.0	
ABR Mean difference (95% CI)			-1.3 (-2.6, 0.1)

10 day (Table 14. 2.6.2 from the submission)			
	7 day	10 day	(7 d – 10 d)
N	7	7	
Median duration (d)	238	240	
AsBR median	0.0	0.0	
AsBR mean	0.0	0.1	
AsBR mean difference (95% CI)			-0.1 (-0.4, 0.2)
Subj 0 bleeds	7	6	
ABR Mean	0.6	0.8	
ABR Median	0.0	0.0	
ABR Mean difference (95% CI)			-0.3 (-1.3, 0.8)

WALDRON comment: This analysis is different from the pre-specified analysis. However, the matched pair analysis is a reasonable attempt to isolate the effect of a longer interval of routine prophylaxis dosing. The number of arm 1 subjects who fit the criteria for the 10 day regimen for at least 12 weeks is very small (n=7). The differences in the 7 day minus 10 day total and spontaneous means of the ABRs was small (< 1), and an upper limit of the 95% CI that was > 0 (meaning the 10 day AsBR could exceed the 7 day). The arm 1 subjects who fit the criteria for the 14 day regimen for at least 12 weeks had numerically greater mean spontaneous and total ABRs (than the 10 day group), and the total ABR mean difference was 1.25. Nevertheless, the upper limits of the 95% CI for the

mean differences of the total and spontaneous ABRs were >0 , indicating that there may be no difference in the ABR and AsBR between these 2 regimens, within these selected populations. The similarity of the 7 day ABR and the AsBR findings to those found using the 10 and 14 day intervals make irrelevant the earlier discussed design issues (concern that an AsBR = 18 may be acceptable).

Other efficacy analyses:

Time from Last Dose of IDELVION to Onset of a Spontaneous Bleeding Episode						
Any dose						
	Arm 1			Arm 2		
	7 day	10 day	14 day	O-D	7 day	all 7 d
Episodes	37	1	36	140	14	51
Median (hr.)	105.0	240.9	207.1	373.2	71.2	99.7

Additional analyses were done using time from last dose to treat a bleed, and time from last prophylaxis dose.

WALDRON comment: This comparison (time from last dose to spontaneous bleed) is inherently problematic. The intervals (7, 10, or 14 day) limit the maximum interval from a dose to a bleed, and therefore bias the outcome rendering a comparison invalid. The criteria for switching to a > 7 day regimen also mean that the subjects who comprise the 7 day regimen group are different in bleed frequency and likely PK parameters from the > 7 day group. The $N=1$ makes the 10 day group uninformative. This set of flaws makes this analysis of no use.

Annualized bleeding rates, by cause (traumatic and non-traumatic) and by site (total and joint) are summarized in the tables below.

Annualized Bleeding Rates Traumatic Episodes (Efficacy Population)				
	Arm 1		Arm 2	
	7d		O-D	
N	38		22	
Mean (SD)	0.7 (1.1)		6.3 (5.2)	
Median	0		5.7	
Max	4.1		18.4	

Annualized Bleeding Rates Non-Traumatic (Spontaneous or Unknown) Episodes (Efficacy Population)				
	Arm 1		Arm 2	
	7d		O-D	
N	38		22	

Mean (SD)	0.5 (1.1)	14.0 (8.7)	0.8 (1.4)	0.6 (1.19)
Median	0	13.3	0	0
Max	4.5	39.5	4.2	4.5

Annualized Bleeding Rates Total Episodes (Efficacy Population)				
	Arm 1	Arm 2		Total
	7d	O-D	7d	7d
N	38	22	18	56
Mean (SD)	1.2 (1.8)	20.3 (8.6)	2.9 (5.0)	1.8 (3.2)
Median	0	18.6	1.2	0.6
Max	6	46.1	21.1	21.1

Annualized Bleeding Rates Joint Bleeding Episodes (Efficacy Population)				
	Arm 1	Arm 2		Total
	7d	O-D	7d	7d
N	38	22	18	56
Mean (SD)	0.9 (1.4)	15.7 (10.7)	2.5 (3.7)	1.4 (2.5)
Median	0	15.3	1.2	0
Max	4.7	46.1	15.5	15.5

Bleeding episodes (additional information, including untreated bleeding episodes)

The efficacy population reported 75 bleeds not requiring treatment. Participants in the 14 day prophylactic regimen had the largest number (43). Twenty-seven occurred during the 7 day prophylaxis regimen (arm 1 = 22, arm 2 = 5). The nasal mucosa was the most common site.

Monthly Consumption of IDELVION versus previous FIX for routine prophylaxis (RP)				
	Arm 1			
	7 day	10 day	14 day	Previous FIX
N on RP	40	7	21	28
Monthly IU/kg				
Mean (SD)	202.7 (47.9)	201.5 (42.6)	157.4 (16.3)	320.7 (208.8)
Median	194.7	222.5	162.3	256.6
Q1, Q3	167, 215	149, 225	159, 164	209, 365

WALDRON comment: This is an exploratory analysis with no regulatory significance. There is no statement regarding the missing data for previous FIX consumption from 12

subjects, so we don't know whether they are different. Since the subjects on > 7 day treatment intervals were selected based on bleeding frequency and PK values, then those groups represent a biased sample for the purpose of comparison of monthly consumption.

6.1.11.3 Subpopulation Analyses – Perioperative management

The surgery subpopulation from all studies is presented and discussed in section 7.1.7.

Waldron Comment: One CSL654-3001 surgery subject (b) (6)) should be excluded for poor data quality. The subject underwent wisdom tooth extraction due to dental caries. The subject did not enter the surgical sub-study. Therefore, the procedures of the sub-study protocol were not performed. The subject received a IDELVION dose (75 IU/kg) 1 day prior to surgery. This day coincided with his routine prophylaxis, and the subject recorded this dose as given for routine prophylaxis. This is not as prescribed in the CSL654-3001 protocol, which states that the dose should be given 1 hour prior to the start of surgery. The surgery narrative (clinical study report p. 1086) had no surgeon's assessment of pre- or post-operative estimated blood loss and no assessment of hemostatic efficacy. The subject gave himself additional IDELVION doses on post-op days 4 and 8 due to bleeding, without reported evaluation by study personnel. He used the additional hemostatic agent, 1 gm tranexamic acid every 8h (d -1 to d+2 and then d+8 to d+10). Table 11-17 in the clinical study report lists an assessment of hemostatic efficacy for 0 hr, 72 hr or discharge, and 14 day or end of study, but these were not in the case narrative. The case narrative is also in conflict with the table accompanying it (Table 14-11). The narrative states:

A day prior to surgery, 75 IU/kg (4350 IU) rIX-FP was administered. As this day was the scheduled prophylaxis day, this dose was recorded as routine prophylaxis by the subject. Plasma FIX activity was not measured. The subject reported a post-surgery bleed 3 days after surgery, and treated the bleed with a single dose of 51.9 IU/kg rIX-FP 17 hours later. The subject reported a second post-surgery bleed 7 days after surgery (6 days after treatment of the first post-surgery bleed), and treated the bleed with a single dose of 51.9 IU/kg rIX-FP 4 hours later. The subject took his routine prophylaxis dose on 29Jul 2013, and at the Week 54 visit, the FIX activity was 30.2% prior to dosing.

However, Table 14-11 indicates that surgery was July 16 (d0), bleed was July 19 (d+3), post-surgery dose was July 20 (d+4), bleed was July 24 (d+8), and the next post-surgery dose was the same day. Table 14-11 (CSR) includes no FIX activity level within 24 hours of surgery for this subject, but the CSR (section 11.4.2.3) states "At the time of surgery, the FIX activity was above 60% for all subjects, as required by WFH guidelines." Listing 16.2.6.7 reports a wound hematoma with no specified date, but a wound hematoma is not mentioned in the narrative.

The non-standard timing of the pre-operative IDELVION dose, the missing measurement of FIX activity, the missing surgeon's assessments of hemostatic efficacy and blood loss (from the narrative) and the inconsistent reports of factor administration and post-operative complications are all barriers to assessment of the hemostatic efficacy during the perioperative course. My judgment is to exclude this subject from the cases reported

in the label due to the poor quality of the data. This subject's procedure (unlike other procedures listed as surgeries) is also listed among the cases of "Additional Procedures Performed on Study" (CSR Table 11-18).

6.1.11.4 Dropouts and/or Discontinuations

Eight of 63 subjects discontinued the study. Three subjects ($3/40 = 7.5\%$) were in arm 1 (prophylaxis), and five were in arm 2 (on-demand; $5/23 = 21.7\%$). The primary efficacy population (completed on-demand regimen and received at least 1 prophylaxis dose) was a subset of the arm 2 efficacy population (all subjects who received a single IDELVION dose).

Four of the five arm 2 discontinuations occurred before the start of the prophylaxis regimen; therefore, those four subjects were not in the primary efficacy population. Two of the four were lost to follow-up (b) (6) one had a protocol deviation (subject (b) (6) failed to start prophylaxis, but continued on-demand), and one discontinued the study in association with an AE (b) (6) AE = headache and eczema). One subject (b) (6) was lost to follow-up after completing the planned on-demand regimen, but had only two prophylaxis doses. His data was imputed for the primary efficacy analysis.

The three subjects who discontinued from arm 1 were due to an AE ((b) (6), infusion reaction), and two subjects (b) (6) were classified as withdrawal by subject. See 6.1.12.2 for narratives of these subjects.

WALDRON comment: There was no suggestion that these subjects were discontinued with an intention to manipulate the outcome. The adverse events (headache and rash) that led to discontinuation are included in the proposed PI.

6.1.11.5 Exploratory and Post Hoc Analyses

See section 6.1.11.2, Other Analyses.

6.1.12 Safety Analyses

6.1.12.1 Methods

All subjects were evaluated in the Safety Population, and endpoints included inhibitors against FIX, the nature and incidence of AEs, local tolerability, the development of antibodies against IDELVION and CHO host cell protein, laboratory safety parameters, activation of coagulation tests, vital signs, and physical examination.

6.1.12.2 Overview of Adverse Events

Exposure days for each arm of the safety population in the study are summarized in the table below.

Exposure Days (Reproduced from CSR Table 12-1)

	Arm 1	Arm 2	Total
N	40	23	63
Mean (SD)	72.4 (22.1)	51.5 (30.6)	64.8 (27.3)
Median	72	51	71
<50 EDs, n (%)	3 (7.5)	11 (47.8)	14 (22.2)
≥50 EDs, n (%)	37 (92.5)	12 (52.2)	49 (77.8)
≥75 EDs, n (%)	16 (40)	8 (34.8)	24 (38.1)
≥100 EDs, n (%)	2 (5)	0	2 (3.2)

Treatment Emergent Adverse Events (TEAEs) are summarized in the table below. A total of 54 out of the 63 subjects experienced 347 treatment emergent AEs during the study. Two subjects experienced an AE that led to subject withdrawal and five subjects were had 11 TEAEs attributed by the applicant to IDELVION (see WALDRON comment below). Five AEs were assessed as severe.

The most frequently reported TEAEs were nasopharyngitis (38 events in 16 [25%] subjects), headache 34 events in 15 [24%] subjects and arthralgia (19 events in 9 [14%] subjects).

WALDRON comment: Five individual subjects reported 11 TEAEs that were related. One subject accounted for 5 rash events, and one subject had 2 related TEAEs; eczema and headache. The other 4 related TEAEs in single subjects were headache, dizziness, injection site hematoma, and hypersensitivity. No pattern or trend was apparent from review of these TEAEs.

Summary of TEAEs in the Safety Population (N=63)						
Reproduced from Table 12-2 from the Clinical Study Report p. 132						
	Arm1		Arm 2		Total	
N	40		23		63	
	Subj's Events		Subj's Events		Subj's Events	
Any TEAE	36	278	18	69	54	347
Relationship						
To IDELVION						
Related	4	8	1	3	5	11
Unrelated	35	270	18	66	53	336
Severity						
Mild	34	228	17	55	51	283
Moderate	18	47	7	12	25	59
Severe	2	3	2	2	4	5
Any SAE						
	1	2	2	2	3	4†

TEAE leading to withdrawal	2	2	1	1	3	3*

† Two SAEs occurred in 1 subject during screening.

*See narratives including a fourth subject withdrawing possibly related to an AE.

Serious Adverse Events (from clinical study report section 14.3.3.2)

NOTE: Only 2 of the SAEs were TE SAE occurring in 2 subjects as summarized below.

Subject (b) (6) an 18 year old white male with a left knee synovitis with bleeding during the on-demand phase, which was diagnosed following a knee bleed that started with trauma (7Dec2012). The subject felt that he had a response to the first treatment, but he developed recurrence of pain and swelling 24 hours later. He gave himself a second treatment (9Dec2012), which had a similar effect (slight improvement followed by recurrence). The investigator evaluated the subject on 12Dec2012 and diagnosed left knee synovitis, which was severe. The subject was hospitalized for management including IV and intra-articular corticosteroid and pain management. The subject was discharged 15Dec2012, “with significant improvement in condition”. The subject had another left knee bleed 3Jan2013, which he treated with a single (38 IU/kg) dose of IDELVION. The investigator evaluated the subject 10Jan2013 and reported no symptoms of left knee pain or joint swelling. The investigator interpreted the SAE, left knee synovitis, to be not related to IDELVION.

NOTE: Listing 16.2.5.4 (p. 358) describes treatment for this subject Dec 4, 15, and Jan 10 (x 2), i.e., no treatment on Dec 7, 9, or Jan. 3. Listing 16.2.5.7 (p. 442) reports an unscheduled uncorrected FIX concentration in this time period on Dec 12 = 30.7%.

WALDRON comment: Synovitis was a basis for exclusion at study entry due to the increased risk of recurrent bleeding. Trauma with bleeding in a joint with chronic hemarthrosis is a mechanism for development of synovitis. This event and course is within the expected range and I agree with the investigator that it was not related to IDELVION.

Subject (b) (6), a 55 year old male with a history of hepatitis and HIV and epilepsy had an “epileptic crisis” requiring hospitalization while enrolled in the on demand treatment arm. He had been treated for over 6 months and was switched to the prophylaxis arm. Three months later he developed persistent aphasia (acquired epileptic aphasia) and was hospitalized and treated with the antiepileptic levetiracetam. The episode resolved and the investigator judged the SAE as unrelated to IDELVION. The subject continued in the study on the prophylaxis regimen, and completed it.

WALDRON comment: I agreed with the investigator’s assessment.

Subject (b) (6), a 15 year old male had two SAEs that occurred during screening and prior to initiation of IDELVION. Therefore, these SAEs were not considered TEAEs. Both events were related to activity or trauma (iliopsoas bleed following a soccer game with no known trauma, and with “unknown” trauma to the right

thigh). The subject was hospitalized for both events, and they resolved. The subject subsequently initiated the study and completed it after 64 ED. He had no treatment emergent AEs, SAEs, or bleeding events reported during treatment with IDELVION.

Adverse Events Leading to Study Withdrawal

Two subjects (one in each study arm) experienced TEAEs that led to study withdrawal.

Subject (b) (6), a 22 year old male in the prophylaxis arm 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. Both the investigator and the Independent Data Monitoring Committee (IDMC) assessed the AE 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.

WALDRON comment: I reviewed the case narrative, and I agree with the IDMC interpretation.

Subject (b) (6), a 30 year old Japanese male, in the on-demand treatment arm experienced headache and eczema of mild severity in the third month of on-demand therapy. The events resolved on the fifth day without treatment. The investigator attributed these AEs to IDELVION, but the subject continued in the study. A second headache event of moderate severity occurred about one month later. This event was also assessed as related to IDELVION and the subject withdrew from the study that day. The timing of HA relative to the infusion was not reported.

WALDRON comment: Section 10.1, Tables 12-2, 12.4.2.3 and Listings 16.2.7.3 include 2 subjects (above) with AEs leading to withdrawal (section 12.3.1: "Only 2/63 (3.2%) subjects experienced an AE that led to IDELVION withdrawal.") Table 12-5 lists 3 subjects (new = (b) (6), below) in the category, related AE Withdrawal. After comparing the narratives, there is no apparent basis for this different classification between the third subject, who was classified as withdrawal by subject, and the other two subjects who withdrew.

Subject (b) (6), a 26 year old White male with a history of hemophilia B was dosed with 50 IU/kg of IDELVION for PK on 27Jun2012 and started prophylaxis on 11 Jul 2012 (37 IU/kg weekly). The subject began experiencing the AE of rash (reported term "exanthem") 10Sept2012 with five separate occurrences of the same AE. The subject was treated with the antihistamine dimetindene maleate administered in various forms (gel, drops, or oral tablets). In all incidences of the adverse event, the investigator reported exanthem as related to IDELVION, and on 08Jan2013, the subject chose to withdraw from the study.

Subject (b) (6), a 58 year old African-American male with a history of hemophilia B, HIV, hepatitis B and C had an ambiguous narrative regarding the reason for discontinuation. He started routine prophylaxis on 02Oct2012. On 22Oct2012 he reported a spontaneous muscle bleed in his right thigh/groin area. He treated himself with IDELVION 50IU/kg on 22Oct2012, his usual prophylaxis dose of 34IU/kg on 23Oct2012 and 30IU on 24Oct2012, although he was evaluated by the investigator who “saw no clinical signs of bleeding”. He had a CT scan that “showed no signs of bleeding in the hip”. He continued to report pain in his hip, and took 3311 IU BENEFIX on 27 and 28 Oct2012. The subject withdrew from the study on 29Oct2012 and the investigator attributed the thigh pain to arthritis rather than a joint bleed.

WALDRON comment: This subject’s initial report of thigh and groin pain indicates a soft tissue site of bleeding. The absence of physical exam findings does not exclude a deep muscle bleed. The CT report of no signs of bleeding in the hip also does not address the possibility of a soft tissue bleed as indicated by the patient’s initial report. Key missing components are the response to the use of the other rFIX product, or an MRI of the thigh and hip. A possible interpretation of this event is that the subject had a bleed, as the reason for thigh and groin pain, which was not effectively treated by 3 doses of IDELVION. Then the adverse event, drug ineffective, led to subject withdrawal.

6.1.12.3 Deaths

There were no deaths.

6.1.12.4 Nonfatal Serious Adverse Events

See above

6.1.12.5 Adverse Events of Special Interest (AESI)

The adverse events of special interest were hypersensitivity, inhibitor development, development of anti-drug antibodies, and thromboembolic events. There was a single AE of special interest, hypersensitivity. The IDMC reviewed the event (noted above related to subject (b) (6)) and interpreted the event as an infusion reaction.

WALDRON comment: I reviewed the submitted narrative of this event, and I agree with the IDMC interpretation.

6.1.12.6 Clinical Test Results

See the Safety section 7 for a discussion of concerns related to abnormal urinalysis testing in four subjects.

6.1.12.7 Dropouts and/or Discontinuations

Eight of 63 subjects did not complete the study. Three of these subjects were in the routine prophylaxis arm (3/40 = 7.5%). All three discontinued in association with adverse events. Five of 23 subjects in the on demand arm discontinued prior to completion, but only one was associated with AEs. The others were lost to follow-up (3) and one subject

was discontinued in association with a major protocol violation. Also see section 6.1.11.4.

6.1.13 Study Summary and Conclusions

This study achieved the agreed primary efficacy endpoint of greater than 50% reduction in the AsBR of subjects managed with an on demand regimen, when switched to a routine prophylaxis regimen. The primary safety endpoint of inhibitor development occurred in none of 63 subjects exposed to the IDELVION. The adverse reactions (adverse events related to IDELVION exposure) that did occur were rare and were not serious. The study demonstrated efficacy and safety for the indication, routine prophylaxis of bleeding episodes in previously treated patients with congenital Factor IX (FIX) deficiency. Previously untreated patients will be the subjects of a future trial.

In terms of efficacy, the indication, 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” (SAP 4.11.3.4, p. 23; FDA agreed to the SAP and this specific criteria in a written response to a meeting request May 12, 2014 (CRMTS #9332)). The subject experience in Study 3001 exceeded this criterion (mean 98.6%; lower limit 95% CI = 96.2%). There is a limitation in this evaluation since no major bleeds were reported. However, a bleed requiring treatment at the hemophilia center from the treating physician defined a major bleed, and included intracranial hemorrhage, gastrointestinal, throat and neck hemorrhage, and severe bleeding into a joint or muscle.

The indication, control and prevention of bleeding episodes in the perioperative setting, did not have pre-specified endpoints. An agreement was reached that favorable safety and efficacy data from at least 5 subjects in 10 elective major surgical procedures would be sufficient to support the proposed surgical indication. Protocol 3001 did not accrue this number of subjects and surgeries. The perioperative indication will be further discussed as part of the integrated summary of efficacy.

6.2 Pediatric Study of Previously Treated Patients CSL654_3002

6.2.1 Objectives (Primary, Secondary, etc.)

The primary objectives were to determine the PK of a single dose of IDELVION, and to evaluate the safety of IDELVION with respect to the development of inhibitors. Efficacy evaluations were among the secondary objectives, which included assessment of prevention of bleeding, evaluation of response to treatment of bleeding episodes, and the safety criteria of characterization of AEs and the development of (non-inhibiting) antibodies to IDELVION.

6.2.2 Design Overview

This was an open label, single arm study.

6.2.3 Population

This study used the same definitions for the safety, pharmacokinetic and efficacy populations as was used for Study 3001 (section 6.1.10.1).

6.2.4 Study Treatments or Agents Mandated by the Protocol

Subjects had IDELVION administered as a bolus IV injection at a rate of approximately 250 IU per minute or in approximately 5 to 15 minutes. Participants received weekly routine prophylaxis with 35-50 IU/kg, and the same dose was used for treatment of bleeding episodes. The protocol permitted a dose modification of 5-15 IU/kg to a maximum dose of 75 IU/kg, for subjects who developed a spontaneous bleeding episode.

6.2.5 Sites and Centers

Country of origin for the pediatric subjects in the study are summarized in the table below.

Country of Origin	< 6 yo	6- < 12 yo
Austria	0	2
Australia	0	2
Canada	1	0
Czech Republic	1	2
Germany	2	1
Spain	0	1
France	3	3
Israel	2	2
Italy	2	1
Russian Federation	1	1
Total	12	15

6.2.6 Surveillance/Monitoring

The schedule of monthly visits for Study 3002 is reproduced from the submission below. This schedule was appropriate for monitoring.

Assessments	Wk 1-2	Wk 4 ^a	Wk 8	Wk 12	Wk 18	Wk 24	Wk 30	Wk 36	Wk 42	≥50 EDs or EoS
Time Window		+1 wk	+1 wk	+1 wk	+1 wk	+1 wk	+1 wk	+1 wk	+1 wk	
Weight and height	50 IU/kg rIX-FP PK	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs		✓				✓				✓
Physical examination		✓				✓				✓
QoL questionnaires for both subject and parent										✓
Concomitant medication		On an ongoing basis								
Serum chemistry ^b and hematology		✓				✓				✓
Inhibitor against FIX		✓				✓				
Inhibitor against FIX, antibodies (rIX-FP and CHO)(CL) ^c				✓				✓		✓
Plasma FIX level (CL) ^c		✓		✓		✓		✓		
Plasma FIX level (LL) ^d				✓				✓		
Retain sample										✓
Investigator assessment		✓	✓	✓	✓	✓	✓	✓	✓	✓
Review subject eDiary		✓	✓	✓	✓	✓	✓	✓	✓	✓
Compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓
AE and SAE observation period	On an ongoing basis									

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CHO = Chinese hamster ovary; CL = central laboratory; ED = exposure day; eDiary = electronic diary; EoS = End-of-study; FIX = factor IX; LL = local laboratory; PK = pharmacokinetic; QoL = Quality of Life; rFIX = recombinant factor IX; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin; SAE = serious adverse event.

^aThe Week 4 visit was to occur at least 28 days after rIX-FP administration for PK (during Week 5) for subjects with body weight <15 kg.

^b Serum chemistry included liver and renal function tests (albumin, ALT, AST, ALP, total bilirubin, conjugated bilirubin, total protein, BUN, and creatinine).

^c The site visit was to occur within 24 hours prior to the next prophylaxis rIX-FP administration in order to test for trough level of FIX and inhibitor against FIX. It was recommended that the visit occur on the dosing day and that the subject receive the rIX-FP treatment during the site visit.

^d FIX activity could also be tested at the local laboratory, as optional tests.

6.2.7 Endpoints and Criteria for Study Success

The efficacy evaluations did not test a specific endpoint, but were descriptive of the experience with bleeding prevention and of the responses of bleeds to factor infusion. The primary safety objective was to evaluate the development of inhibitors. This was done by scheduled sampling at weeks 4, 12, 24, 36 and at end of study.

6.2.8 Statistical Considerations & Statistical Analysis Plan

Descriptive statistics were done for bleeding rates as an indicator of efficacy.

6.2.9 Study Population and Disposition

The enrolled population (12 subjects < 6 years old, and 15 subjects 6 to < 12 years old) were identical to the safety, PK, and efficacy populations. All subjects completed the study.

6.2.9.1 Demographics – Study 3002

WALDRON comment: This was a small pediatric study and races other than white were poorly represented among the study subjects, as were subjects of Hispanic ethnicity. Severe FIX deficiency is a rare disorder, and difficulty recruiting subjects, who are in the minority populations in countries from which the subjects were drawn, is expected. A role of race and ethnicity in response to factor replacement is not defined in severe FIX deficiency.

Demographics of Study 3002		
	< 6 yo N=12	6- < 12 yo N=15
Age (yr.)		
Median	3.5	8.0
Range	1, 5	6, 10
Race White	11	15
Race African American	1	0
Ethnicity not Hispanic	11	14
Weight (kg)		
Median	15.6	31.0
Range	11, 24.6	19.6, 51.6

6.2.9.2 Medical/Behavioral Characterization of the Enrolled Population

WALDRON comment: These histories were notable for the representation of children with chronic hemarthroses. Chronic hemarthrosis represents a greater challenge to hemostasis compared to uninvolved joints. The small number of affected joints is expected for young persons who received routine prophylaxis for the majority of their lives. These are summarized in the table below.

Study 3002 Enrolled Population Relevant Medical History

	< 6 yo		6 - < 12 yo	
	N	Events	N	Events
Surgical procedures	3	8	3	4
Musculoskeletal (active)	1	1	2	4
^a Neoplasm	2	2	0	0
^b Chronic hemarthrosis	2	2	2	2
ED prior to study entry				

Mean (SD)	199 (202)	547 (340)
Median	109	400
Range	53, 651	151, 1200

^aThese were benign dermal neoplasms.

^bEach subject had 1 involved joint of possible 6 involved joints per subject.

6.2.9.3 Subject Disposition

All subjects completed the study.

6.2.10 Efficacy Analyses

6.2.10.1 Bleeding rate and responses to bleeding treatment

The efficacy evaluations did not test a specific endpoint, but were descriptive of the experience with bleeding prevention and of the responses of bleeds to factor infusions. These evaluations are summarized in the table below.

Efficacy Evaluations Study 3002		
	< 6 yo	6- < 12 yo
ABR mean (SD)	4.2 (3.6)	3.4 (3.18)
ABR median	2.6	3.4
Range	0, 10.7	0, 9.5
Subjects with no bleeds	1 (8%)	3 (20%)
Subjects requiring treatment	1 (8%)	3 (20%)
AsBR mean (SD)	0.1 (0.3)	
AsBR median	0	0.8
Range	0, 1.0	0, 3.5
Subjects with no spontaneous bleeds	8 (67%)	6 (40%)
Subjects requiring treatment	11 (92%)	6 (40%)

Treatment Infusions

Age group	< 6 yo	6 - < 12 yo
All bleeding episodes requiring treatment	45 ^a	61
Number of infusions given n(%)		
1	40 (89)	54 (88.5)
2	5 (11)	4 (6.5)
>2 ^b	0	3 (5)
% bleeds treated < 2 infusions	100	95.1

^aTwo of the bleeds in this group fit the major bleed definition. They occurred in one subject at separate times; they were associated with falls and trauma to the hip (coded as the preferred term (PT), arthralgia). The patient was hospitalized for both events; one event was treated with 2 infusions, and the other with one infusion.

^bThese 3 subjects received 3 doses for treatment of bleeds. All bleeds were into joints and two of the bleeds were associated with trauma. The narratives did not report whether the third treatment was for ongoing symptoms or for sustained treatment of the bleeds. None of the subjects initiated treatment of the bleeds within the protocol specified 4 hours from initial detection. Two subjects did not follow the protocol regarding the timing of resumption of routine prophylaxis, resulting in ambiguity of the purpose of the third dose.

WALDRON comment: The mean ABR for the < 6 year olds is similar to the ABR reported by Manco-Johnson (2007) for the same age group with severe FVIII deficiency ($3.27 \pm SD = 6.24$), and it is similar to the finding among the adults in the 3001 study. This finding is consistent with effective therapy. The assessment of effectiveness is supported by the high proportion of subjects with no spontaneous bleeds requiring treatment during on-study, routine prophylaxis, and the high proportion of subjects whose bleeding events were treated with 2 or fewer infusions. The subjects and events which required 3 doses to treat a bleed were associated with trauma (2) and with event reports (2) that did not allow a distinction between continued treatment of a bleed or resumption of routine prophylaxis.

6.2.10.2 Analyses of Primary Endpoint(s)

The primary objective was the safety indicator of inhibitor development. No subject developed an inhibitor during the study.

6.2.10.3 Pharmacokinetic results

See the PK review for full results of the PK investigations. The applicant reported these PK values for the 0-<6 and 6 to < 12 year olds. Most PK values appear to be the similar except for a notable difference in a longer half-life in the older group

PK parameter (Unit) ^a	rIX-FP 50 IU/kg		
	0 to <6 years (N=12)	6 to <12 years (N=15)	Total (N=27)
	Mean (%CV) ^b		
IR (IU/dL)/(IU/kg)	0.951 (21.5)	1.06 (22.6)	1.01 (22.5)
C _{max} (IU/dL)	48.3 (19.0)	52.9 (23.2)	50.9 (21.8)
t _{max} (h)	0.59 (0.50 – 3.58)	0.58 (0.50 – 3.00)	0.58 (0.50 – 3.58)
AUC _{0-∞} (IU*h/dL)	4583 (33.2)	5123 (31.4)	4894 (32.0)
AUC _{last} (IU*h/dL)	3891 (32.2)	4369 (26.6)	4157 (29.0)
t _{1/2} (h)	89.6 (12.5)	92.8 (20.5)	91.4 (17.5)
CL (mL/h/kg) ^c	1.184 (27.8)	1.059 (28.5)	1.112 (28.2)
V _z (dL/kg) ^c	1.511 (26.2)	1.361 (20.4)	1.424 (23.5)
V _{ss} (dL/kg) ^c	1.425 (24.1)	1.316 (19.7)	1.362 (21.8)
MRT (h)	122.8 (14.2)	129.2 (19.0)	126.5 (17.1)

Abbreviations: AUC = area under the concentration time curve; CL = clearance; C_{max} = maximum concentration; %CV = percent coefficient of variation; FIX = factor IX; IR = incremental recovery; MRT = mean residence time; PK = pharmacokinetic; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin; t_{1/2} = half-life; t_{max} = time to reach maximum concentration; V_{ss} = volume of distribution at steady-state; V_z = volume of distribution ^aAll values are baseline-uncorrected, with the exception C_{max} and IR which are presented as baseline-corrected.

^bTabulated values are mean (%CV) except for t_{max} where median (minimum - maximum) are presented.

^cClearance and volume of distribution are normalized for body weight.

Note: For the parameters, AUC_{0-∞}, t_{1/2}, CL, V_z, V_{ss}, and MRT, the N for subjects <6 years of age was 11, and the total N was therefore 26.

6.2.11 Dropouts and/or Discontinuations

None

6.2.12 Safety Analyses

6.2.12.1 Methods

See section 6.2.7. Subject e-diaries and scheduled in person evaluations, including samples for inhibitor detection, were the method of detection for adverse events.

6.2.12.2 Overview of Adverse Events

Exposure of subjects in Study 3002 are summarized below.

	< 6 yo	6- <12 yo
	N=12	N=15
Median days on study	344	442
N > 50 EDs	10/12	15/15

Treatment emergent adverse events (TEAE) by system organ class (SOC) with > 5 events per SOC are summarized in the table below. The preferred terms that the highest proportion of subjects experienced were: fever, contusion, nasopharyngitis, arthralgia, cough, ear infection, gastroenteritis, and head injury.

SOC of TEAE	N = 27	Events
Infections and infestations	18	42
Injury, poisoning, and procedural complications	10	35
Gastrointestinal disorders	10	15
General disorders and administration site conditions	9	15
Musculoskeletal and connective tissue disorders	8	10
Respiratory, thoracic, and mediastinal disorders	7	10
Skin and subcutaneous tissue disorders	3	7

Each SOC is comprised of a set of preferred terms (PT).

WALDRON comment: The TEAE were expected events for this pediatric patient population with severe hemophilia observed closely over the period of approximately 1 year.

6.2.12.3 Deaths

No deaths occurred.

6.2.12.4 Nonfatal Serious Adverse Events

The 6 TEAE that met the serious criteria were all associated with trauma: arthralgia (2), forearm fracture, groin pain, head injury, and tongue injury. The investigators assessed the arthralgia events and the fracture as severe, and the others as moderate or mild. Hospitalization was the basis for the serious classification for all SAEs, except 1 arthralgia event. (See section 8.4.2 for details of SAEs). None of the TEAEs were associated with the use of IDELVION.

6.2.12.5 Adverse Events of Special Interest (AESI)

No subject developed a hypersensitivity or thromboembolic event.

6.2.12.6 Clinical Test Results

Hematology and serum chemistry values were assessed during the study. Urine chemistry and indicators of coagulation activation were not evaluated in this study as they were evaluated in Study 3001. Clinical laboratory abnormalities were identified during the course of the study. Four subjects had hematology lab findings that were judged clinically relevant. None of these findings were judged treatment related. Serum chemistry abnormalities were also noted.

WALDRON comment: I reviewed the individual lab abnormalities. None of the abnormalities were different from the expected findings for the study group (low MCV +/- anemia, and periods of elevated WBC number), or were mild and transient (chemistry).

6.2.12.7 Local tolerability

Subjects reported slight or very slight infusion reactions during the 1197 assessed infusions, except for one report of a moderate reaction. The investigators reported a single local tolerability AE (of 338 observed infusions), which was very slight pain.

6.2.12.8 Dropouts and/or Discontinuations

All subjects completed the study.

6.2.13 Study Summary and Conclusions

The results of this study demonstrated safety in previously treated pediatric subjects by demonstrating **no inhibitor development in 25 subjects who had at least 50 ED**. In addition, there were no TEAE attributable to drug exposure, including the events of special interest, thromboembolism and hypersensitivity reactions. The efficacy evaluation accomplished determination of PK parameters for < 12 year old subjects and showed similar rates of annual total bleeding and annual spontaneous bleeding compared to the adult subjects in Study 3001 on the routine prophylactic regimen.

6.3 Initial PK and dose finding study – Phase 1 Study CSL654_2001

6.3.1 Design and objectives

This study was the first use of IDELVION in humans. Its objectives were to assess safety by evaluating adverse events (AEs) and laboratory changes over time. The study also evaluated PK following a single IV dose of 50 IU/kg of IDELVION. An exploratory objective was evaluating PK with doses of 25 and 75 IU/kg IDELVION.

6.3.2 Population

The inclusion and exclusion criteria were the same criteria as the criteria for study 3001. One subject was < 18 years old. Of the 25 subjects enrolled and treated; 22 subjects had PK data analyzed. The study duration ranged from 2 to 4 months; the range of duration was due to variation by subject in the number of PK dose evaluations. All subjects completed the study.

6.3.3 Findings

6.3.3.1 Pharmacokinetics

Subjects (3) were excluded from the PK analysis if they had insufficient analyzable PK samples, or if they received additional FIX treatment for a bleed during the PK sampling period.

PK values from 13 subjects who received a single dose of 50 IU/kg IDELVION are summarized in the table below. Mean Half-life was noted to be 92 hours, suggesting potential for less frequent dosing.

Mean PK Results from Study 2001 (N=13) Single Dose 50 IU/kg	
*IR	1.38 IU/dL/IU/kg
*t _{1/2}	92 hr
*AUC _{0-inf}	7090 hr*IU/dL
*Cl	0.75 mL/hr/kg
MRT	127 hr
V _z	0.95 dl/kg

* baseline adjusted mean values

6.3.3.2 Safety

No SAE, events of special interest, or deaths occurred. Twenty-two TEAE occurred among 13 subjects. The SOC in which the AE most frequently occurred were musculoskeletal and connective tissue disorders SOC (7 events) and in the injury, poisoning and procedural complications SOC (5 events). The most commonly reported event was arthralgia (4 events reported by 3 subjects). The AEs judged possibly related by investigators were constipation, headache, feeling hot, and injection site erythema. All possibly related events resolved without intervention.

WALDRON comment: I agree with the investigators' assessments regarding relationship of AE to drug exposure, in that a causal relationship could not be excluded among the events judged possibly related.

6.3.4 Conclusions

The PK parameters indicate that less frequent dosing, compared to rFIX and plasma derived FIX, can achieve and maintain FIX levels for routine prophylaxis. The safety profile demonstrated adverse events similar to those expected for approved FIX replacement products.

6.4 Phase 1/2 study of PK, Safety, and Clinical Response - CSL654_2004

WALDRON comment: This study involved 2 centers and 17 subjects. Its principal purpose was safety and was utilized as a pilot study for the phase 3 study.

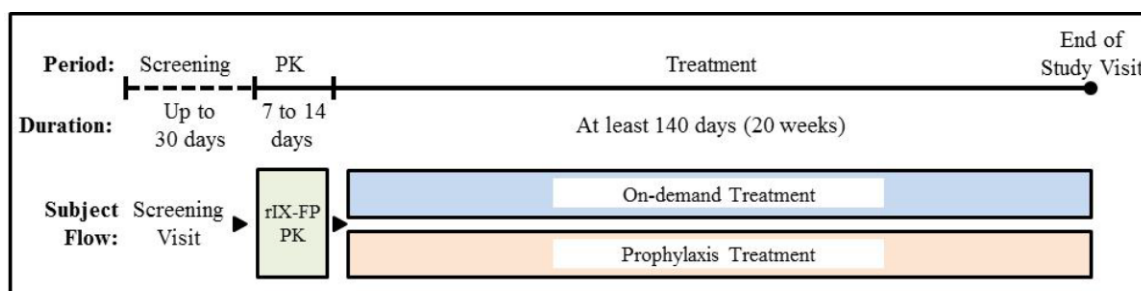
6.4.1 Design and objectives

Study CSL654 2004 was a two-center, prospective, open label, single arm study. The primary objective was to evaluate safety. The secondary objectives were to evaluate PK and the clinical response to routine prophylaxis.

6.4.2 Population

The inclusion and exclusion criteria were the same as Study 3001. The study enrolled 17 subjects. Fourteen were treated on the prophylaxis regimen and 3 subjects were treated on the on-demand regimen. Subjects were treated with the prophylaxis or on-demand regimen based on subject's preference and in agreement with the investigator.

6.4.3 Study treatments



The IDELVION dose used for PK was either 25 or 50 IU/kg. For routine prophylaxis subjects, weekly routine prophylactic treatment was initiated at a starting dose of IDELVION between 15 to 35 IU/kg, or at the Investigator's discretion, which may use PK data. For subjects on the on-demand regimen, the dose was determined by the subjects PK data, but was at least 25 IU/kg. Both groups could have doses adjusted to a maximum dose of 75 IU/kg.

6.4.4 Study monitoring

The Screening and PK phase schedule of assessments are reproduced from the submission below. These assessments appeared reasonable for the purposes of the study.

Schedule of Assessment: Prophylaxis or On-demand treatment phase

Assessments	Day 10 or Day 14	Week 4	Week 8 ¹	Week 12 ¹	Week 16 ^{1,4}	End of Study
Time Window	--	28d ± 7d	56d ± 7d	84d ± 7d	112d ± 7d	140d ± 7d
Concomitant therapy	On an ongoing basis					
Administration of rIX-FP at study site ²	✓					
Vital signs		✓		✓		✓
Physical examination		✓		✓		✓
Weight		✓	✓	✓	✓	✓
Serum chemistry & hematology		✓		✓		✓
Urinalysis		✓		✓		✓
Inhibitor against FIX (central & local lab)		✓		✓		✓
Antibodies against rIX-FP ³ (central lab)		✓		✓		✓
Plasma FIX level ⁵	(see Table 1)	✓	✓	✓	✓	✓
Retained sample ⁶ (central lab)						✓
Training for self-administration of rIX-FP	✓					
Investigator assessment		✓	✓	✓	✓	✓
Review subject diary		✓	✓	✓	✓	✓
Drug accountability		✓	✓	✓	✓	✓
AE and SAE observation period	On an ongoing basis					

Notes to Schedule of assessment tables

1. If patients receiving on-demand treatment do not experience a bleeding episode since the previous visit, the procedures at Weeks 8, 12 and 16 do not need to be performed.
2. Study subjects will be under medical supervision for at least 3 to 6 hours following the first two rIX-FP treatments.
3. A sample positive for antibodies against rIX-FP will be re-tested to discriminate between plasma-derived FIX, rFIX and albumin antibodies.
4. If a subject remains in the study past the Week 20 Visit, the Week 16 procedures should be performed every 4 weeks until the End of Study Visit.
5. FIX activity level may be tested at local laboratory after qualification.
6. Retained samples will be collected for potential later testing of virology and CHO cell antibodies.

6.4.5 Endpoints

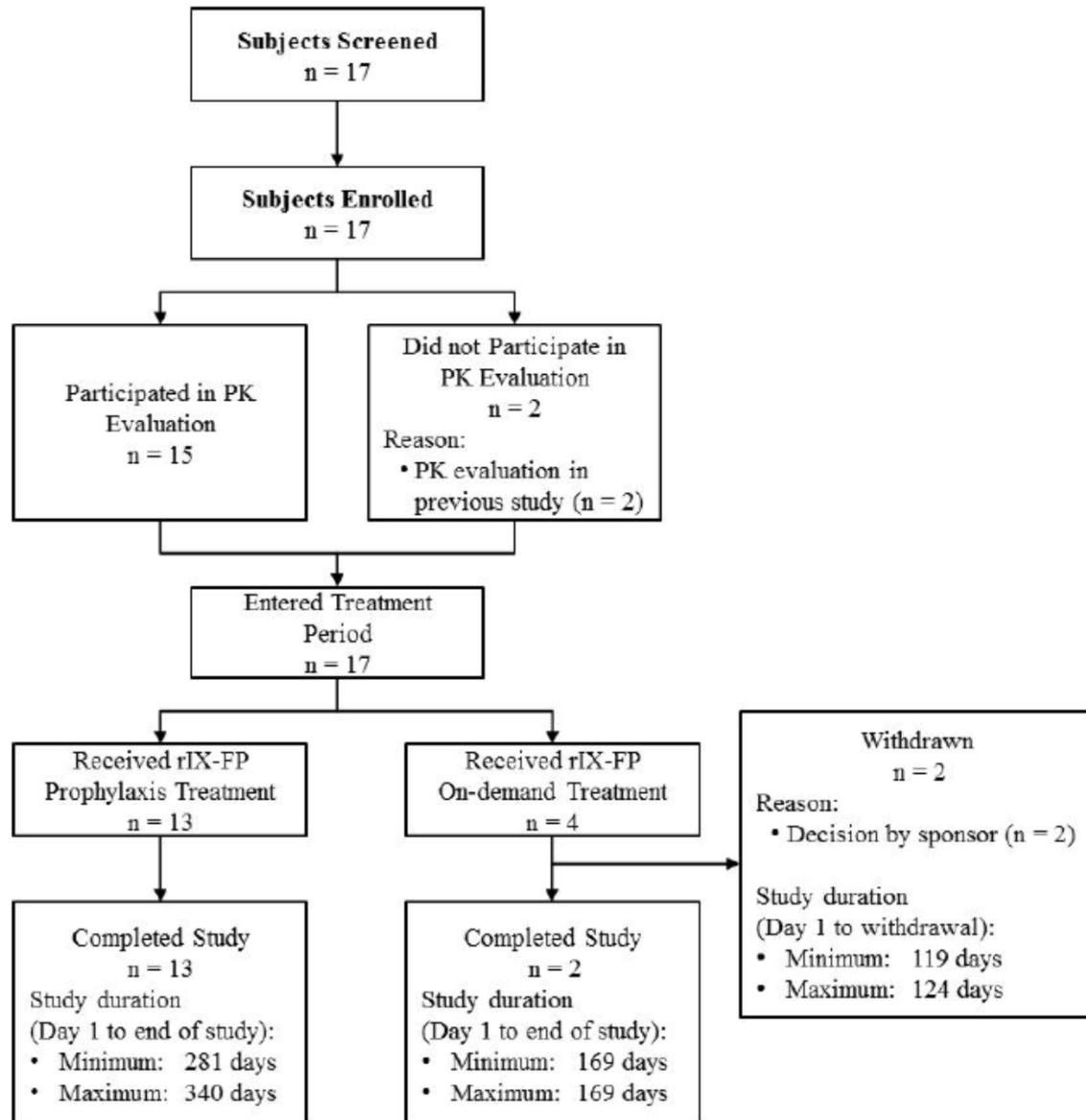
The primary endpoints of study 2004 were:

- The frequency of related AE to IDELVION over the course of the study
- Occurrence of inhibitors against FIX
- Occurrence of antibodies against IDELVION

The secondary endpoints of this study are determination of PK parameters for the enrolled population.

6.4.6 Study population and disposition

Disposition of the 17 subjects in study 2004 is summarized in the graphic below reproduced from the submission.



NOTE: Two subjects ((b) (6)) withdrew from the study (completion of < 140 days) in order to participate in study 3001.

WALDRON comment: The 15 of 17 study completion rate is consistent with a hemophilia replacement product that was well tolerated, and performed in prevention and treatment of bleeds as expected by these PTPs. The 2 subjects who discontinued had ~120 days on study, and departed the study to enroll in Study 3001.

6.4.7 PK and Efficacy analysis

6.4.7.1 PK findings

The data in the table below are means for the prophylaxis population following a single infusion of 25 IU/kg (N=15). The mean half-life of IDELVION in this study was slightly shorter at 69 hours.

Mean PK Results of Study 2004 (N=15)	
Single dose 25 IU/kg	
*IR	1.45 IU/dL/IU/kg
*t _{1/2}	69 hr
*AUC _{0-inf}	2698 hr*IU/dL
*Cl	0.96 mL/hr/kg
Vz	0.87 dL/kg
*FIX activity day 10	3.88

* baseline corrected

6.4.7.2 Prevention and control of bleeding

Results of the control of bleeding both for routine prophylaxis and on demand treatment are summarized in the table below.

Results for reduction in ABR Study 2004		
	Routine prophylaxis (N=13)	On-demand (N=4)
ABR mean (SD)	4.4 (4.7)	26.8 (2.7)
ABR median	2.3	26.9
AsBR mean (SD)	1.3 (1.5)	21.7 (4.0)
AsBR median	1.1	22.2
	Efficacy population N=17	
% bleeds ≤ 2 infusions (N=85)	100 (1 infusion=89; 2 infusions=11)	

WALDRON comment: The on-demand population had a greater reported ABR prior to study enrollment than the prophylaxis group. This history confounds the observation of the lower ABR observed with prophylaxis compared to on-demand treatment. All treated bleeds were classified as minor or moderate.

6.4.8 Safety Analysis

Exposure

Thirteen subjects on the prophylaxis regimen had 593 prophylactic exposures (mean = 45. 6). Nine of 13 subjects had > 50 ED. The 4 subjects in the on-demand group had a range of ED of 12-14.

Adverse events

No SAEs, no AE leading to withdrawal, and no deaths occurred. There were no hypersensitivity or thromboembolic events. No inhibitors were detected.

Forty-six AE were reported among 14 of 17 subjects. The majority (93%) of the AE were mild. The most common PTs were: arthralgia (11), upper respiratory tract infection (4), headache (3), injection site swelling (3), and 2 each for synovitis, hand fracture, and laceration. The only AE judged related to IDELVION by the applicant were local reactions (injection site swelling (3) and ecchymosis (1)).

WALDRON comment: I reviewed the AEs and, within the limits of the reporting, I agree with the attributions of relatedness. The product was well tolerated in this study.

6.4.9 Summary

Study 2004 developed data in a small number (17) of previously treated subjects that demonstrated a low risk of use. No SAE and no AEs of interest occurred. The 4 AE that were considered by the applicant to be related to the IDELVION were mild and self-limited. Two subjects withdrew, but to enroll in the phase 3 Study 3001. The 7 day interval of prophylactic administration yielded an ABR and AsBR similar to findings in other studies of prophylaxis with similar or more frequent administration. All treated bleeds (85) were managed with 1 or 2 infusions, consistent with effective treatment of the bleeds.

6.5 Phase 3b Extension Study - CSL654_3003 – (Ongoing at time of review)

6.5.1 Design and objectives

This is an open-label multi-center study with three components. The first component is an extension study to collect additional safety data from subjects enrolled in studies 3001 and 3002. The second is to evaluate patients in the perioperative and postoperative periods, which may include subjects who did not participate in other trials. The third is to evaluate the safety and efficacy in previously untreated patients (PUPs) with severe FIX deficiency. The data lock for the interim report of this ongoing study was January 9, 2015. The planned individual study duration is 100 cumulative ED on all IDELVION studies; this is expected to occur within 3 years.

6.5.2 Population

The target accrual is 115, including 20 PUPs. The extension and the perioperative study have an age range of 2-65. The PUPs study excludes subjects older than 18. The majority

of subjects will enroll from another IDELVION study. Participation in the previous trial is the inclusion criterion for those subjects. The inclusion criteria for subjects undergoing surgery who have not participated in an IDELVION study are the same as for the surgical sub-study of Study 3001.

The PUP study has the following inclusion and exclusion criteria that appear reasonable for the purposes of the study:

Inclusion Criteria

- Male, up to 18 years of age
- Documented severe hemophilia B (FIX activity of $\leq 2\%$), or confirmed at screening by local or central laboratory
- Subjects who have never been treated with FIX clotting factor products (except previous exposure to blood components)
- No confirmed history of FIX inhibitor formation

Exclusion Criteria

- Known congenital or acquired coagulation disorder other than congenital FIX deficiency (except for vitamin K deficiency of the newborn)
- Known kidney or liver dysfunction or any condition which, in the investigator's opinion, place the patient at unjustifiable risk

6.5.3 Study treatments

The IDELVION dose is based on the previous experience for those subjects who participated in earlier studies. The target FIX activity level for routine prophylaxis is $>2\%$, but optimally between 5% and 15%. The total dose of IDELVION administered for routine prophylaxis over a 28-day period was not to exceed 250 IU/kg, and the targeted FIX activity trough level was not to be $\geq 20\%$. The recommended IDELVION doses for on-demand treatment were 35 to 75 IU/kg.

At 6 month intervals from a subject's start of Study 3003 the Investigator could choose to change the treatment interval to a 7, 10, or 14-day treatment interval, based on an assessment of efficacy, safety, subject treatment compliance, and/or subject preference. Subjects ≥ 18 years of age could also be switched to a (b) (4) after completing ≥ 6 months of a 14-day prophylaxis regimen and after completing a PK evaluation with 100 IU/kg IDELVION. During each 6 month treatment period, the treatment interval was to remain the same unless a subject safety concern arose. A preventive dose (35-50 IU/kg) before vigorous physical activity or physical therapy was a new category in Study 3003. A dose under this category could be administered only one time per month. If activity or therapy required more frequent dosing, then the routine prophylaxis dose and or schedule was to be modified.

WALDRON comment: The previous PK data support the possibility of (b) (4) dosing for select subjects, and the above approach implies appropriate selection.

PUPs were encouraged to start weekly prophylaxis at the beginning of the study, but could also use an on-demand regimen only and/or intermittent prophylaxis (treatment given to prevent bleeding for short periods of time), or preventative treatment during the first 12 months. The starting dose was 25 to 50 IU/kg. The dose could be increased up to 75 IU/kg ; dose adjustments were based on the subject's clinical response, PK information, or FIX trough activity. After no more than 12 months, all PUPs would receive routine prophylaxis using a 7-day treatment interval for the rest of the study.

The treatment plan for the surgery sub-study was the same as that in Study 3001.

6.5.4 Study monitoring

The study monitoring for those enrolled in previous studies is similar to the monitoring during earlier studies. The monitoring for the PUP subjects is as shown in the table below.

Assessments	Screen ^A (up to 28 days)	(PK ^B)				Months ^C (±1 week)												Months (±2 week)						50 EDs	EoS			
		Prior dose	30±5 min	Day 3	Day 7	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	27	30			33		
Informed consent	X																											
Demographics	X																											
Eligibility assessment	X																											
Relevant medical history	X																											
Physical examination	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Vital signs ^D	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Body weight and height	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Biochemistry&hematology ^E	X ^F																X			X					X			
Inhibitors against FIX (CL)	X ^F					X	X	X	X	X	X			X			X		X		X			X	X			
Ab to rIX-FP/CHO (CL) ^G	X ^F										X						X			X				X	X			
Plasma FIX activity (CL) ^H		X	X	X	X	X	X	X			X						X			X					X			
Plasma FIX activity (LL)	X ^I																											
Retention blood sample ^J		X																							X			
Dispense subject eDiary ^K																	X											
Review subject eDiary						<----- On an ongoing basis during eDiary usage ----->																			X			
Review treatment efficacy						<----- On an ongoing basis ----->																			X			
Adverse events	<----- On an ongoing basis ----->																											
Concomitant therapy	<----- On an ongoing basis ----->																											

Ab = antibody; CHO = Chinese hamster ovary; CL = central laboratory; ED = exposure day; eDiary = electronic diary; FIX = coagulation factor IX; LL = local laboratory; pdFIX = plasma-derived coagulation factor IX; PK = pharmacokinetic(s); rFIX = recombinant coagulation factor IX; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin; EoS=End of Study.

Notes

Subjects are treated in the study center or medical facility under medical supervision during the initial 10 to 20 treatments with IDELVION. The first 2 injections have to be monitored on-site for at least 3 hours.

- Tests that require blood sample for screening period (from ICF day to Day 1 prior to dose) may be divided over multiple days or combined with Day 1 tests. The screening day may be the same day as the day of the first dose of rIX-FP (either on-demand, prophylaxis, or PK dose).
- PK may start at Day 1 as the first dose or/and during the study after ≥7 days washout from the previous rIX-FP dose, when the subject is in non-bleeding state.
- If subjects receive treatment for less than 3 doses per month, they may omit the study center visit(s) until they received ≈5 doses.
- Vital signs include blood pressure, temperature, and heart rate.

- Including liver and renal function test (albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, direct bilirubin, protein, blood urea nitrogen or urea, and creatinine).
- Documented biochemistry and hematology results from 6 months prior to Screening are acceptable; otherwise, samples may be collected during the screening period or at Day 1. Samples for antibodies/inhibitor have to be collected during the screening period or prior to first dose of rIX-FP.
- A sample that tested positive for antibodies against rIX-FP is retested to discriminate between pdFIX, rFIX, and albumin antibodies.
- Optional samples at Days 3 or 7 of PK assessment, or during Month 1, 2, or 3 for FIX activity if feasible.
- FIX activity tested at local laboratory if no previous FIX data are available in medical records.
- Retention samples are collected prior to the first dose of rIX-FP for potential serology testing at a later date.
- K: Subject eDiary dispensed once caregiver was trained to administer rIX-FP at home, but not prior to receiving a minimum of 10 injections at the study center or medical facility under medical supervision.

WALDRON comment: The monitoring, including the medical supervision with (at least) the first 10 treatments is appropriate for FIX deficient PUPs due to the increased risk of allergic or hypersensitivity reactions.

6.5.5 Endpoints

This study did not have a primary efficacy endpoint. The primary safety endpoint was inhibitor development. The secondary endpoint was description and incidence of AE. The surgical sub-study has the same endpoints as were used in the 3001 study.

6.5.6 Study population

Ongoing. No subject had completed the study at the time of the January 9, 2015 data cut-off.

6.5.7 Safety analysis

Ongoing. At the time of data cut-off no inhibitors had been identified among the PTP subjects. The PUP subjects had not begun treatment.

See section 8.4.3 for description of 1 subject who discontinued the study associated with an event unlikely related to IDELVION.

See integrated overview of efficacy subpopulation (Section 7.1.7) for surgery sub-study subjects enrolled in Study 3003.

6.5.8 Summary

Study 3003 is ongoing. It is designed to complete the accrual of 100 exposure days (ED) to fully assess the IDELVION safety profile among subjects enrolled in earlier trials, to accumulate the agreed minimum number of perioperative subjects (5) and major procedures (10) for consideration of a surgical indication, and to evaluate the safety of IDELVION in previously untreated patients.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Routine prophylaxis to reduce the frequency of bleeding episodes

7.1.1 Methods of Integration

Study 3001 provided the majority of all efficacy data with 63 subjects on study for a median of 316 days. All of the primary efficacy population was included within Study 3001. Therefore, the analysis of the efficacy data of Study 3001 (section 6.1.11) comprises the majority of the efficacy evaluation. Study 2004 provides some additional efficacy data on routine prophylaxis, and Study 3002 provides data for subjects < 12 years old. At completion, Study 3003 should provide additional efficacy data for perioperative management and a small contribution to the data on the effectiveness of control of bleeding. All individual studies are described in section 6.

The within subject comparisons, between AsBR during the on-demand regimen and during the routine prophylaxis regimen, in Study 3001 comprise the primary efficacy analysis (section 6.1.1). Study 2004 also compared subjects during on-demand and routine prophylaxis. However, that comparison was confounded due to the groups being separate and not randomized, and the subject number in the on-demand arm (n=4) was smaller than the routine prophylaxis arm (n=13). Subjects were treated on the regimen that they used prior to entering the trial, and they remained on that regimen. Results for the Study 2004 comparison between on-demand and prophylaxis groups are shown in the table below.

Study 2004 data for comparison of on-demand treatment with routine prophylaxis

	2004	
	On-demand (N=4)	Weekly Prophylaxis (N=13)
Duration of treatment period (days)		
N	4	13
Mean	131.3	314.7
SD	27.50	20.13
Median	132.5	322.0
Q1, Q3	107.5, 155.0	315, 323
Min, Max	105, 155	259, 355
Total number of subjects with spontaneous bleeding episodes requiring treatment (N[%])	4 (100)	7 (53.8)
Annualized spontaneous bleeding rate (bleeding episodes/year/subject)		
N	4	13
Mean	21.740	1.255
SD	3.9983	1.4967
Median	22.218	1.134
Q1, Q3	18.737, 24.743	0.000, 2.269
Min, Max	16.60, 25.92	0, 4.52

Study 2004 data (ISE Nov. 12 version Table 3-5) demonstrated an AsBR for subjects on the routine prophylaxis regimen that was 94.2% lower than the AsBR of the subjects treated with the on-demand regimen. This is supportive of the finding on Study 3001 (section 6.1.11) of 93.5% reduction in AsBR in the primary efficacy analysis.

7.1.5 Analysis of Secondary Endpoint(s)

7.1.5.1 On-demand treatment of bleeding episodes

Study 3001 subjects contributed 81% (358/443) of the bleeding events requiring treatment. The remainder of events (N=85) was contributed by the Study 2004 subjects. The success definition (treatment with 2 or fewer doses) was achieved by 98.6% of the Study 3001 subjects and 98.9% of the combined Study 2004, and 3001 subjects. (Refer to ISE, November 12 version, Table 3-9). It is anticipated that Study 3003 will contribute additional data on number of infusions to treat bleeding episodes. Control of bleeding in

the Study 3002 pediatric patients had a similar proportion treated with 2 or fewer infusions.

WALDRON comment: The finding across studies of > 95% of bleeds treated with 2 or fewer infusions indicates IDELVION is effective for the on demand treatment of mild and moderate bleeding episodes.

7.1.7 Subpopulations

7.1.7.1 Subjects undergoing surgery – Perioperative Management of Bleeding

See section 6.1.4 for the protocol plan for treatment of these subjects. The approach used in Study 3001, was the same treatment approach used in Studies 3002 and 3003 that also acquired data on perioperative management. The applicant reported results from these three studies on the use of IDELVION in 15 subjects undergoing procedures with a risk of bleeding (see the table below) which included 3 subjects < 12 years old. All three studies used a consistent definition of major surgery, i.e., “a surgical procedure that involves anesthesia (general, spinal, epidural or regional block) or respiratory assistance (including but not limited to orthopedic and cardiac surgery)”. The reported outcomes of surgeries were the surgeon’s assessment of hemostasis, and a comparison of the surgeon’s forecast of estimated blood loss (EBL) prior to surgery with the reported EBL after surgery. The use of blood products and FIX levels prior to a repeat dose of IDELVION were also reported.

WALDRON comment: The above definition of major surgery included no aspect of bleeding risk. Patients undergoing invasive procedures may have anesthesia due to age or developmental considerations, and emotional/anxiety concerns may also influence the decision. Thus, subjects undergoing endoscopy or tooth extraction may fit the major surgery category, when their bleeding risk is minimal. This is illustrated in 3 cases, which fit the major surgical criteria, but had EBL of < 5 ml. Classification of surgeries by anatomic location and by procedure, e.g. total knee replacement, may provide a more uniform approach to assessing the hemostatic challenge and outcome.

As of the cutoff date of January 9, 2015, 15 surgeries had been performed on 13 subjects including 3 in subjects < 12 years of age. Investigator assessment of all surgeries in the development program are summarized in the table below, reproduced from the submission in the Summary of Clinical Efficacy Table 3-5.

Perioperative Hemostasis Response with IDELVION in the Surgical Substudies of Studies 3001, 3002, and 3003

Surgical procedures	Study number	Subject number	Assessment of hemostasis response		
			Wound closure (0 h)	72 hours/ discharge ^a	EOS/ POD 14
Double mastectomy	3001	(b) (6)	Excellent	Excellent	Excellent
Total knee replacement	3001	(b) (6)	Excellent	Excellent	Excellent
Total knee replacement	3001	(b) (6)	Excellent	Excellent	Excellent
Hemorrhoidectomy	3001	(b) (6)	Excellent	Excellent	Excellent
Wisdom tooth extraction (1 tooth)	3001	(b) (6)	Excellent	Good	Excellent
Tooth extraction (1 tooth)	3001	(b) (6)	Excellent	NR	Excellent
Tooth extraction (4 teeth)	3002	(b) (6)	NR	NR	Good ^b
Tooth extraction (2 teeth)	3002	(b) (6)	Excellent	NR	Excellent ^b
Excision of pigmental nevus – lumbar area	3003	(b) (6)	NR	Excellent	NR
Rhinoplasty, submucosal resection, and inferior turbinectomy	3003	(b) (6)	Excellent	Excellent	NR
Endoscopic mucosal resection	3003	(b) (6)	Excellent	Excellent	NR
Root canal	3003	(b) (6)	NR	NR	Excellent ^c
Right ankle arthroplasty	3003	(b) (6)	Excellent	Excellent	NR
Total knee replacement, left	3003	(b) (6)	Good	NR	NR
Total knee replacement, right	3003	(b) (6)	Excellent	Excellent	Excellent ^c

Abbreviations: EOS = end of study; h = hours; NR = not reported; POD = postoperative day; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin.

^a Whichever occurred first.

^b Assessment of hemostasis response provided on POD 7.

^c Overall assessment of hemostasis response; timing of assessment not available.

Note: Data based on cutoff of 09 January 2015. Final results will be reported in a full Clinical Study Report. Source: [Module 2.5, Sequence 0000, Section 2.5.4.2.3](#) and [Study 3003 abbreviated CSR, Tables 11-2 and 14.4.1 and Listing 16.2.6.4](#).

The procedures classified as major included 4 total knee replacements. All other procedures were single events. The CSR for Study 3001 (Listing 16.2.6.8) stated that the average intraoperative blood loss for this procedure was 1500 ml. A 2015 study reported mean blood loss of 695 ml in TKR subjects (Seo JG, J Arthroplasty 2014). The EBL for the 4 joint replacement surgeries had a range of 50 to 1110 ml.

WALDRON Comment: The reports of bleeding during the surgical procedures and follow-up are consistent with intraoperative and postoperative bleeding that is within the expected range for these procedures. The investigators consistently rated the hemostasis as effective.

Procedures with an amount of blood loss above some threshold, e.g. at least 50 ml in adults, demonstrate a hemostatic challenge, whereas procedures with minimal blood loss, e.g., < 10 ml leave uncertainty how well the invasive procedures test the ability of the product to restore FIX function and hemostatic efficacy. Of the 9 procedures that fit the protocol definition of major surgeries, 6 had EBL \geq 50 ml and 3 had EBL < 10 ml. The applicant should be encouraged to accrue subjects in whom the efficacy of IDELVION in perioperative management can continue to be tested.

7.1.8 Persistence of Efficacy

There were no reports of change of efficacy with time as an indicator of persistence of efficacy. Study 3001 included a repeat assessment of PK at week 26 (Study 3001 CSR Table 11-9) for arm 1 subjects. This analysis showed no change of statistical significance in the PK parameters between the initial and week 26 time points. Since FIX activity is a surrogate of effectiveness, this absence of change in PK with time is a reasonable indicator of persistence of efficacy and supports the clinical observation.

7.1.10 Additional Efficacy Issues/Analyses

None

7.1.11 Efficacy Conclusions

Study 3001 achieved the agreed primary efficacy endpoint of greater than 50% reduction in the annual spontaneous bleeding rate (AsBR) among subjects managed with an on demand regimen, when switched to a seven day routine prophylaxis (RP) regimen (mean reduction = 93.49% (SD = 8.03). The study demonstrated efficacy for the indication, RP of bleeding episodes in PTPs with congenital FIX deficiency.

The indication, 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. Across all studies > 98% of bleeds were treated with 1 or 2 doses.

WALDRON comment: The indication, control and prevention of bleeding episodes in the perioperative setting, included 7 subjects undergoing 9 major procedures across all trials. This is less than the prespecified agreed number, of 5 subjects with 10 elective major surgical procedures, necessary to evaluate efficacy in the perioperative setting. The applicant plans to submit another supplement to the BLA in September 2015, which may provide additional subjects with perioperative management.

CHAZIN comment: Despite the low amount of blood loss, IDELVION was used successfully in all surgeries and the applicant has provided enough evidence to support approving the perioperative indication.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

See section 6.1.7 for a summary of the monitoring plan for Study 3001. All five clinical trials incorporated monitoring for inhibitor development, the primary safety endpoint, and for adverse events. Study 3001, included a comprehensive laboratory monitoring plan, in addition to the clinical monitoring.

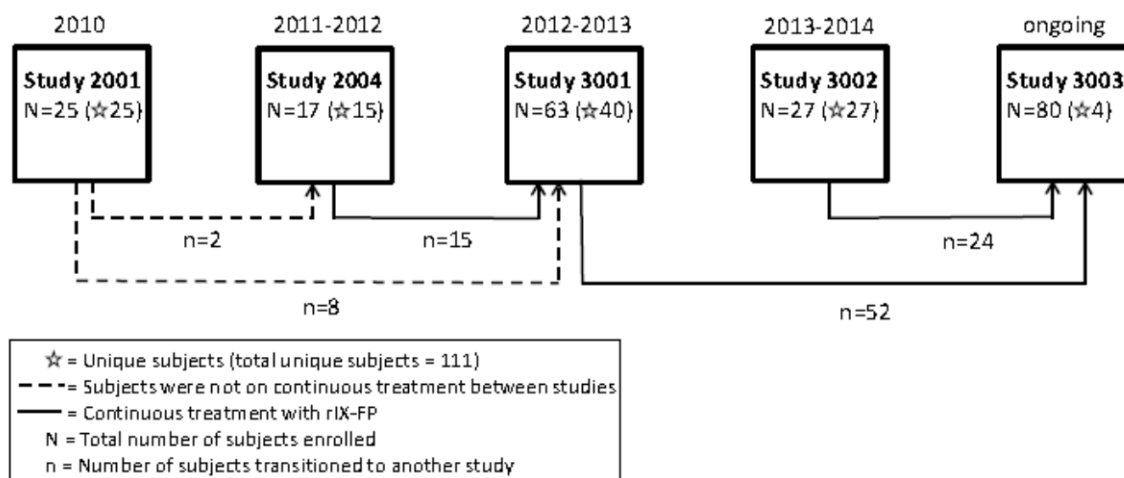
8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

All clinical trials evaluated safety. See section 6.1.10.1 for the definition of the safety population.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The design of the 5 clinical studies allowed for each subject to participate in more than one trial. The figure below summarizes the relationship of the subjects who entered one study and then participated in an additional study. The overall safety population included 111 unique subjects as noted by the “star” and number within parentheses in the figure below.



8.2.2.1 Exposure to IDELVION in the Overall Safety Population

The overall safety population exposures are summarized in the table below (derived from SCS table 1-3).

Overall safety population	N=111
Exposure days (ED)	
Mean (SD)	74.4 (49)
Exposure distribution	
in population n (%)	
≥ 50 ED	82 (73.9)
> 100 ED	35 (31.5)
Total ED all subjects	8257
Duration of exposure (days)	
Mean (range)	614.8 (395)

8.2.2.2 Demographic Characteristics of Overall Safety Population

The demographic characteristics of the overall safety population are summarized in the table below, derived from SCS table 1-4)

Demographics of the Safety Population	
N=111	
Age in years	
Mean (SD)	26.5 (16.6)
Race n (%)	
White	95 (86)
Asian	12 (11)
African	3 (2.7)
Other	1 (0.9)

Medical History

Selected medical history of the overall safety population is summarized in the table below derived from SCS table 1-5.

Virus test positive n (%)	
HBV	3 (2.7)
HCV	26 (23.4)
HIV	12 (10.8)
Joint disorders n (%)	
Hemophilic arthropathy	26 (23.4)
Arthropathy	9 (8.1)
Synovitis	5 (4.5)
Joint ROM decreased	3 (2.7)
Previous ED	
Mean	653
Median	500
Bleeding episodes in previous 12 months	
Mean(SD)	12.4(20)

WALDRON comment: The medical histories are in general representative of the target population, and the important chronic infectious and musculoskeletal disorders are well represented.

8.2.3 Categorization of Adverse Events

Categories of treatment emergent adverse events by SOC reported by > 5% of subjects in the overall safety population is noted in the table below derived from the ISS table 14.3.2.1 including information from the 120 day safety summary.

System Organ Class (SOC) of TEAE by SOC Reported for >5% of subjects in the Overall Safety Population (N=111)	
SOC	Number of events
Infections and Infestations	141
Musculoskeletal and Connective Tissue	104
Injury, Poisoning and Procedural Complications	87
Nervous system	61
General and administration site	38
Skin	24
Respiratory	19

Waldron comment: The SOC distribution of adverse events judged unrelated to drug exposure is as expected for a population observed over a period of time with a history of severe hemophilia.

8.3 Safety Results

8.3.1 Deaths

No deaths occurred among the study subjects.

8.3.2 Nonfatal Serious Adverse Events

Summary of Treatment-Emergent Adverse in the Overall Safety Population			
	Subjects	Events	
Any TEAE	94	562	
Any related TEAE	9	16	
Any TE SAE	6	8	
Any related TE SAE	0		
Any TEAE leading to withdrawal	3	3	
Any fatal TEAE	0		
TEAEs Severity (maximum)		N=94	
	Subjects	Events	% by severity
Mild	55	468	83.3
Moderate	33	86	15.3
Severe	6	8	1.4

Waldron comment: The totals of any TEAE (662) in the ISS Tables 12-1 and 12-2 are incorrect. The correct total (562) is in ISS Tables 14.3.1 and 14.3.2.1.

Related TEAE: See section 6.1.12 for additional information on the 5 subjects with 11 events in Study 3001. The remaining related TEAE were among 3 subjects who had 4 events in Study 2001. The events were constipation in one subject, one subject with mild injection site erythema, starting at 30 minutes and resolving at 180 minutes, and one subject with mild headache and feeling hot that began 50 minutes after the infusion and lasted 10 minutes. The discrepancy with the above table (8 vs 9 subjects and 15 vs 16 events) is due to 1 subject who had an event that overlapped participation in 2 trials, and had the event counted in both trials.

SAEs: See section 6.1.12 for SAEs in the 3001 study (3 subjects had 4 events - 2 subjects had 2 TE SAE, 1 subject had 2 SAEs occur during screening).

Study 3002

The following narratives are summarized from the clinical study report from Study 3002. **Study 3002 total** = 4 subjects had 6 serious TEAE. One subject had 1 SAE that occurred prior to treatment initiation and is included here for completeness.

- Subject (b) (6) - A 5-year-old White male subject fell on ice with subsequent pain in hip. Interval from injury to infusion was 16 hr. MRI showed bilateral hip hemarthroses. The subject was admitted for pain control, prednisone, and daily IDELVION treatment. The event (injury) was rated as an SAE. The same patient had a second severe and SAE of arthralgia associated with a fall in the snow and subsequent hip pain. An ultrasound of the left hip revealed a new left hip hemarthrosis. His dose of IDELVION was unchanged and the investigator noted the efficacy of IDELVION to be good.
- Subject (b) (6) - A 5-year-old White male, with a history of Hemophilia B on BENEFIX, had a head injury before his 1st dose of IDELVION. He was admitted for overnight observation. No bleeding was observed. The severity of the event (head trauma) was rated moderate. *WALDRON comment: This occurred prior to 1st dose, so it is not technically a TE SAE*
- Subject (b) (6) - An 8 year old Hispanic male with severe hemophilia B developed acute groin pain while cycling. He received IDELVION 18 hr after onset of pain, but the pain persisted. The investigator gave him an 85 IU/kg dose and he had immediate pain relief. He was hospitalized overnight for observation and an ultrasound showed normal iliopsoas muscles. The severity was rated mild. The same patient had a second event of head trauma. He was treated the same day with 2 mL tranexamic acid 4 times daily for three days along with a maintenance dose of IDELVION (59IU/kg) with good efficacy.; no bleed was detected by imaging. He was observed in the hospital overnight. Severity was rated moderate and the subject continued in the study. Six months later he had an SAE of head trauma and was dosed with 44.3 IU/kg for the injury. The investigator assessed the SAE as mild, not related to IDELVION and the subject continued in the study.

- Subject (b) (6) - A 6 year old White male with severe hemophilia B had a “deep tongue injury” on 6Mar 2014, three days after beginning routine prophylaxis with IDELVION. He was treated with 46.3 IU/kg of IDELVION and the following day he had sutures placed to stop the bleeding. Due to slow healing, he had another suture placed three days later along with with his routine prophylaxis dose of IDELVION. Due to continued bleeding, on 13Mar2014 he was placed under general anesthesia and all sutures were removed and replaced. He was hospitalized for management of this event until 20Mar2014. The tongue injury SAE resolved on 22Apr2014. The investigator rated it moderate in severity but not related to IDELVION. *CHAZIN Comment: This SAE is notable for continued bleeding in a patient on routine prophylaxis and despite treatment with IDELVION and minor surgery on his tongue, he continued to bleed for several weeks requiring one week of hospitalization. This SAE narrative indicates that IDELVION was not effective in treating oral bleeding from deep tongue injury. It is also possible that the dosing was subtherapeutic as it was never given any higher than his routine prophylaxis dose but only more frequently.*
- Subject (b) (6) - A 5 year old White male with severe hemophilia B fell and fractured his left forearm. The repair required closed reduction and fixation with wires and hospitalization. He received a waiver to allow continued study participation. During the course of this event (22Apr2014 to 26May2014) he received BENEFIX at varying intervals. The event occurred Apr 20 and was declared resolved 24Apr2014. The reason for continued BENEFIX exposure beyond the declared date for resolution was not reported. The event was rated severe but the subject reentered the study on 30May2014. *CHAZIN comment: This narrative notes a waiver to discontinue routine prophylaxis with IDELVION in order to be treated for an acute surgical emergency. Continuing on IDELVION would not be appropriate as it is an investigational treatment. Having the subject reenter the study is consistent with a protocol violation, but considering the rarity of this disease and the very small numbers of subjects in this age category (N=12), the applicant may have had little choice but to have the subject restart his prophylaxis treatment with IDELVION.*

Study 3003: Two subjects had TE SAEs as summarized in the narratives below.

- Subject (b) (6) - A 56 year old Asian male with a hemophilia B and a PMH of hepatitis C, who had been on a stable dose of 75 IU/kg every 14 days for routine prophylaxis from Study 3001 had an SAE of weight loss (3 kg) and occult blood in stools. He was hospitalized for management of colonic polypectomy with mucosal resection by endoscopy. The investigator rated the AE as mild and unrelated. This subject is included in the perioperative management narrative cases and continued in the study after surgery on routine prophylaxis.
- Subject (b) (6) - A 28 year old White male with a history of hemophilia B who had completed Study 3001, developed an SAE of esophagitis. He initially developed heartburn symptoms, which worsened after one week and resulted in

hospitalization for management of reflux and weakness. Endoscopy was used to establish the diagnosis. He was discharged the following day on a regimen of omeprazole and weekly iron sucrose injections. The AE was judged moderate, unrelated to IDELVION, and was ongoing at the time of reporting. The subject continued in the study.

8.4.3 Study Dropouts/Discontinuations

In the overall safety population, three subjects, two in Study 3001 and one in Study 3003 discontinued treatment due to TEAEs.

No subjects discontinued from Studies 2001 and 3002. One subject in Study 2004 discontinued enrolling in Study 3001.

Study 3001

See 6.1.12.2 for subjects who discontinued from Study 3001 related to adverse events. Four discontinuations were associated with adverse events and four had no reported associated adverse event (dropouts). See also sections 6.1.11.4.

Study 3003

Subject (b) (6), a 58 year old Asian male with hemophilia B and a PMH of HIV, hepatitis C, hypertension and alcoholic liver disease was discontinued from Study 3003, which is ongoing. The discontinuation was in association with a clinical lab abnormality AE, gamma glutamyl transaminase (GGT) elevation. The subject had participated in Study 3001 (started 28Sept2012) before transitioning to Study 3003 (21Feb2014). The investigator considered the > ULN GGT levels to be likely related to alcohol use. The subject had 100 EDs over the period of his participation in both studies when he discontinued on 05Sept2014. The investigator rated the AE, GGT elevation, mild in severity and possibly related since a drug effect could not be excluded definitively.

8.4.4 Common Adverse Events

CSLB proposes including all AEs from clinical studies for which, after thorough data analysis and evaluation a causal relationship between the product and the AE is at least a reasonable possibility. CSLB uses two requirements for a reasonable possibility: 1) a pharmacologically plausible relationship exists between IDELVION or other products in the same class and the AE under evaluation; 2) a temporal relationship exists including treatment emergent (a temporal relationship exists such that the AE was first detected, or became more severe, following exposure) and a positive rechallenge (event occurs >1 time with a similar temporal relationship). The investigator assessment as related is also cited as an influence. CSLB quotes from the 2006 FDA Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, “The definition of adverse reactions does not include all adverse events observed during use of a drug. It is limited to those events for which there is some

basis to believe there is a causal relationship between occurrence of an adverse event and the use of a drug (§ 201.57(c)(7)).” to support this approach.

Proposed labeling

Summary of Adverse Reactions

MedDRA Standard System Organ Class	Adverse Reaction	Number of subjects n (%), (N=107)
Nervous system disorders	Headache	2 (1.9)
	Dizziness	1 (0.9)
Skin and subcutaneous tissue disorders	Rash	1 (0.9)
Immune system disorders	Infusion related reaction*	1 (0.9)

* One patient reported a non-serious hypersensitivity reaction with atypical symptoms. This was later considered to be an infusion related reaction.

WALDRON comment: The adverse reactions are similar in type and frequency to the adverse reactions for Alprolix. The use of biological plausibility is a reasonable criterion for causality with this product, since it is not a new molecule introduced into the physiology, but it replaces a deficient endogenous molecule. Similarly, since this product is used on a regular frequency for an extended time the expectation of reproducibility (positive rechallenge) of the AE is reasonable. I have some concern with the use of investigator assessment of relatedness as a component of the evaluation in the absence of a blinded control, since the assessment can have a large subjective component, and there is the potential for bias. The AEs that were related and associated with subject withdrawal (headache, rash, infusion related reaction) are in the adverse reactions. In consideration of the total assessment, I consider it acceptable.

8.4.5 Clinical Test Results

Safety Concern – Abnormal Urinalysis

CSLB provided a full listing of lab tests according to the monitoring schedule for each clinical trial. Study 3001 included the greatest number of lab tests and the most frequent monitoring. A review of all lab tests identified no indication of a drug effect on lab values with one exception. Four Study 3001 subjects had normal screening urinalysis results and subsequently developed more than one episode of a positive urine protein test simultaneous with an absence of blood in the urine. No subjects had other changes suggesting clinically important renal disease such as changes in serum creatinine values or new onset hypertension.

An information request (IR) to CSLB produced a response that focused on serum chemistry results, and ignored the urinalysis results. A consultant (Aliza Thompson, MD) in the CDER Division of Cardiovascular and Renal Products, hereafter CDER

CardioRenal consultant, concluded that there was insufficient information, and had these additional IR requests to CSLB:

The results in the laboratory data set (Study 3001) for urine protein were positive or negative. The typical result of a urine dip stick for protein is negative or a graded result from 1+ to 4+. What were the actual test results in these subjects?

Subject (b) (6).

In the applicant's laboratory dataset, the end-of-study value for urine protein is given as "1". Please clarify what "1" means. The applicant should also provide additional information on the medications that were taken (names and dates of administration). It seems likely that the proteinuria seen in this subject was caused by other factors, but the applicant should provide the requested information.

There is no apparent cause for urine protein findings in Subject (b) (6). Please provide a possible explanation for this finding, and additional information on the subject's course.

The total response to the IR was 14 pages (date May 26, 2015). An abbreviated summary is that CSLB considers the urinalysis findings of no clinical significance based on an absence of a pattern of change in the relevant serum biochemical markers and the investigators' assessments that the urinalysis results were of no clinical significance.

An additional IR was sent June 9, 2015 with a request for a response by the close of business June 16, 2015. The request was:

In your laboratory dataset titled (b) (4), analysis values for urine protein are reported as trace, positive, negative, or given a numerical value. Your response to our May 26 information request indicates that urinalysis was performed by the local laboratory and that local laboratory results were recorded in the eCRF. Hence, as we understand, you aren't reporting the results in a standardized fashion in your dataset.

Your dataset contains the information shown below for Subject (b) (6) (i.e., a negative screening value for urine protein and positive values at weeks 12, 28 and EOS). In your response, you state that the subject had "...fluctuations in urine protein as measured by urine dipstick. Positive trace urine protein (document range: positive or negative) was measured at Week 12, 28 and EoS ..." We are trying to reconcile the information in your dataset with the information provided in your response. Please clarify your use of the terms "trace", since all results were "positive" and "fluctuations", when this subject's results during the study were invariant.

Unique Subject Identifier	Analysis Visit	Analysis Value
(C)		
CSL654_3001-(b) (6)	SCR	Negative
CSL654_3001-(b) (6)	WK12	Positive
CSL654_3001-(b) (6)	WK28	Positive

CSL654_3001-(b) (6) EOS Positive

In response to FDA's concerns, the applicant noted that the "out of range urine results were reviewed in each of the five Independent Data Monitoring Committee meetings throughout the study."

Dr. Lisa Faulcon's memo summarizes the additional information that was requested and resolved the issues related to this potential safety concern. Below is a summary of those efforts without the additional lab data that was included in Dr. Faulcon's review. Some of this summary material is copied directly from Dr. Faulcon's draft reviews.

In the CDER CardioRenal consultant's review, none of the four subjects had a pattern of increasing serum creatinine or hypertension and no blood was noted on more than one sample. Short narratives and adjudication of each of the four subjects with abnormal urinalyses are noted below.

1. Subject (b) (6) - A 15-year-old white male who had a urinalysis that was positive for protein at weeks 12, 28, 44, 60 and at the end-of-study visit. There were no significant differences in urinary concentration at each of the time points and serum albumin measurements were all within the reference range. The CDER CardioRenal consultant concluded that interpretation of these findings were limited by the fact that the screening/baseline value was made almost one year prior to the measurement at 12 weeks.
2. Subject (b) (6) - A 54-year-old Asian male with a history of hepatitis C and hypertension with a urinalysis that was positive for protein at weeks 12 and 44 and negative for protein at weeks 28, 60, 76, 92 and the end-of-study visit. The CDER CardioRenal consultant concluded that the finding was intermittent and was not seen at later time points in the trial and that the patient had underlying conditions (e.g., hypertension) that could cause proteinuria.
3. Subject (b) (6) - A 43-year-old white male with a history of hepatitis C and urinalysis that was negative for protein at baseline, weeks 12 and 28 and positive at week 44 with a value of 1 g/L (range: 0.0-0.3 g/L) listed for the end-of-study visit which occurred (more than 6 months after the week 28 visit. One serum albumin measurement was above the reference range (55 g/L; <1%) but all other measurements were within the reference range. The subject had two reported urinary tract infections during the study (from week 16 to week 40) and syphilis (from week 56 to week 68) and was treated with several drugs that could have caused or contributed to the proteinuria, including the fluoroquinolone, ofloxacin, which has a labeled adverse event of proteinuria.
4. Subject (b) (6) - A 26-year-old white male with a urinalysis that was positive for proteinuria at weeks 12 and 28 and the end-of study visit (approximately 3 months later). There were no significant differences in

urinary concentration at each of the time points and serum albumin measurements were all within the reference range. The applicant stated that a dose of paracetamol (acetaminophen) taken 48 hours prior to the Week 28 visit. The applicant also suggested that in addition, an elevated, but within range (1.001 to 1.035), specific gravity suggested dehydration that likely contributed to the observed proteinuria. *FAULCON comment: This is highly speculative.*

Per the CDER CardioRenal consultant, in each of the four cases a causal relationship between the use of IDELVION and abnormal proteinuria by urinalysis can be established. Per the prespecified protocol defined categories, the first three cases would be considered at least possibly related (event or laboratory test abnormality with reasonable time relationship to intake of the investigational product but could also be explained by disease or other drugs). However, the fourth case (subject (b) (6)) had unexplained observations and should be considered probably related.

FAULCON Comment: In an information request, CSLB was informed that additional information was needed to further evaluate the possible association between proteinuria and IDELVION. Because urine protein: creatinine ratio was considered more informative, CSLB was asked to obtain and submit follow-up data (spot urine protein/creatinine ratio, dipstick urinalysis, serum chemistry and hematology testing) for the three subjects with proteinuria that were enrolled in the extension study. CSLB was advised that these findings may be included in the label and that additional data in a larger cohort may be needed to assess the risk and to further inform the label. CSLB was advised that the protocol for the extension study would need to be revised to include urinalysis and spot urine protein/creatinine ratio testing in a pre-specified number of naive subjects. The recommended changes were:

- *Testing should be done every 6 months, and at the end of the trial as per recommendations from the CDER CardioRenal consultant.*
- *The protocol should also be revised to specify a clinical work up for subjects with increased protein creatinine ratios. A threshold of >0.2 mg protein/mg creatinine in children greater than two years of age and ≥500 mg/g in adults should trigger further evaluation.*
- *The revised extension study would then be considered a postmarketing commitment study. There was insufficient evidence for product relatedness (i.e., strength of association, consistence of the finding across several trials, and biological plausibility) to support a postmarketing requirement study.*

FAULCON comment/overall conclusion opinion (reproduced from her draft clinical memo) Conclusion: In this reviewer's opinion, these findings do not raise significant concerns for renal safety and are not sufficient to support a request for a postmarketing study or a risk Evaluation and Mitigation Strategy as 1) a clear biologically plausible reason why this product should cause proteinuria (the albumin load and clearance should not result in proteinuria) is not evident, 2) none of the cases were reported as adverse events and no associated clinical sequelae was documented, and 3) based on expert opinion from the CDER CardioRenal consultant and consultation with OBE, there

is insufficient evidence to suggest that this is a safety signal. Although there are limitations to the safety database, namely it was derived from small observational studies of patients with confounding comorbidities that could make interpretation of a possible clinically significant signal difficult, the submitted follow-up data from the three subjects enrolled in the extension study suggest that persistent proteinuria is not an issue even after long-term exposure to the product. These findings do not need to be included in the label.

8.4.6 Local Reactogenicity

One subject (b) (6) reported 4 moderate and 2 severe events (Study 3001). This subject was observed in clinic during an infusion, and no AEs were observed. The subject ultimately withdrew due to headaches. The investigator assessments of local tolerability identified no AEs.

8.4.7 Adverse Events of Special Interest

The following types of AEs were designated of special interest in evaluating the safety profile of IDELVION: immunogenic events (most importantly inhibitor formation), hypersensitivity reactions, and thromboembolic events.

8.4.7.1 Immunogenic Events

No inhibitors were reported. Antibody testing against CHO proteins was done in studies 3001 and 3002, and no subjects tested positive. No treatment-emergent antibodies to IDELVION were reported in Studies 2001, 2004, 3001, or 3002. At the January 9, 2015 data cut-off, no treatment-emergent antibodies to IDELVION were reported in study 3003.

One subject (b) (6) in study 2004 tested positive for antibodies against BENEFIX, pdFIX, and rIX-FP before the first injection of IDELVION (day 1), and during the PK assessment (day 10). Subsequently, the subject tested positive for antibodies against pdFIX only at week 4 and negative for BENEFIX, pdFIX, and rIX-FP at Week 12.

8.4.7.2 Hypersensitivity Reactions

No anaphylactic reactions were reported among study subjects.

Two subjects had an event in this category. See section 6.1.12.2, Adverse Events Leading to Withdrawal for a description of one subject (b) (6). This event was judged an infusion reaction, rather than a hypersensitivity reaction by the IDMC.

Another study 3001 subject (b) (6) had 5 events of rash (NOS) that were judged related to IDELVION. The subject stopped study participation after 28 EDs. The events were treated with an oral antihistamine.

8.4.8.3 Thromboembolic events

No thromboembolic events were reported. Studies 2001 and 3001 obtained samples to evaluate prothrombin fragment 1+2, thrombin-antithrombin (TAT) and D-dimer as

markers of activation of coagulation. One Study 2001 subject had slight and short term increases in TAT and D-dimer following IDELVION. None of these test results were abnormal among the study 3001 subjects.

8.5 Additional Safety Evaluations

None

8.6 Safety Conclusions

The clinical trials provided an adequate exposure to characterize the safety concerns with the exception of the PUPs and surgical subjects (to date). None of the events of special interest (i.e. inhibitor development, hypersensitivity reaction, thromboembolic event) were reported for any 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. CSLB proposed a limited list of events in the Adverse Reactions section of the PI. 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. The abnormal urinalyses concern has been addressed.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No women were studied in the clinical trials and no developmental or reproductive toxicity studies were done. Therefore, no conclusions can be made about these areas.

9.1.2 Use During Lactation

No women were studied in the clinical trials.

9.1.3 Pediatric Use and PREA Considerations

IDELVION has orphan designation and therefore PREA does not apply.

Study 3002 only enrolled < 12 year olds. See section 6.2 for a full review of this study. Twenty-seven subjects entered the study, 12 subjects ages 0 to 5, and 15 subjects ages 6 to <12. The primary objectives were to evaluate the safety endpoint of inhibitor development and to evaluate PK parameters. The secondary objectives were evaluation of clinical responses, prevention of bleeding episodes (once-weekly prophylaxis regimen) and response to the treatment of bleeding episodes, and the secondary safety objective was evaluation of AEs during use of IDELVION.

The PK findings are described in the Clinical Pharmacology section 4.4 above and section 6.2.10.3 Pharmacokinetic results. The median AsBR for the efficacy

subpopulations was 2.6 for those children <6 yo and 3.4 for children 6-<12 yo 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 3.4 (3.2), and the AsBR for the 0 to 5 year old was 4.2 (3.6). One hundred and six bleeding episodes were treated during the study. One hundred and three (103/106 = 97.2%) were treated with 2 or fewer infusions. The three subjects who required > 2 doses to treat the bleed initiated treatment later than the protocol-specified interval of 4 hours. The investigator assessment of hemostatic efficacy was excellent for 75% (78/104) and good for 21.2% (22/104) of the events.

The mean number of exposure days was 61.9, with a range of 42-94, and 25/27 (92.6%) had ≥ 50 EDs (83% of <6 yo, and 100% of 6-<12 yo). No inhibitors or treatment emergent antibodies were detected during the study. Six serious TEAE were reported by 4 subjects, and 146 non-serious TEAEs were reported. None of the AEs were assessed as related by the investigators.

WALDRON comment: I reviewed the SAEs, and I agree with the assessment that these events were unrelated to the use of IDELVION.

In summary, IDELVION appears safe for use in pediatric subjects < 12 year old, and the data on efficacy appears similar to the findings in older subjects.

Surgical Subjects in Study 3002

Two major surgeries were reported in Study 3002. Both surgeries were tooth extractions. An 8 year old child [Subject (b) (6)] developed a tooth abscess and required urgent surgery to extract 4 teeth. There is no report whether the teeth were primary or secondary. The patient was treated 4 hours prior to surgery with 50 IU IDELVION/kg. He received subsequent doses on post-op days 2, 5, and 9. No FIX activity levels were reported. The investigator assessed the hemostatic efficacy as good at day 7 post-op.

A 9 year old child underwent non-emergency extraction of two teeth. There is no report whether the teeth were primary or secondary. The patient was treated 1.7 hours prior to surgery with 40 IU IDELVION/kg. He received subsequent doses on post-op days 2, 5, and 9. No FIX activity levels were reported. The investigator assessed the hemostatic efficacy as excellent at 7 days post-op.

One 5 year old child underwent a minor surgical procedure (nevus excision) in Study 3003. There was minimal information provided; a single report of hemostatic efficacy was excellent.

WALDRON comment: The agreed number of major surgeries has not been accrued by the studies to date. Tooth extractions are a minor hemostatic challenge.

9.1.4 Immunocompromised Patients

Twelve Study 3001 subjects (19% of 63) were HIV positive, but there are no additional comments regarding their immune competence and its effect on the efficacy and or safety of IDELVION.

9.1.5 Geriatric Use

No subjects older than age 65 were included in the clinical studies.

10. Conclusions

The clinical trials provided an adequate exposure to characterize the safety concerns with the exception of the PUPs and surgical subjects (to date). None of the events of special interest (i.e. inhibitor development, hypersensitivity reaction, thromboembolic event) were reported for any 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. CSLB proposed a limited list of events in the Adverse Reactions section of the PI. 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. The abnormal urinalyses concern has been addressed.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Risk Benefit considerations are summarized in the table below.

Risk Benefit Considerations for IDELVION

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Severe hemophilia B is a potentially life threatening disorder that requires FIX replacement for survival, and for normal function. 	<ul style="list-style-type: none"> Hemophilia B (FIX) deficiency is a life threatening disease and requires replacement for survival and normal functioning
Unmet Medical Need	<ul style="list-style-type: none"> None. There are 5 other approved FIX replacement products. 	<ul style="list-style-type: none"> Not applicable, but this product is the first FIX-albumin fusion protein and therefore may offer longer half-life and longer treatment durations, which are advantages over the existing products.
Clinical Benefit	<ul style="list-style-type: none"> The benefit of this product derives from its ability to replace the deficient FIX. The benefits of FIX replacement include prevention of bleeding. This application demonstrated efficacy for bleeding prevention using within subjects comparisons of periods using an on demand regimen and periods using routine prophylaxis. The observed >90% reduction in the annual spontaneous bleeding rate indicates an effective capacity to provide this benefit. A second benefit is the ability to control bleeding and to prevent recurrence of bleeding at the initial site of injury. IDELVION has clinical benefit for the perioperative treatment of both major and minor surgeries 	<ul style="list-style-type: none"> The clinical evidence is adequate based on the results of all clinical studies.
Risk	<ul style="list-style-type: none"> The principal identified risks of hemophilia replacement products are inhibitor development, hypersensitivity reactions, and thromboembolic events. None of these events occurred in the clinical trials populations. 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 studied. 	<ul style="list-style-type: none"> IDELVION was well tolerated with no major risks of inhibitor development, hypersensitivity reaction or thromboembolic events.
Risk Management	<ul style="list-style-type: none"> The product has orphan designation, so no pediatric studies are required. The applicant amended study 3003 to include 20 PUP subjects, which is the only pediatric group that has not been studied. If the PUP study is not complete at the time of approval, then this could be considered for a proposed PMC. No PMRs are recommended for safety concerns. There is no indication for a REMS for this product. 	<ul style="list-style-type: none"> The package insert and the current routine pharmacovigilance plan, including postmarketing studies in PUPs are adequate to manage the risks

11.2 Risk-Benefit Summary and Assessment

Severe hemophilia B is a potentially life threatening disorder that requires FIX replacement for survival, and for normal function. The benefit of this product derives from its ability to replace the deficient FIX. The benefits of FIX replacement include prevention of bleeding. This application demonstrated efficacy for bleeding prevention using within subjects comparisons of periods using an on demand regimen and periods using routine prophylaxis. The observed >90% reduction in the annual spontaneous bleeding rate indicates an effective capacity to provide this benefit.

A second benefit is the ability to control bleeding and to prevent recurrence of bleeding at the initial site of injury. The applicant proposed, and FDA agreed, that control of bleeding could be assessed by analyzing the proportion of bleeds that subjects treated with 2 or fewer infusions. The study population of the combined trials treated bleeds with 2 or fewer infusions in 98.6% of 443 treated bleeding events (96.2% = lower limit of the 95% CI). This is evidence of efficacy in providing this benefit. The small number (2) of bleeding events that fit the criteria for major hemorrhage is a limitation, but these are often difficult to capture in a clinical trial. The observation of effectiveness (4 of 5 treated with < 2 infusions) in iliopsoas bleeds (section 6.1.11.2) is helpful in addressing this deficit. Another indicator of effective control of major bleeding is perioperative management of procedures with more than minimal blood loss in a population with normal hemostasis.

The potential benefit of control of perioperative bleeding awaits additional subjects to allow for full evaluation. The benefit of the pharmacokinetics that allows less frequent administration for these indications is incremental relative to available products. The long term benefit of factor replacement using a product with a longer half-life requires studies of longer duration.

The principal identified risks of hemophilia replacement products are inhibitor development, hypersensitivity reactions, and thromboembolic events. None of these events occurred in the clinical trials populations. The identified adverse effects were not severe or frequent, and the types of events were similar to the events in other approved hemophilia products. 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 studied.

In summary, this product has a favorable benefit risk profile due to its clear efficacy in prevention and treatment of bleeding episodes, and its adverse effects which were not severe or frequent.

11.3 Recommendations on Regulatory Actions

Recommend approval in all age groups for previously treated patients for the indications:

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

WALDRON comment: There are not enough subjects with major surgical bleeds to assess efficacy for perioperative bleeding at this time. The applicant reported results on the use of IDELVION in 15 subjects undergoing procedures with a risk of bleeding, which included 3 subjects < 12 years old. All three studies used a consistent definition of major surgery, i.e., “a surgical procedure that involves anesthesia (general, spinal, epidural or regional block) or respiratory assistance (including but not limited to orthopedic and cardiac surgery)”. The reported outcomes of surgeries were the surgeon’s assessment of hemostasis, and a comparison of the surgeon’s forecast of estimated blood loss (EBL) prior to surgery with the reported EBL after surgery. The use of blood products and FIX levels prior to a repeat dose of IDELVION were also reported. Only four of the surgeries were considered major with significant blood loss. This reviewer would await further surgical subjects results in order to continue efficacy and safety assessment for this indication.

CHAZIN comment: On further evaluation of the major and minor surgeries across all trials, there were 15 surgeries among 13 patients of which 9 would be considered major and 6 would be considered minor. These data are adequate to recommend approval for the perioperative indication.

11.5 Labeling Review and Recommendations

The only major issue in review of the clinical data in the label is in section 2.2 Routine prophylaxis. The applicant proposed:

2.2 Routine Prophylaxis

For routine prophylaxis, appropriate FIX trough levels are required and are maintained by regular infusions. The recommended dose is 25-40 IU IDELVION per kg body weight every 7 days or 50-75 IU IDELVION per kg every 14 days. Adjust the dosing regimen based upon the individual patient’s clinical condition and response.

WALDRON comment: This statement implies that the doses and schedules, 25-40 IU IDELVION per kg body weight every 7 days or 50-75 IU IDELVION per kg every 14 days, can be applied with complete equivalence. However, the study design tested equivalence between the 7 day and 14 day dose schedule only among subjects who had all of: fewer bleeds prior to study entry, fewer bleeds on study, and a favorable PK profile. Informing prescribers of this selection process is necessary for them to have accurate prescribing information. Similar statements in support of section 2.2 are made in section 14. These should be amended with consistency.

11.6 Recommendations on Postmarketing Actions

The product has orphan designation, so no pediatric studies are required. The applicant amended study 3003 to include 20 PUP subjects, which is the only pediatric group that has not been studied. If the PUP study is not complete at the time of approval, then this could be considered for a proposed PMC. No PMRs are recommended for safety concerns. There is no indication for a REMS for this product.

