25 February 2016
EMA/CHMP/213825/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Idelvion

International non-proprietary name: albutrepenonacog alfa

Procedure No. EMEA/H/C/003955/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

aPTT	activated partial thromboplastin time
ABR	Annualized bleeding rate
ADR	Adverse Drug Reaction
ADA	Anti-drug antibody
AE	Adverse Event
AsBR	Annualized spontaneous bleeding rate
AUC	Area under the concentration-time curve
AUC_T	Area under the plasma concentration-time curve during a dosing interval at steady state
AUC0-tlast	Area under the plasma concentration-time curve from zero up to the last
AUC0-24	Area under the plasma concentration-time curve from zero up to 24 hours
blq	Below limit of quantification
BMI	Body mass index
BU	Bethesda Units
CD	circular dichroism
CHO	Chinese hamster ovary
CHMP	Committee for Medicinal Products for Human Use
CL	Clearance
C_{max}	Maximum plasma concentration
CSR	Clinical Study Report
DSC	differential scanning calorimetry
ED	Exposure Day
EGF	epidermal growth factor
ELISA	Enzyme-linked immunosorbent assay
EVA	ethylene vinyl acetate
FcRn	neonatal Fc receptor
FCS	fetal calf serum
FIX	coagulation factor IX
FIXa	activated FIX
FIXα	factor IX alpha
Gla	y-glutamic acid
i.a.	Intra-arterial
i.v.	Intravenous
HCP	host cell protein
HIC	hydrophobic interaction chromatography
HPLC	high performance liquid chromatography
HSA	human serum albumin
IDMC	Independent Data Monitoring Committee
IPAC	in process acceptance criteria
IPC	in process control
IR	Incremental Recovery
IU	international units
MAA	Marketing Authorisation Application
MCB	master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MSX	L-Methionine Sulfoximine

na	not applicable
Nab	Neutralizing antibody
NGNA	N-glycolyl-Neuraminic acid
NOAEL	No Observed Adverse Effect Level
NZW	New Zealand White rabbit
PACE	Paired basic amino acid cleaving enzyme (syn. Furin)
pdFIX	plasma-derived FIX
PPCB	post production cell bank
PT	Preferred Term
PTP	Previously Treated Patient
PUP	Previously untreated patient
p.v.	Perivenous
rFIX	Recombinant Factor IX
rIX-FP	Recombinant Fusion Protein linking Coagulation Factor IX with Albumin
PDCO	Paediatric Committee
PUP	Previously Untreated Patient
qPCR	quantitative polymerase chain reaction
QRA	Quantitative radiochemical analysis
QWBA	Quantitative whle-body autoradiography
QTPP	quality target product profile
RCB	research cell bank
rMSB	reduced menadione sodium bisulphite
RP-HPLC	reversed phase HPLC
SAE	Serious Adverse Event
S/D	solvent/detergent
SD	Sprague Dawley
SEC	size exclusion chromatography
TEAE	Treatment Emergent Adverse Event
TAT	Thrombin-Antithrombin
T½	Half-life
t1/2	Terminal half-life
TFF	tangential flow filtration
TGA	thrombin generation assay
TnBP	tri-N-butyl phosphate
TSE	transmissible spongiform encephalopathy
WBCT	Whole blood clotting time
WCB	working cell bank
WFI	Water for injection
WFH	World Federation of Hemophilia

1. Background information on the procedure

1.1. Submission of the dossier

The applicant CSL Behring GmbH submitted on 9 March 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Idelvion, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 February 2014.

Idelvion was designated as an orphan medicinal product EU/3/09/723 on 4 February 2010. Idelvion was designated as an orphan medicinal product in the following indication: treatment of haemophilia B.

The applicant applied for the following indication:

Prophylaxis and treatment of bleeding in all patients with haemophilia B (congenital factor IX deficiency) including control and prevention of bleeding in surgical settings.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Idelvion as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that albutrepenonacog alfa was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0269/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0269/2014 (PIP 1107) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance albutrepenonacog alfa contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 8 February 2010 and 22 May 2014. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: United States, Canada, Switzerland, Australia and Japan.

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Andrea Laslop

- The application was received by the EMA on 9 March 2015.
- The procedure started on 25 March 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2015.
- The PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report was adopted by PRAC on 9 July 2015.
- During the meeting on 23 July 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 July 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 September 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 October 2015.
- The PRAC RMP advice and assessment overview was adopted by PRAC on 6 November 2015.
- During the CHMP meeting on 19 November 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 26 January 2016.
- The PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report was adopted by PRAC on 11 February 2016.
- During the meeting on 25 February 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Idelvion.
- The CHMP adopted a report on the claim of new active substance (NAS) status of albutrepenonacog alfa (Recombinant fusion protein linking Coagulation Factor IX with Albumin (rIX-FP)) contained in Idelvion.

2. Scientific discussion

2.1. Introduction

Haemophilia B is a rare bleeding disorder which is x-linked recessively inherited and affecting ~1 in 20,000 of the male population worldwide (Konkle et al. 2000). The disease is caused by coagulation factor IX (FIX) deficiency and classified based on remaining in vitro clotting activity, which in turn is closely associated with the clinical phenotype (Giangrade 2005).

Signs and symptoms of Hemophilia B are variable; depending on severity of the factor deficiency and the location of the bleeding. Thereby, bleeding is characterized by spontaneous or trauma-induced hemorrhage into joints, muscles and soft tissues. Severe haemophilia B is characterised by spontaneous or traumatic bleeding episodes into soft tissues and joints, but also life-threatening gastrointestinal or intracranial bleeding may occur. Recurrent joint bleeding may lead to chronic arthropathy and disability.

Hemophilia B can successfully be managed with FIX replacement therapy. Besides of acute treatment of bleeding episodes, prophylactic treatment with the deficient clotting factor should be the goal of haemophilia therapy to preserve normal musculoskeletal function (World Federation of Haemophilia 2013). Therapeutic formulations of FIX are available as both plasma-derived FIX (pdFIX) and recombinant FIX (rFIX) products for treatment. Half-life of both pdFIX and rFIX is ~18 hours and prophylactic treatment is usually required 2 to 3 times a week in order to achieve a significant reduction of bleeding episodes.

The applicant CSL Behring has developed albutrepenonacog alfa, a recombinant human coagulation factor IX product designed with the aim of a prolonged half-life in order to support a longer dosing interval for routine prophylaxis treatment, along with effective acute treatment of bleeding episodes. The product is referred to either using its scientific name “recombinant fusion protein linking coagulation factor IX with albumin” (rIX-FP), or the company code “CSL654” throughout the application. The active ingredient, rIX-FP, is a purified protein derived from a Chinese Hamster Ovary (CHO) cell line and produced by recombinant DNA technology, generated by the genetic fusion of recombinant albumin to recombinant coagulation factor IX. The recombinant factor IX portion is identical to the Thr148 allelic form of human plasma-derived factor IX. The cleavable linker between the recombinant Factor IX and 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) only when it is needed for coagulation.

Idelvion is formulated as a sterile, non-pyrogenic, preservative-free, lyophilized, pale yellow to white whole or cracked plug intended for intravenous administration provided in a single-use vial. Each single-use vial contains nominally 250 IU, 500 IU, 1000 IU or 2000 International Units (IU) of rIX-FP for reconstitution with liquid diluent (Sterile Water for Injection), which is provided in glass vials (2.5 ml sWFI: 250 IU, 500 IU, 1000 IU; 5.0 ml sWFI: 2000 IU).

The rIX-FP clinical development programme was designed to meet the requirements as set out in the EMA guideline on the clinical investigation of recombinant and human plasma-derived FIX products (EMA/CHMP/BPWP/144552/2009).

Idelvion is intended for the indication of the “Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).” Idelvion can be used for all age groups.

The required dose for on demand treatment is determined using the following formulae:

Required dose (IU) = body weight (kg) x desired factor IX rise (% of normal or IU/dl) x {reciprocal of observed recovery (IU/kg per IU/dl)}

Expected factor IX rise (IU/dl or % of normal) = Dose (IU) x Recovery (IU/dl per IU/kg)/body weight (kg)

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

For determination of adequate maintenance dose take into consideration the extended half-life of the product.

The proposed posology for routine prophylaxis to prevent bleeding in patients with haemophilia B, the recommended regimen is 35 to 50 IU/kg once weekly. Some patients who are well-controlled on a once-weekly regimen might be treated with up to 75 IU/kg on an interval of 10 or 14 days.

CHMP Scientific advice (EMEA/H/SA/1500/1/2010/III and EMEA/H/SA/1500/1/FU/1/2010/PA/III-corr) was given and has been followed by the applicant.

2.2. Quality aspects

2.2.1. Introduction

Idelvion is a recombinant fusion protein linking recombinant coagulation factor IX (rIX-FP) with recombinant human albumin and is presented as lyophilized powder in four strengths of 250, 500, 1000 and 2000 IU to be reconstituted with sterile water for injections (WFI). The product is intended for intravenous injection.

2.2.2. Active Substance

General information

The active substance of Idelvion (rIX-FP) was generated by the genetic fusion of albumin to factor IX (FIX) (INN: albutrepenonacog alfa). FIX complementary DNA (cDNA) was joined to human albumin cDNA by a FIX-derived linker sequence to obtain rIX-FP. The construct is expressed in a Chinese Hamster Ovary (CHO) cell line.

The linker sequence between FIX and albumin is derived from an endogenous FIX sequence involved in FIX activation, thus enabling the cleavage of the fusion protein by the same enzymes (FXIa or the FVIIa/tissue factor (TF)) which activate FIX during the process of blood coagulation. Thus, as a result of activation, active recombinant FIX (FIXa) is cleaved from the linker sequence, concomitantly releasing the albumin carrier moiety from FIXa.

The FIX moiety of rIX-FP is similar to naturally occurring plasma-derived FIX and contains two N-linked glycosylated residues and at least two O-linked glycosylated residues. FIX has up to 12 gamma (γ) carboxylated glutamic acid (Gla) residues and 11 internal disulphide bonds.

rIX-FP has an extended half-life in circulation due to linking human FIX with recombinant human albumin (rIX-FP).

Manufacture, characterisation and process controls

The manufacturing process has been described in sufficient detail in line with ICH Guideline Q11. For all sites involved in manufacture and testing of rIX-FP bulk drug intermediate (BDI) and active substance valid compliance to cGMP has been confirmed by respective certificates issued by EU Competent Authorities.

The active substance manufacturing process consists of 13 steps, including fed-batch cell culture, column chromatography purification and concentration unit operations. The upstream cell culture process involves WCB vial thawing and inoculum expansion, followed by a production bioreactor. Following clarification a clarified harvest containing full length rIX is produced.

The rIX is purified from the clarified harvest in several chromatographic and filtration steps and two dedicated virus reduction steps as follows:

- A first chromatography column serves as a primary capture and concentration step for the rIX and is effective as a viral clearance step.
- The buffer exchange and concentration is designed to exchange the chromatography elution buffer and to concentrate the product.
- The solvent detergent treatment is a dedicated virus inactivation step.
- The initial downstream processing stage produces a bulk drug intermediate (BDI) which is stored as a frozen bulk before further manufacture into active substance.
- BDI is loaded onto the second chromatography column for further purification.
- The eluate is loaded onto a third chromatography column to further purify the rIX.
- A fourth chromatography step serves as a final purification step.
- The eluate is concentrated and dialyzed.
- The product is filtered for virus removal.

The active substance manufacturing process has been sufficiently described. The ranges of critical process parameters and routine in-process controls along with acceptance criteria have been described for each step and are considered adequately set to control the manufacturing process.

Origin, source, and history of the cell line development

The CHO host cell line used to create the rIX-FP cell substrate was confirmed to be free from contamination by viruses, bacteria (including mycoplasma) and fungi (moulds and yeasts). Cell bank characterisation test reports have been provided and the integrity of the final expression vectors was verified.

The methods used to construct the cell substrate, select and genetically characterise the production clone and prepare the research cell bank (RCB) have been provided. In line with ICH Q5B “Quality of biotechnological products: Analysis of the expression construct in cell lines used for production of r-DNA derived protein products” the selection of the most productive sub-clone used to generate the production cell line and the generation of the RCB has been described in sufficient detail. No components used in the cell line construction were of animal or human origin.

In line with ICH Q5D “Derivation and characterisation of cell substrates used for production of biotechnological/biological products” detailed reports regarding the origin of the host cell bank and its characteristics have been provided. Sterility of this cell bank, viability, and absence of adventitious agents has been demonstrated.

In line with ICH Q5A (R1) “Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin” and ICH Q5D the comparability of the MCB, the WCB and the post production cell bank (PPCB) with respect to identity, the absence of adventitious agents and the genetic stability has been demonstrated.

Raw materials, buffers, solutions and auxiliary materials (resins and filters) are of compendial quality or have been qualified by vendors or by the Applicant.

Characterisation

A detailed physico-chemical and biochemical characterisation of rIX has been performed, including primary, secondary and higher order structures, as well as functional properties. The expected amino acid sequence of the fusion construct has been fully confirmed.

The impurity profile of rIX-FP has been investigated in detail using state-of-the-art methodology. Major and minor product- and process-related impurities have been identified and characterised by sensitive analytical methods. It is demonstrated that the manufacturing process effectively and consistently reduces impurities, and that rIX-FP active substance contains only low level of product- and process-related impurities which seem to be of no risk for the quality, safety and efficacy of the product.

Process Controls

Critical steps

The control strategy developed is intended to appropriately control sources of process variability such that the desired process performance and product quality are consistently achieved. For all operating parameters, activities were undertaken to understand which parameters have the greatest potential to impact process performance and product quality attributes (i.e. critical quality attributes (CQAs)). “Critical Steps” have been defined as those containing critical process parameters (CPP), in-process controls (IPC), and/or in-process acceptance criteria (IPAC). All steps in the rIX active substance manufacturing process are considered critical steps. This designation is primarily associated with definition of the process control strategy and subsequent verification of the process control strategy during verification (also referred to as process performance qualification (PPQ)). The categorization of process parameters has been described in detail in the Manufacturing Process Development.

Defined ranges for identified CPP at each manufacturing step are presented as normal operating ranges (NOR) or proven acceptable ranges (PAR) which were determined from analysis of historical data, process characterisation studies and evaluation of process capabilities.

Critical intermediates

The Bulk Drug Intermediate (BDI) is the only intermediate in the manufacture of the active substance. The BDI specifications include an adequate set of test parameters for which respective method descriptions and validations are provided. All tested BDI batches met the acceptance criteria. The quality of the BDI is ensured by extended validation studies.

Process validation

The Applicant has followed a risk- and science–based approach for process validation in line with ICH Q8-Q10. This Quality by Design approach is outlined in detail in the Process Validation section; relevant additional information is presented in the Process Development section.

In line with the process validation guideline (EMA/CHMP/BWP/187338/2014) the manufacturing process development was designed to establish a commercial manufacturing process with defined input and output parameters. Based on the quality target product profile (QTPP) the process operating ranges and CQAs were defined. An assessment of parameters via a failure mode effect analysis (FMEA) was performed for both the rIX BDI and active substance process. The results of these FMEA risk assessment have been summarised in separate reports.

Assessments of other potential sources of process variability were undertaken, including raw material, equipment, components, rooms/ environment, process steps, and critical utilities. In the process performance qualification (PPQ) the process control strategy was verified. It is demonstrated that the process, when operated within the defined ranges, produces rIX active substance that consistently meets all in-process controls, in-process acceptance criteria, additional testing requirements, and release specifications. PPQ runs under GMP conditions were conducted for BDI and active substance production process.

The process validation also addressed the following aspects:

i) The capability of the process to remove process-related impurities. Additional information on leachables from chromatography resins was provided.
ii) Establishment of in-process hold times including “cumulative” hold times to address process hygiene were validated at small and full scale, demonstrating that the hold time conditions do not affect product quality and safety.
iii) The resin and membrane life times have been defined. Appropriate data from process validation studies on chromatography resins life time has been provided.
iv) Confirmation that homogeneity was achieved at all mixing steps.

Manufacturing process development

The manufacturing process has been developed in four distinct stages, which reflected increasing knowledge and experience gained during development.

The first stage involved development of an initial pilot process to manufacture the novel molecule. The second stage manufacturing process was adapted to better remove process-related impurities, while supplying the initial clinical studies and the primary product specific reference standard. The third stage was defined following completion of the transfer and scale-up activities to the commercial manufacturing sites. Material from this process was used to initiate pivotal clinical studies. During the pivotal clinical trials, some further manufacturing process changes were introduced and process validation studies were undertaken. The resulting process, incorporating the totality of the process development activities and validation studies, was designated as the fourth stage. The Validated Commercial Process is the manufacturing process intended for production of the marketed product. The development from the initial to the validated commercial process included several changes. Comparability assessment of process performance and product quality parameters demonstrated that the initial commercial scale process and the validated commercial process are highly similar.

Specification

The set of analytical procedures for the control of the active substance is adequate to ensure a consistent purity and quality of the active substance. The parameters and their specifications have been mostly selected in line with ICH Q6B Note for Guidance on specifications. For each analytical procedure a brief method description has been provided and all methods have been validated according ICH Q2(R1).

With respect to FIX potency assay activated partial thromboplastin time (aPTT), it is clearly specified which type of test kit and test system is used to measure FIX potency of this modified rFIX in routine batch analysis of BDI, AS and FP. More details on different test assays have been described and their influence on potency of this long-acting FIX is clear.

The FIX primary standard (PRS1) is calibrated relative to the IS FIX concentrate and the secondary working reference standard (WRS1) is calibrated against PRS1, maintaining a link between the working standard and the WHO IS FIX concentrate. The labeling of rIX-FP in International Units has been justified. In addition, updated information has been provided for the reference materials used in the other active substance control tests.

Stability

The stability of the active substance under long-term and accelerated conditions has been investigated in line with ICH Q5C “Stability testing of Biotechnological/Biological products”. Real time/real temperature data have been presented for three commercial scale active substance batches. Stability data provided no evidence that quality parameters show a negative trending and the proposed shelf life can be accepted.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is a sterile lyophilized powder presented in four strengths of 250 IU, 500 IU, 1000 IU and 2000 IU per vial. After reconstitution with sterile water for injections (sWFI), concentrations of 100 IU/mL, 200 IU/mL and 400 IU/mL are obtained for intravenous administration.

The finished product is aseptically filled into single-use type I glass vials of 6 mL (250 IU, 500 IU and 1000 IU per vial strengths) or 10 mL (2000 IU per vial strength) nominal capacity. The vials are closed with a rubber stopper and sealed with an aluminum/polypropylene flip-off sealing combi cap using different colours for the various strengths.

The active substance, rIX-FP, is formulated in a citrate buffer containing stabilizers and a bulking agent. The formulation contains the following excipients: sucrose, polysorbate 80, mannitol, tri-sodium citrate dihydrate. For pH adjustment, small amounts of hydrochloric acid (HCl) compliant to compendial standards are used.

Pharmaceutical Development

The development of the finished product manufacturing process occurred in two stages, the pilot scale (finished product for use in early clinical development) and the commercial scale (finished product for pivotal clinical studies).

The first stage of the finished product development led to the pilot scale process for the 500 IU and 1000 IU strengths. The pilot scale process supplied finished product for pre-clinical pharmacology and toxicology studies as well as early clinical development.

The formulation development studies resulted in a formulation procedure allowing all strengths to be formulated using the same two solutions – stabilizer solution (containing mannitol, sucrose, tri-sodium citrate, polysorbate 80) and a dilution solution (containing tri-sodium citrate and polysorbate 80). The two formulation solutions developed are free of animal-derived materials.

The second stage, the commercial scale process development, included site and scale changes as well as process optimization changes regarding the production of the 500 IU and 1000 IU strengths and the introduction of the two additional strengths 250 IU and 2000 IU.

The unit operations were consistent throughout development. Process changes included mostly site and scale-up changes and also process optimizations were performed.

Specific lyophilization cycles were developed for the 250 IU, 500 IU/1000 IU and 2000 IU strengths taking into account the different fill volumes for the different strengths (2.2 ml: 250 IU, 500 IU, 1000 IU; 4.4 ml: 2000 IU). The development studies of the lyophilization process lead to a robust commercial freeze-drying process which yields a product with consistent quality attributes.

No overages are applied during the filling of finished product.

The finished product formulation was shown to be stable. The stability data support compatibility of the active substance with the finished product excipients. The lyophilized finished product is a pale yellow to white whole or cracked plug.

Manufacture of the product and process controls

Description of manufacturing process and process controls

The finished production manufacturing process contains 5 process steps, including formulation and sterile filtration, filling, lyophilization, crimping and labelling and packaging.

A detailed process flow diagram including a summary of the IPC and IPAC tests conducted at each stage of the manufacturing process and interim storage conditions has been provided.

The development of the rIX-FP Process Control Strategy (PCS) was the basis for the process validation. During process development, a risk-based and science-based approach was used to reveal the relationship between manufacturing process variables and product quality attributes.

The Process Control Strategy ensures consistent manufacture of the finished product that meets its defined critical quality attributes (CQAs). All process parameters were evaluated with regard to risk of failure, taking into account scientific rationale, data from process characterisation studies and historical manufacturing data. The suitability of the control strategy was confirmed during PPQ.

A Process Validation Master Plan was developed and established for rIX-FP, which defines the strategy to assure a reliable and consistent manufacturing process capable of delivering product of appropriate quality.

The rIX-FP manufacturing process was qualified according to a prospective PPQ protocol which defined the sampling, analytical testing and acceptance criteria for each process step. The results have been presented. Taken together, all study objectives of the PPQ were met and the defined PCS was successfully validated for the manufacture of rIX-FP.

Validation data was presented covering the finished product manufacturing steps including formulation, sterile filtration, filling and lyophilization. In addition, information on the hold times as well the reprocessing at the sterile filtration step was provided. The process validation data cover all critical manufacturing steps.

Regarding the validation of the lyophilization step, sufficient validation data has been provided in order to cover the intended use during the routine production regarding the number of freeze-dried vials (for each strength).

The process validation strategy provided is acceptable. An ongoing process verification (also known as continued process verification (CPV)) plan is in place to ensure the validated state of the rIX-FP manufacturing process throughout the commercial life cycle.

Comparability exercise for finished medicinal product

The comparability of the finished product manufactured using the pilot or commercial scale process was evaluated. The evaluation included both non-clinical animal studies (high dose toxicology and PK study in rats) and analytical comparability studies.

The analytical studies evaluated results of release tests and characterisation assays including structural and functional assays. The data from the comparability exercise demonstrate that the non-clinical and clinical data obtained using rIX-FP from the pilot scale process was supportive for the pivotal clinical studies using material manufactured by the commercial scale process.

In addition, no major process changes regarding the finished product manufacturing process occurred during development, indicating that the Phase I and Phase I/II clinical trial material (pilot scale: 500 IU, 1000 IU) and the Phase III clinical trial material of the commercial scale process (250 IU, 500 IU, 1000 IU, 2000 IU) as well as the commercial product are manufactured by the same process and are of comparable quality.

In conclusion, the comparability studies are in compliance with the guideline ICH Q5E “Comparability of Biotechnological/Biological products subject to changes in their manufacturing process”.

Product specification

The rIX-FP finished product specification used for release/shelf life testing is considered appropriate including adequate tests for integrity, potency, purity and quality. The acceptance criteria are based on historical data. The specification parameters and their acceptance criteria are adequate and meet the requirements of guideline ICH Q6B. The proposed control strategy ensures that rIX-FP meets consistent quality.

The description of the analytical procedures and their validations were provided. A more detailed description regarding the FIX potency assay (aPTT) was also provided.

The information provided on the batch analysis data as well as on the characterisation on the process- and product-related impurities is considered appropriate. Product-derived impurities and degradation products are well controlled in both the active substance and the finished product manufacturing process. Specifications for known product-related impurities were established.

No new process-related impurities were identified in the finished product when compared to the active substance.

In addition, studies on the leachables and extractables were presented. An evaluation of leachables and extractables was performed on stored finished product lots on filled final bulk lots and on finished product stabilizer and formulation solutions. The evaluations assessed non-volatile and semi-volatile substances as well as inorganic elements.

The issue of possible leachables and extractables derived from the rubber stopper including a risk assessment was addressed and the respective studies were included in the dossier.

Reference Standard

The strategy for establishing and maintaining reference standards for release and stability testing of commercial rIX-FP active substance and finished product was described.

A primary reference standard (PRS) was established in order to ensure that the quality of the active substance remains consistent and to avoid a drift in quality over time. Working reference standards (WRS) are established for routine release and stability testing of active substance which are qualified against the primary reference standard, and the stability of both reference materials is monitored to assess the suitability of these reference standards over their lifetime.

The potency of PRS calibrated against the WHO International Standard (IS) (NIBSC code 07/182) for plasma-derived Factor IX and the labelling of the Primary Reference Standard PRS1 in International Units was adequately described. Thus, traceability to the International Standard was considered established and the use of International Units (IU) for potency labelling rIX-FP justified.

The information on the initial potency assignments for a new PRS and a new WRS was presented, and the acceptance criteria for the establishment of a new PRS and a new WRS were outlined.

The stability monitoring program for the PRS and the WRS including the test parameter for the FIX activity and the respective acceptance criteria as well as the testing intervals were provided.

Stability of the product

The stability of rIX-FP was investigated in accordance with ICH Q5C. The batches included into the stability studies used the container closure system of the routine production. The container closure system consists of 6 ml and 10 ml type I glass vials and a rubber stopper. The packaging materials for storage of the finished product are in compliance with Ph. Eur. and USP requirements and are suitable for the intended use.

A number of long-term stability studies for commercial scale batches at +5°C, +25°C and at +40°C (stress condition) were performed in order to monitor the physical, chemical and biological integrity of the finished product over time.

The proposed shelf life for the 250 IU and the 500 IU strengths is 24 months when not stored above +25°C. The proposed shelf life for the 1000 IU and the 2000 IU strengths is 36 months when not stored above +25°C. The proposed shelf life is based on long term studies performed with pilot and commercial scale batches of finished product and is supported by real time data.

Stability after reconstitution was also tested. Stability of rIX-FP for up to 8 hours at room temperature in solution was shown for all four strengths at the end of the proposed shelf life (250 IU: 36 months; 500 IU: 36 months; 1000 IU: 36 months; 2000 IU: 36 months).

In addition, a photo stability study was performed demonstrating, rIX-FP finished product must be stored protected from light.

The stability studies provided are acceptable. Additional real time/real temperature data (250 IU, 500 IU: 24 months when not stored above 25 °C; 1000 IU, 2000 IU: 36 months when not stored above 25 °C) for commercial scale batches (representative of the validated commercial process) was presented to support the claimed shelf life and storage temperature as well as the reconstitution stability claimed in the SmPC.

Solvent Water for Injections

The information provided in the dossier for the solvent shows that the sWFI is manufactured under GMP compliant conditions using a validated process and meets Ph. Eur. requirements for sterile WFI.

sWFI is provided as 2.5 ml and 5.0 ml fill sizes in 6 ml type I glass vials which are closed with a rubber stopper. The proposed shelf life conditions are supported by real time stability data.

Regarding the immediate packaging materials sufficient information has been provided (compliance with Ph. Eur. monographs, Certificates of Analyses).

Adventitious agents

TSE compliance

Compliance with the TSE Guideline (EMEA/410/01 – current version) has been sufficiently demonstrated. The active substance is produced in a serum-free medium. No other material of bovine origin is added during fermentation of rIX-FP. The MCB which has been established is free from TSE-risk substances.

Virus safety

The fermentation process of rIX-FP occurs in a chemically-defined medium. The cells used for production of rIX-FP have been sufficiently screened for viruses.

The purification process of rIX-FP includes several steps for inactivation/removal of enveloped viruses. The effectiveness of these steps has been sufficiently demonstrated. In addition, the capture chromatography also contributes to the virus removal. The removal capacity of small non-enveloped viruses is mainly based on the dedicated filtration step. Screening for viruses including Minute Virus of Mice (MMV) is routinely performed at the end of the fermentation runs. During the manufacture of the

active substance, column chromatography resins are used during purification. Studies of reuse of chromatography resins have been provided. In summary, the viral safety of rIX-FP has been sufficiently demonstrated.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information about the active substance and finished product was of acceptable quality. Sufficient evidence regarding the manufacturing processes has been provided. The results of tests carried out indicate mostly a satisfactory consistency and uniformity of important product quality characteristics. The justifications concerning the control of certain process-related impurities were provided. Specification limits and analytical methods are suitable to control the quality of the active substance and the finished product. The finished product was well characterised. The stability program is considered satisfactory. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

The finished product is manufactured by a process that operates reproducibly within established parameters leading to a product that meets its pre-determined quality attributes. The process was validated in a continuous process verification approach, and the respective Master Validation Plan was provided.

An adequate set of control parameters, IPCs and IPACs including the limits and acceptance criteria was established based on a risk analysis to control the quality of the finished product. The chosen control strategy is considered appropriate.

The finished product specification including the testing parameters as well as the acceptance criteria is suitable and represents the commercial and validated process.

Detailed information was presented especially for the FIX coagulation assay (aPTT). Due to the variability of the FIX potency which is dependent on the test performance, the routine potency test method and equipment was specified in detail.

The calibration of the Primary Reference Standard potency against the WHO IS resulted in significantly different FIX potency values due to the use of different equipment, test kits and particular aPTT reagents. The Applicant clarified that the FIX potency value of PRS1 was used to label all the batches manufactured to date. This value was also used to label the Secondary Working Standards.

The labelling of the Primary Reference Standard PRS1 in International Units was explained and justified (calibration data provided; linearity and parallelism versus the IS, NIBSC code 07/182, shown).

The general strategy for the calibration and the stability monitoring of the rFIX-FP Reference Standards (PRS and WRS) was described.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The active substance and the finished product have been appropriately characterised and in general satisfactory documentation has been provided. Overall, the data presented indicate that Idelvion is manufactured by a validated, controlled process taking into consideration relevant guidance documents. The results indicate that the active substance as well as the finished product can be reproducibly manufactured.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended some points for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

An initial pharmacodynamic investigation was carried out *in vitro* to identify pharmacologically relevant test species. In-vivo pharmacodynamic studies were performed in two animal species deficient in FIX, i.e. FIX deficient mice and dogs. In terms of safety pharmacology the effects of rIX-FP administration on pulmonary functions (e.g. respiration rate, tidal volume and minute volume) were investigated in conscious rats using plethysmo-graphy. Safety pharmacological assessment of effects on the cardiovascular system was covered by the repeat-dose toxicology study in cynomolgus monkeys. Potential effects on the central nervous system were evaluated during the single-dose toxicity studies in rats and cynomolgus monkeys as well as during the repeat-dose toxicity studies in rats and cynomolgus monkeys based on clinical observations as well as macroscopic and histopathological evaluations.

The i.v. single dose toxicity of rIX-FP was evaluated in rats and monkeys using doses of up to 500 IU/kg. Repeat-dose toxicity of rIX-FP was evaluated in rats and monkeys after i.v. administration at doses of 75, 150 and 500 IU/kg/day for 28 consecutive days. Further toxicology studies comprise two investigations concerning genotoxicity, one local tolerance study and a Wessler test to address possible thrombogenicity.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In-vitro

Study No. IVX 01/09: Effects on coagulation Parameter aPTT following spiking of rIX-FP and BeneFIX into plasma of various species

The aim of this study was to establish a concentration-response relationship regarding the effects of spiking plasma samples of various species with rIX-FP. Activated partial thromboplastin time (aPTT) was used as the primary endpoint representing a sensitive measure for effects on the coagulation system, which has been indicated for screening defects of functional clotting factors such as Factor VIII, IX, XI or XII. BeneFIX was used as comparator. It appeared that aPTT decreased dose-dependently following spiking of human, cynomolgus monkey, rat and rabbit plasma with rIX-FP. In rabbits, BeneFIX was significantly more effective in decreasing aPTT compared to rIX-FP. *In-vivo*

Study No. 040200011: rIX-FP: Single Dose Pharmacokinetic and Pharmacodynamic Study by Intravenous (Bolus) Administration to Hemophilia B Dogs

In this study three hemophilia B dogs (1F, 2M) were treated with rIX-FP and two (2F) with BeneFIX with a single intravenous dose of 100 IU/kg. Thereafter, blood samples were taken up to Day 36 for assessment of pharmacodynamic (i.e. aPTT and whole blood clotting time (WBCT)) and pharmacokinetic parameters, as well as for haematology, clinical chemistry and immunogenicity investigations. Furthermore, clinical signs, bodyweight and mortality were recorded throughout the study.

Following the single intravenous injection of rIX-FP and BeneFIX® in hemophilia B dogs, no test item-related changes could be observed in bodyweight gain, haematology and clinical chemistry.

Both treatment groups demonstrated a clear haemostatic efficacy. WBCT and aPTT values were decreased after treatment and returned to pretreatment values after the study drugs were cleared from the circulation. However, aPTT values stayed below 0.6 times the baseline value more than three times longer in the rIX-FP group (5.4 days) than in the BeneFIX group (1.6 days), whereas WBCT values of about 10 min were kept in both treatment groups for about seven days.

The results of the immunogenicity testings revealed that an antibody response with neutralizing properties against the study drugs (i.e. rIX-FP and BeneFIX) appeared after a single intravenous injection.

Study No. NBM 04/09: Correction of Hemostasis in FIX ko Mice with rIX-FP

A single intravenous bolus of rIX-FP and BeneFIX, respectively, at 50, 100 and 200 IU/kg was given to FIX deficient mice (15 mice/ group). One group receiving isotonic saline (0.9 %) served as control. A tail tip bleeding assay with resection of about 3 mm of the tail tip was performed 15 minutes after drug administration to assess bleeding parameters. Measurement of total blood loss and time to hemostasis was used to determine the haemostatic efficacy.

Both, rIX-FP and BeneFIX at all dose levels tested showed a clear haemostatic effect compared to the control group, i.e. a significant reduction in time to hemostasis and total blood loss.

Study No. NBM 05/09: Correction of Coagulation (aPTT) in FIX ko Mice following Treatment with rIX-FP and BeneFIX

A single intravenous bolus of rIX-FP and BeneFIX®, respectively, at 50, 100 and 200 IU/kg was given to FIX deficient mice, whereas one group receiving isotonic saline (0.9 %) served as control (14-17 mice/group). Measurement of aPTT was used to detect the effects on coagulation.

Both, rIX-FP and BeneFIX, showed a clear significant decreasing effect on aPTT compared to the control group at all investigated dose levels. Thereby, the efficacy did not differ from BeneFIX®.

Secondary pharmacodynamic studies

No studies were submitted (See discussion on non-clinical pharmacology) performed.

Safety pharmacology programme

Respiratory system

Evaluation of respiratory parameters (respiratory rate, tidal volume and minute volume) was performed in conscious rats using whole body bias flow plethysmography after intravenous application of rIX-FP (study APQ0003). A total of 40 male rats were allocated to 5 groups of 8 animals each. rIX-FP was administered via bolus injection at doses of 75, 150 and 500 IU/kg. An additional control group received an equivalent volume (2.5 mL/kg) of isotonic saline (0.9 %), mimicking the highest dose volume used for test substance administration. Baclofen at a dose of 15 mg/kg, was administered to a further group of animals as a positive control (2.5 mL/kg). Respiratory parameters were recorded for a minimum of 60 min prior to dosing. Immediately after dosing, the rats were placed back into the whole body plethysmographs and respiratory parameters were recorded continuously for 4 h.

rIX-FP, administered intravenously at 75, 150 or 500 IU/kg produced no statistically significant effect on any of the respiratory parameters measured in this study. Thus, the No Observed Adverse Effect Level (NOAEL) was considered to be at least 500 IU/kg as no statistically significant changes occurred in any of the respiratory parameters at this level, compared with placebo (saline)-treated animals.

Cardiovascular system

The potential effects of rIX-FP on electrophysiological parameters and blood pressure were assessed as part of a repeat-dose toxicity study performed in cynomolgus monkeys following daily intravenous (bolus) administration of rIX-FP over a period of 4 weeks, with a Day 6 interim period (study APQ0001). Three groups of 4 male and 4 female monkeys received rIX-FP at doses of 75, 150 or 500 IU/kg/day for up to 4 weeks. Interim animals were dosed for 5 days and all other animals were dosed for 28 days. A similarly constituted control group received isotonic saline (0.9 %) with the same frequency as the treated groups but at a dose volume similar to the high dose group.

The electrophysiology of the heart was considered unaffected by rIX-FP treatment. Blood pressure and pulse rate measurements were considered to be unaffected by rIX-FP treatment..

Central nervous system

The potential effects on the central nervous system were evaluated during the single-dose toxicity studies in rats (APQ0005) and cynomolgus monkeys (APQ0007) as well as during the repeat-dose toxicity studies in rats (APQ0009) and cynomolgus monkeys (APQ0001) based on clinical observations as well as macroscopic and histopathological evaluations. In all these studies, no changes were observed which were considered to be indicative of a test item related effect on the central nervous system.

Pharmacodynamic drug interactions

Studies on pharmacodynamics drug interactions have not been submitted (See discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

In order to evaluate the pharmacokinetics of rIX-FP, a study with single intravenous administration was performed in monkeys and in hemophilia B dogs. Furthermore, a quantitative whole-body autoradiography (QWBA) study was conducted in rats to evaluate tissue biodistribution of rIX-FP. Further kinetic analyses were carried out as part of the single- and repeat-dose toxicity evaluations in rats and monkeys.

Study No. APQ0002: rIX-FP: Single-Dose Pharmacokinetic Study by Intravenous (Bolus) Administration to Cynomolgus Monkeys

The objective of this study was to assess the pharmacokinetics and dose proportionality of rIX-FP following single intravenous dosing at dose levels of 50 and 100 IU/kg. In addition, the systemic exposure to rIX-FP following administration was compared to that following administration of BeneFIX at the same two dose levels. Furthermore, appearance of an immune response against rIX-FP and BeneFIX, respectively, was investigated.

Four groups of cynomolgus monkeys, each comprising of one male and one female animal, received single intravenous doses of rIX-FP or BeneFIX at dose levels of 50 IU/kg and 100 IU/kg, respectively. Blood samples were taken from each monkey over a 19 day period.

Immunogenicity investigations as well as determination of human factor IX concentrations in the monkey plasma samples were performed using validated ELISA methods.

No adverse effects of treatment were observed following intravenous administration of either rIX-FP or BeneFIX. During the course of the study, no antibody formation both against human factor IX or human albumin (both components of rIX-FP) and against human factor IX (i.e. BeneFIX) was detectable.

Following intravenous administration, the pharmacokinetics of rIX-FP were dose proportional for AUC and Cmax and independent of sex. rIX-FP was cleared slowly and the individual terminal half-life (t1/2) values were within the range 39.8 to 44.4 hours over the dose range (mean value= 42.2 hours).

Study No. 040200011: rIX-FP: Single Dose Pharmacokinetic and Pharmacodynamic Study by Intravenous (Bolus) Administration to Hemophilia B Dogs

The aim of this study was to assess the pharmacological efficacy, pharmacokinetic characteristics and immunogenicity of rIX-FP in a single dose study by intravenous (bolus) administration in hemophilia B dogs and, in addition, to compare acquired data with BeneFIX. Three hemophilia B dogs were treated with rIX-FP and two with BeneFIX with a single intravenous dose of 100 IU/kg. Thereafter, blood samples were taken up to Day 36 for assessment of pharmacodynamic (i.e. aPTT and whole blood clotting time (WBCT)) and pharmacokinetic parameters, as well as for haematology, clinical chemistry and immunogenicity investigations. Clinical signs, bodyweight and mortality were recorded throughout the study.

Following the single intravenous injection of rIX-FP and BeneFIX in hemophilia B dogs, no test item-related changes could be observed in bodyweight gain, haematology and clinical chemistry.

Both treatment groups demonstrated a clear haemostatic efficacy. WBCT and aPTT values were decreased after treatment and returned to pretreatment values after the study drugs were cleared from the circulation. Thereby, aPTT values stayed below 0.6 times the baseline value more than three times longer in the rIX-FP group (5.4 days) than in the BeneFIX group (1.6 days).

Pharmacokinetic investigations revealed that the clearance was 3.5 times lower for rIX-FP (2.6 mL/h/kg) than for BeneFIX (9.3 mL/h/kg). A human factor IX level of minimum 50 IU/L (suggested protective level in hemophilia B patients) was kept more than three times longer with rIX-FP (7.3 days) than with BeneFIX (2.3 days).

The results of the immunogenicity testings revealed that an antibody response with neutralizing properties against the study drugs (i.e. rIX-FP and BeneFIX) appeared after a single intravenous injection. It can be concluded that rIX-FP administration demonstrated a clear haemostatic efficacy in hemophilia B dogs. Thereby the pharmacokinetic properties were superior to BeneFIX. Both, rIX-FP and BeneFIX induced an antibody response in hemophilia B dogs.

Study No. CSL/01 and CSL/03: Protein labeling and metabolism studies in the rat

Biodistribution of human coagulation factor IX (FIX) was studied in quantitative whole body autoradiography (QWBA) studies following administration of rIX-FP, BeneFIX or human albumin (Recombumin) to rats.

[3H]-rIX-FP, [3H]-BeneFIX or [3H]-albumin, labeled using the N-Succinimidyl [2,3,-3H] propionate (NSP) method, were administered i.v. to male rats at a single radioactive dose of approximately 400 µCi/kg. Using QWBA, tissue radioactivity was determined over 24 ([3H]-BeneFIX) or 240 ([3H]-rIX-FP, [3H]-albumin) hours. In addition to full body sections, the hind limbs were separately subjected to QWBA to obtain more detailed information on the products' distribution within the bone marrow and knee joint region. In parallel, plasma, urine and feces were collected at several time points throughout the observation period to calculate excretion balance and assess physiological elimination pathways. The radioactivity associated with the [3H]-labelled proteins was determined by quantitative radiochemical analysis (QRA) and high performance liquid chromatography (HPLC). The radioactivity associated with plasma, urine and feces samples was also determined using QRA. Biological activity of BeneFIX and rIX-FP after [3H]-labeling was confirmed by a chromogenic assay *in vitro*.

The results obtained confirmed that elimination of [3H]-rIX-FP and [3H]-BeneFIX occurred primarily via the urine. After 240 hours, 73% of radioactivity was recovered in urine (associated with only low molecular weight components), ≤5% eliminated in feces and about 20% remained in tissues.

The tissue distribution of [3H]-rIX-FP and [3H]-BeneFIX was comparable, both penetrating predominantly into well vascularized tissues and/or excretion organs including the adrenal gland, spleen, lung, liver, kidney, myocardium, peridontal membrane, nasal mucosa, stomach wall and gastrointestinal mucosa. Both proteins were also rapidly present within bone marrow and synovial or mineralized regions of knee joint sections where they seemed to mostly localize to the zone of calcified cartilage within the growth plate regions of long bones. The longest retention times were observed for bone marrow and the endosteum of long bones. Overall, these results suggest similar tissue distribution profile of [3H]-rIX-FP and [3H]-BeneFIX independent of albumin fusion. In contrast, the biodistribution of [3H]-albumin appeared to be different with only very low initial penetration of bone marrow and liver but rapid, homogeneous distribution throughout the whole body including muscle and connective tissue. Intriguingly, however, both [3H]-rIX-FP and [3H]-albumin derived radioactivity was detectable over 120 hours, whereas the radioactivity associated with [3H]-BeneFIX was only detectable over 24 hours, further supporting the notion of extended tissue half-life of [3H]-rIX-FP due to albumin fusion.

Metabolism

Metabolism studies were not submitted (see discussion on non-clinical aspects).

Excretion

No separate elimination or excretion studies were submitted (see discussion on non-clinical aspects).

Non-clinical drug – drug interactions

No nonclinical drug interaction studies were performed.

Other pharmacokinetic studies

No other PK studies have been submitted.

2.3.4. Toxicology

Single dose toxicity

The i.v. single dose toxicity of rIX-FP was evaluated in two studies in rats and in one study in monkeys using doses of up to 500 IU/kg.

Study No. APQ0005: rIX-FP: Single Dose Toxicity Study by Intravenous (Bolus) Administration to CD Rats

The systemic toxic potential and toxicokinetics of rIX-FP was assessed over a 5 day period following a single dose by intravenous (bolus) administration in rats.

Three groups, each comprising 5 male and 5 female rats received rIX-FP at doses of 75, 150 or 500 IU/kg. A similarly constituted control group received isotonic saline (0.9 %) at the same volume-dose as the highest treated dose group (2.5 mL/kg). A further 3 males and 3 females were allocated to the control group and 9 males and 9 females were allocated to each treated group and were used for toxicokinetic evaluation. Blood samples for toxicokinetic evaluation were taken at pre-dose, 0.25, 1, 3, 8, 24, 72 and 120 h. Clinical condition, mortality, bodyweight, food consumption, haematology, blood chemistry, toxicokinetics, urinalysis, organ weight, macropathology and histopathology investigations were undertaken.

Cmax and AUC following a single intravenous administration of rIX-FP increased proportionally with increasing dose over the range 75 to 500 IU/kg. The systemic exposure was similar for males and females. Over the dose range, the terminal half-life (t1/2) values were found to be in the range of 15.7 – 20.7 h. There was no indication of dose dependency regarding half-life, volume of distribution and total plasma clearance.

There were no unscheduled deaths.

In conclusion, a single intravenous injection of rIX-FP at doses up to 500 IU/kg was well tolerated in the rat with no findings indicative of adverse toxicity and no irritation at the site of injection. Under the conditions of this study, the NOAEL was considered to be 500 IU/kg.

Study No. 8244656: rIX-FP and rIX-FP-B: Single dose Intravenous (Bolus) Administration Toxicity Study in the Rat Followed by a 5 Day Treatment-free Period

The objective of the study was to determine the toxicity of rIX-FP whereby the effects of the test articles were compared after increasing the production scale from pilot to commercial scale. The assessment of toxicity was made following intravenous (bolus) administration to the rat and an

assessment of delayed onset toxicity and / or reversibility was made during a 5 day treatment-free period. Additionally, an evaluation of the potential influence of the increased levels of the process derived impurity, i.e. bilirubin, following transfer from pilot scale to commercial scale, was made on the test article's toxicity profile.

The systemic toxic potential and toxicokinetics of rIX-FP pilot scale and commercial scale material were assessed in rats. Two groups, each comprising five male and five female rats, received rIX-FP at the high dose of 500 IU/kg. A similarly constituted control group received isotonic saline (0.9 %) at the same volume-dose (2.5 mL/kg). A further 3 males and 3 females were allocated to the control group and 9 males and 9 females were allocated to each treatment group - used for toxicokinetic evaluation.

Blood samples for toxicokinetic evaluation were taken at pre-dose, 0.25, 1, 3, 8, 24, 72 and 120 h. Toxicokinetic evaluation showed that there were no differences between both formulations regarding half-life, volume of distribution and total plasma clearance. The t1/2 values ranged from 16.8 to 20.5 hours. The plasma concentrations and therefore the toxicokinetic parameters were comparable for females and for males.

There were no unscheduled deaths during the study. There were no clinical signs observed throughout the study nor were there any effects on body weight, food consumption, haematology, plasma chemistry or urinalysis in any treated group. There were also no macroscopic findings due to either local or systemic effects of rIX-FP independent of the production scale.

A NOAEL of 500 IU/kg was designated in this study.

Study No. APQ0007: Single Dose Toxicity Study by IV (Bolus) Administration to Cynomolgus Monkeys

The systemic toxic potential and toxicokinetics of rIX-FP was assessed in a single dose study by intravenous (bolus) administration in cynomolgus monkeys. Three groups of 3 male and 3 female monkeys received a single dose of rIX-FP at 75, 150 or 500 IU/kg on study Day 1. A similarly constituted control group received isotonic saline (0.9 %) at the same frequency.

Two male and 2 female animals from each group were killed on Day 6 of the study, and the remaining 1 male and 1 female from each group were killed on Day 11.

During the study, clinical condition, mortality, bodyweight, haematology, blood chemistry, toxicokinetics, urinalysis, organ weights, macropathology and histopathology investigations were undertaken. Blood samples for toxicokinetic evaluation were drawn at baseline and at 0.25, 1, 5, 24, 72, 120 hours of all animals/ group and at 240 hours of 1 male and 1 female animals/group after administration of rIX-FP.

Systemic exposure to rIX-FP in the treated animals was confirmed, with none detected in the controls. Over the dose range, individual t1/2 values ranged from 14.2 – 71.2 h (mean values: 39.8 – 55.9 hours). For the four animals, in which suitable values were obtained up to 240 h after dosing, the individual t1/2 values were in the range 49.7 – 83.4 h over the dose range.

The Cmax and AUC0-tlast increased with dose for both male and female animals and the increase in exposure was proportional to dose after the single intravenous (bolus) administration of rIX-FP up to 500 IU/kg. There was no indication of dose dependency regarding half-life, volume of distribution and total plasma clearance.

There were no unscheduled deaths.

In conclusion, a single intravenous injection of rIX-FP at doses up to 500 IU/kg was well tolerated in cynomolgus monkeys with no toxicologically significant changes. Under the conditions of this study, the NOAEL was considered to be 500 IU/kg.

Repeat dose toxicity

Study No. APQ0009: rIX-FP: Toxicity Study by Intravenous (Bolus) Administration to CD Rats for 4 Weeks Followed by a 2 Week Recovery Period

The systemic toxic potential and toxicokinetics of rIX-FP to rats by intravenous (bolus) administration was assessed over a period of up to 4 weeks. The potential for any treatment-related effect to show recovery was assessed in a subsequent 2-week recovery period in selected satellite animals. Five animals from each group were killed on Day 6 as part of the interim kill to investigate initial toxicity before the development of any potential immune response. Three groups, each comprising ten male (plus 5 interim kill) and ten female (plus 5 interim kill) rats received rIX-FP at doses of 75, 150 or 500 IU/kg/day. A similarly constituted control group received isotonic saline (0.9 %) at the same volume-dose as the high dose group. A further three males and three females were allocated to the control group, and nine males and nine females were allocated to each treated group and were used for toxicokinetic evaluation (satellite animals). Blood samples for toxicokinetic assessment were drawn at pre-dose and at 0.25, 1, 3, 8, 24, 72 and 120 hours after 28th administration of rIX-FP. Furthermore, three male and three female rats were assigned from the control and high dose group satellite animals to assess recovery from any treatment-related effect. These animals were treated for four weeks, followed by a 2-week period without treatment.

During the study, clinical condition, mortality, bodyweight, food consumption, ophthalmoscopy, haematology, blood chemistry, toxicokinetics, anti-product antibodies, urinalysis, organ weight, macropathology and histopathology investigations were undertaken.

Systemic exposure to rIX-FP in treated animals was confirmed, with none detected in controls. Dose linearity and proportionality of AUC_T and Cmax after multiple intravenous administrations of rIX FP was demonstrated over the dose range 75 – 500 IU/kg. The terminal half-life (t1/2) values were found to be in the range 15.7 – 27.7 h (using $mean_{ar}$-plasma concentrations) and 20.8 – 28.5 h (using maximum plasma concentrations) over this dose range. Terminal half-life and total plasma clearance were independent of dose, and no sex difference was apparent in the measured plasma concentrations after repeated dosing for 28 days.

There was no evidence of an immune response to the human albumin or the human factor IX (both components of rIX-FP) at Day 6. However, at Day 16 there was a response observed in 3 animals from the rIX-FP treated groups (1 against human albumin and 2 against human factor IX), indicating the potential onset of a response. The percentage of animals positive for anti-drug-antibodies (ADA) against rIX-FP increased from 3% on Day 15 to 26% on Day 28.

There were no deaths or clinical findings that were considered to be associated with treatment.

In conclusion, administration of rIX-FP by intravenous injection at doses up to 500 IU/kg/day was well tolerated in the rat with no findings indicative of adverse toxicity. Under the conditions of this study, the NOAEL was considered to be 500 IU/kg.

Study No. APQ0001: rIX-FP: Toxicity Study by Intravenous (Bolus) Administration to Cynomolgus Monkeys for 4 Weeks

The systemic toxic potential and toxicokinetics of rIX-FP to cynomolgus monkeys by intravenous (bolus) administration was assessed over a period of 4 weeks, with a Day 6 interim period. Three groups of 4 male and 4 female monkeys received rIX-FP at doses of 75, 150 or 500 IU/kg/day for up to 4 weeks. Interim animals were dosed for 5 days and all other animals were dosed for 28 days. A similarly constituted control group received isotonic saline (0.9 %) with the same frequency as the treated groups but at a dose volume similar to the high dose group. From each group, one male and female were killed after the interim period (Day 6), two males and females were killed 1-2 days after the 28 days of treatment (i.e. Day 29 and 30) and the remaining male and female were killed on Day 38.

During the study, clinical condition, mortality, bodyweight, ophthalmic examination, electrocardiography, blood pressure, haematology, blood chemistry, toxicokinetics, antibody analysis, urinalysis, organ weight, macropathology and histopathology investigations were undertaken.

For toxicokinetic analysis blood samples were drawn as follows: Day 1: before (predose) and 0.25, 1, 5, 24 (24 h sampling before next dosing on Day 2) and 72 h (72 h sampling before next dosing on Day 4) after administration (all animals) Day 28: before and 0.25, 1, 5 and 24 h after administration (remaining 3 male and 3 female animals of each group after the interim kill). Day 28: 48, 72, 120 and 240 h after administration (remaining 1 male and 1 female animal of each group).

Systemic exposure to rIX-FP in the treated animals was confirmed, with none detected in the controls. Over the dose range, individual terminal half-life (t1/2) values ranged from 14.0 - 28.9 hours (mean values: 16.6 - 25.2 hours) for Day 1 and 17.7 - 45.7 hours (mean values: 18.6 - 33.3 hours) for Day 28. The exception was for one male in the 500 IU/kg group which had t1/2 of 3.0 hours (Day 28) as a consequence of increased systemic clearance, considered to be mainly a result of the elevated anti-human albumin antibodies. For the five animals, in which suitable values were obtained up to 240 h after dosing on Day 28, the individual t1/2 values were in the range 21.6 - 69.1 h over the dose range. The Cmax and AUC0-24 (Day 1) or AUC_{τ} (Day 28) increased with dose for both male and female animals and the increase in exposure was proportional to dose after single and repeated dosing. Terminal half-life and total plasma clearance were independent of dose. Some accumulation occurred, with 2-3 fold increase observed for both sexes after repeated dosing. Continuous exposure to rIX-FP was also demonstrated throughout the study and no sex differences were observed.

There were no unscheduled deaths. Similar to the situation in rats, anti-human factor IX antibodies occurred in a number of animals and one animal at the 500 IU/kg/day dose developed anti-human albumin antibodies. Overall, 67% of all treated monkeys tested positive for rIX-FP antibodies on Day 28 compared to 17% on Day 14. There were no similar findings in the controls.

In conclusion, intravenous injection of rIX-FP at doses up to 500 IU/kg for up to 28 days was well tolerated in cynomolgus monkeys with no adverse changes. Anti-human factor IX antibodies occurred in a number of rIX-FP treated animals and one animal at the 500 IU/kg/day dose had anti-human albumin antibodies. Under the conditions of this study, the NOAEL was considered to be 500 IU/kg.

Genotoxicity

Two investigations concerning genotoxicity were performed.

Study No. APQ0004: rIX-FP: Bacterial Reverse Mutation Test (Ames test)

This *in vitro* assay was performed to assess the mutagenic potential of rIX-FP. Histidine-dependent auxotrophic mutants of Salmonella typhimurium, strains TA1535, TA1537, TA98 and TA100, and a

tryptophan-dependent mutant of Escherichia coli, strain WP2 uvrA (pKM101), were exposed to rIX-FP dissolved in water for injection (WFI) and diluted in isotonic saline (0.9 %). Isotonic saline was also used as a negative control.

Two independent mutation tests were performed in the presence and absence of liver preparations (S9 mix) from rats treated with phenobarbital and 5,6-benzoflavone. The first test was a standard plate incorporation assay; the second included a pre-incubation stage.

Nominal concentrations of rIX-FP ranging from 0.1 to 200 IU per plate were tested. 200 IU per plate is the maximum concentration achievable using the test substance formulated as directed by CSL Behring, and thus complies with the recommendations of the regulatory guidelines that this assay follows. Other concentrations used were a series of dilutions of the highest concentration.

No signs of toxicity were observed towards the tester strains in either mutation test following exposure to rIX-FP. No evidence of mutagenic activity was seen at any concentration of rIX-FP in either mutation test. The concurrent positive controls demonstrated the sensitivity of the assay and the metabolising activity of the liver preparations. Thus, rIX-FP showed no evidence of mutagenic activity in this bacterial system under the test conditions employed.

Study No. APQ0006: rIX-FP: In Vitro Mammalian Chromosome Abberation Test In Human Lymphocytes

Human lymphocytes, in whole blood culture, were stimulated to divide by addition of phytohaemagglutinin, and were exposed to the test substance both in the absence and presence of S9 mix derived from rat livers. Negative and positive control cultures were also included. Two hours before the end of the incubation period, cell division was arrested using Colcemid®, the cells harvested and slides prepared, so that metaphase cells could be examined for chromosomal damage.

In order to determine the toxicity of rIX-FP to cultured human lymphocytes, the mitotic index was assessed for all cultures treated with the test substance and negative control (chosen diluent, isotonic saline, 0.9 %). Justification for concentration selection was based on the maximum achievable nominal concentration of 200 IU/mL using the test substance formulation procedure as directed by CSL Behring. On the basis of these data, the following three highest concentrations were selected for metaphase analysis:

First test: In the absence of S9 mix - 3 hour treatment, 18 hour recovery: 7.2, 12 and 20 IU/mL. In the presence of S9 mix (2 % v/v) - 3 hour treatment, 18 hour recovery: 7.2, 12 and 20 IU/mL.

Second test: In the absence of S9 mix - 21 hour continuous treatment: 7.2, 12 and 20 IU/mL. In the presence of S9 mix (5 % v/v) - 3 hour treatment, 18 hour recovery: 7.2, 12 and 20 IU/mL.

In the absence and presence of S9 mix, rIX-FP caused no statistically significant increases in the proportion of metaphase figures containing chromosomal aberrations, at any concentration, when compared with the negative control, in either test. No statistically significant increases in the proportion of polyploid cells were observed during metaphase analysis, in either test.

All positive control compounds caused statistically significant increases in the proportion of aberrant cells, demonstrating the sensitivity of the test system and the efficacy of the S9 mix.

Carcinogenicity

Carcinogenicity studies were not submitted.

Reproduction Toxicity

Reproduction toxicity studies were not submitted.

Toxicokinetic data

Local Tolerance

Study No. APQ0008: rIX-FP: Local Tolerance Study in the Rabbit following Intravenous, Intra-arterial or Perivenous Injection (GLP-compliant)

This study was performed to assess the local tolerance of rIX-FP when administered by the intended clinical dose route (intravenous) and potential clinical missdose routes (intra-arterial or perivenous).

Three groups, each comprising four female NZW rabbits received rIX-FP.

Group 1: Four rabbits received an intravenous injection of 1.2 mL of rIX-FP into the lateral ear vein of the right ear on a single occasion (Day 1). The lateral ear vein of the left ear of each animal received the same volume of isotonic saline (0.9 %) and acted as a Control.

Group 2: Four rabbits received an intra-arterial injection against the blood flow of 1.3 mL of rIX-FP into the median auricular artery of the right ear on a single occasion (Day 1). The median auricular artery of the left ear of each animal received the same volume of isotonic saline (0.9 %) and acted as a Control.

The amount administered i.v. or i.a. was, or exceeded, the clinical dose of 75 IU/kg.

Group 3: Four rabbits received a perivenous injection of 0.2 mL of rIX-FP alongside the lateral ear vein of the right ear on a single occasion (Day 1); the lateral ear vein of the left ear of each animal received 0.2 mL of isotonic saline (0.9 %) and acted as a Control.

All animals were observed for four days. There was no sign of toxicity or ill health in any rabbit during the observation period and bodyweight gain was considered to have been unaffected by treatment.

No local irritation was apparent at any time during the study period, at any injection site treated with rIX-FP, irrespective of route of administration. One case of very slight erythema was evident at a single control intra-arterial injection site, 24 hours after administration.

Bruising at the site of injection was common and it was considered that this was due to the administration procedure. There was no treatment-related macroscopic or microscopic pathology finding.

Taken together, intravenous, intra-arterial and perivenous injection of rIX-FP was well tolerated in rabbits with no local or systemic signs of reaction to treatment. Macropathological and histological findings were considered to be due to the administration procedure.

Other toxicity studies

Study No. S22456: In vivo Thrombogenicity Test in the Rabbit

The thrombogenic potential was assessed in rabbits using a venous stasis model (Wessler test). Three groups with 3 male and 3 female NZW rabbits each were administered intravenously with 75, 150 and 500 IU/kg rIX-FP, respectively. One additional group was treated with placebo (i.e. isotonic saline, 0.9 %). After administration of the test article or the placebo the Vena jugularis was ligated. Formation of

thrombi in the right or left Vena jugularis according to a score system was determined after 10 and 20 minutes, respectively. In conclusion, rIX-FP showed no thrombogenic activity after intravenous administration of 75, 150 and 500 IU/kg.

2.3.5. Ecotoxicity / environmental risk assessment

Idelvion is a recombinant replacement protein catabolized during human metabolism and no active molecule is excreted by the patient. In accordance with the guideline CHMP/SWP/4447/00 it is exempted from an environmental risk assessment since proteins are unlikely to result in a significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

An initial pharmacodynamic investigation carried out *in vitro* to identify pharmacologically relevant test species indicated that rIX-FP is pharmacologically active in cynomolgus monkeys, rats and rabbits with effects on aPTT higher or comparable to the effects seen in human plasma. In-vivo pharmacodynamic studies were performed in two animal species deficient in FIX, i.e. FIX deficient mice and dogs. In hemophilia B dogs rIX-FP (100 IU/kg i.v.) demonstrated a shortening of the aPTT and the whole blood clotting time (WBCT). Of note, both, rIX-FP and BeneFIX® induced an antibody response after single dose application in the hemophilia B dogs. The i.v. administration of 50, 100 and 200 IU/kg rIX-FP, respectively, to FIX deficient mice revealed a significant dose-dependent reduction of total blood loss, time to hemostasis and aPTT compared to the control group.

No secondary pharmacology studies were conducted, which is considered acceptable based on the type of product.

In terms of safety pharmacology the effects of rIX-FP administration on pulmonary functions (e.g. respiration rate, tidal volume and minute volume) were investigated in conscious rats using plethysmography. In this study no effects of rIX-FP treatment on respiratory parameters were observed (NOAEL 500 IU/kg). Safety pharmacological assessment of effects on the cardiovascular system was covered by the repeat-dose toxicology study in cynomolgus monkeys. In brief, electrophysiology of the heart, blood pressure and pulse rate measurements were considered to be unaffected by rIX-FP treatment. Potential effects on the central nervous system were evaluated during the single-dose toxicity studies in rats and cynomolgus monkeys as well as during the repeat-dose toxicity studies in rats and cynomolgus monkeys based on clinical observations as well as macroscopic and histopathological evaluations. In all these studies no signs of toxic effects on the central nervous system were noted.

The type and amount of safety pharmacology studies are considered sufficient. Inclusion of safety pharmacology parameters into repeat-dose toxicity studies is state-of-the-art proceeding. Evaluation of safety pharmacology in terms of cardiovascular, respiratory and central nervous system obviously revealed no safety concerns against the use of rIX-FP within the intended dosage range.

In order to evaluate the pharmacokinetics of rIX-FP, a study with single intravenous administration was performed in monkeys and in hemophilia B dogs. In terms of extended half-life of rIX-FP antigen levels reveal favourable results. Of note, antibody measurements yielded interesting results as the monkeys did not develop any antibodies after the single dose application whereas the haemophilia B dogs did.

In order to evaluate tissue biodistribution of rIX-FP, a quantitative whole-body autoradiography (QWBA) study was conducted in rats. In this study it was demonstrated that the tissue distribution of

[3H]-rIX-FP and [3H]-BeneFIX was comparable, both penetrating predominantly into well vascularized tissues and/or excretion organs whereas biodistribution of [3H]-albumin appeared to be different. The notion of extended tissue half-life of [3H]-rIX-FP due to albumin fusion was supported as [3H]-rIX-FP and [3H]-albumin derived radioactivity was detectable over 120 hours, whereas the radioactivity associated with [3H]-BeneFIX was only detectable over 24 hours. These findings support the notion that rIX-FP has an extended half-life.

In terms of toxicology three single dose and two repeat dose toxicology studies were performed. Rats and monkeys were selected as they represent the standard animals for these types of toxicological investigations and rIX-FP was shown to be pharmacologically active in these species.

A single intravenous bolus injection of rIX-FP at doses up to 500 IU/kg was well tolerated in cynomolgus monkeys and rats with no toxicologically significant changes. The NOAEL was considered to be 500 IU/kg for both species.

An additional toxicity study in rats following a single intravenous administration of the high-dose (500 IU/kg) including a toxicokinetic analysis was performed to compare the toxicity profile of pilot scale (500 L) and commercial scale (2500 L) material. Overall it could be concluded that there were no significant toxicities observed after a single intravenous administration of either pilot scale or commercial scale material at a nominal dose of 500 IU/kg. There were also no significant differences between pilot scale and commercial scale material despite the presence of higher bilirubin concentrations within commercial scale material.

Administration of rIX-FP by intravenous injections on 28 consecutive days at doses up to 500 IU/kg/day was well tolerated in the rat with no findings indicative of adverse toxicity and a NOAEL of 500 IU/kg was considered under the conditions of this study. The same was observed following repeated dosing in cynomolgus monkeys leading to a NOAEL of 500 IU/kg.
Repeat-dose toxicity studies in rats and monkeys showed that rIX-FP elicited a strong immune response in the majority of animals characterized by the formation of neutralizing anti-drug-antibodies (ADA) against rIX-FP. The number of ADA positive animals increased with the number of dosing occasions and the dose level resulting in reduced exposure levels as indicated by reductions in AUC and Cmax in ADA positive animals.

To evaluate the potential genotoxicity risk, two in vitro studies were performed with rIX-FP, i.e. the bacterial reverse mutation test (Ames test) and the chromosome aberration test in human lymphocytes. Both assays showed no evidence of mutagenic activity.

Local tolerance investigations were included in the single-dose and repeat-dose toxicity studies in rats and monkeys. Furthermore, a separate local tolerance study was performed in rabbits with no local or systemic signs of reaction to treatment leading to the overall conclusion that rIX-FP was locally well tolerated following repeated intravenous bolus injections in the rat and cynomolgus monkey and following a single intravenous, intra-arterial and perivenous administration to rabbits.
The thrombogenic potential of rIX-FP was evaluated using a modified Wessler stasis model in rabbits, a standard model to investigate thrombogenicity. In this study there was no indication of thrombogenic activity at the three doses of rIX-FP tested, i.e. 75 IU/kg, 150 IU/kg and 500 IU/kg.

Carcinogenicity studies were not submitted and are required for as the proteins in rIX-FP (human factor IX and human albumin) are naturally occurring proteins in the human body. For the same reasons a justification for omission of studies on reproductive and developmental toxicity is acknowledged. However, macro- and histopathological investigations of male and female reproductive organs were included in the single-dose and repeat-dose toxicity studies (rats and monkeys) with the result that there were no findings indicative of adverse toxicity. Moreover, there is no necessity to

conduct studies on embryo toxicity and fetal development as the patient population is male. Based on the rare occurrence of haemophilia B in women, experience regarding the use of rIX-FP during pregnancy is not available. Animal reproduction studies have not been conducted with rIX-FP. Therefore, rIX-FP should be used during pregnancy and lactation only if clearly indicated.

There is no information on the effects of rIX-FP on fertility (See SmPC section 4.6.).

No investigations on carcinogenicity and reproductive toxicology have been conducted.

In accordance with the guideline CHMP/SWP/4447/00 rIX-FP as a protein is exempted from an environmental risk assessment since proteins are unlikely to result in a significant risk to the environment.

Overall, type and amount of investigations on toxicology of rIX-FP are considered sufficient to support marketing authorization application of rIX-FP. The results of the toxicology studies do not raise safety concerns regarding the use of rIX-FP within the intended dose range.

2.3.7. Conclusion on the non-clinical aspects

Overall, the extent of the non-clinical toxicology program is considered adequate. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeat dose toxicity, genotoxicity, thrombogenicity and local tolerability.

The non- clinical aspects of rIX-FP are satisfactorily described and all available information has been appropriately included in the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1 Overview of Clinical studies

Study No	Design	Primary objective	Population	Treatment, dose
2001	Phase 1 prospective multicenter, open label	Safety (AEs, laboratory changes)	25 male subjects with haemophilia B Total PK population=22 Previous FIX PK n=15	rIX-FP IV 25, 50, 75 IU / Kg previous FIX IV 50 IU/kg
2004	Phase 1/ 2 prospective multicenter, open label	Safety (AEs, laboratory changes, inhibitor formation, antibody development)	17 male subjects with haemophilia B Total PK population=13	rIX-FP IV 25, IU / Kg
3001	Phase 2 / 3 prospective multicenter, open label pivotal	Efficacy in prophylaxis, safety (development of inhibitors)	63 male subjects with haemophilia B Total PK population=57 Previous FIX PK n=13	rIX-FP IV 25, 50, 75 IU / Kg previous FIX IV 50 IU/kg
3002	Phase 3 prospective multicenter, open label paediatric	PK of a single dose, safety (development of inhibitors)	27 male subjects with haemophilia B Total PK population=27 Previous FIX n= 17	rIX-FP IV 25, 50, 75 IU / Kg previous FIX IV 50 IU/kg
3003	Phase 2 / 3 prospective multicenter, open label	Safety (in terms of inhibitor formation, antibody development) Surgical substudy: Efficacy in the prophylaxis and treatment of bleeding in surgical procedures	80 male patients with haemophilia B	

2.4.2. Pharmacokinetics

Analytical methods

For determination of FIX activity in human plasma a one-stage clotting assay was used. In addition, for clinical studies 2001 and 2004, a validated enzyme-linked immunosorbent assay (ELISA) antigen assay to measure FIX antigen levels in clinical samples was used for correlation purposes.

Study subjects were tested for inhibitory antibodies against FIX and for antibodies against rIX-FP and for the formation of antibodies against Chinese Hamster Ovary (CHO) host cell proteins.

All assays were validated for the determination of clinical study samples. Assay validation studies included evaluation of linearity, concentration dependence, sensitivity, specificity, precision, accuracy, matrix effects, robustness, and influence of residual study drug. Results from all bioanalytical validation studies have been provided.

Plasma samples in which antibodies against CHO host cell proteins are detected above the cut-off in the ELISA screening assay undergo further *confirmation assays* using Surface Plasmon Response (SPR) technology. Samples are defined as "positive" as soon as the "enhancement level" is detected above the plasma enhancement cut-off. If the confirmation assay is negative, the initial positive response is considered to be a false positive result. The assay was validated for determination of antibodies against CHO host cell proteins in human plasma samples. Accuracy, precision, repeatability, linearity, limit of quantitation and robustness were assessed in the validation. All assessments met pre-defined acceptance criteria outlined in the validation protocol.

Pharmacokinetics in the target population

Studies 2001, 2004, 3001 and 3002 assessed the Pharmacokinetics (PK, based on FIX activities) of rIX-FP in 107 unique subjects with hemophilia B (FIX activity ≤ 2%) using at least 1 of 3 different doses (25, 50 or 75 IU/kg). The PK of 50 IU/kg previous FIX (pdFIX or rFIX) was also evaluated in a subset of subjects in studies 2001, 3001 and 3002. FIX activity measurements from adult and pediatric subjects were analyzed using a non-compartmental PK analysis. In addition, population PK analyses were conducted on data from studies 2001, 2004, 3001, and 3002 to further characterize the PK of rIX-FP. Potential determinants (demographic and clinical covariates) of rIX-FP PK variability and simulated FIX activity-time profiles for various dosing regimens of rIX-FP were identified.

Study 2001

This phase 1, dose-escalation study in 25 previously treated adult and adolescent subjects (age: 15 to 58 years) with hemophilia B, evaluated the safety and PK of 25, 50, and 75 IU/kg rIX-FP. Dose was applied at least 4 days after administration of their previously given FIX product. Blood samples for PK assessment were taken before injection of rIX-FP and at the following time points after injection of rIX-FP: 30 minutes, and 3, 6, 9, 24, 48, 72, 120, 168, 240 and 336 hours. The study recorded incremental recovery, in vivo half-life ($t_{1/2}$), area under the curve (AUC) and clearance (CL). All subjects completed the study and no subjects were discontinued.

A summary of the plasma FIX activity PK parameters are presented in Table 2:

Table 2 Study 2001: Summary of Mean (CV%) FIX Activity PK Parameters following a single injection of 25, 50, and 75 IU/kg rIX-FP, and 50 IU/kg of previous rFIX and pdFIX (PK Population)

	rIX-FP			rFIX	pdFIX
Parameter, Units	**25 IU/kg (n = 7)[a]**	**50 IU/kg (n = 13)**	**75 IU/kg (n = 8)**	**50 IU/kg (n = 8)**	**50 IU/kg (n = 4)**
IR[b], (IU/dL)/(IU/kg)	1.65 (11.3)	1.38 (20.1)	1.08 (19.8)	0.945 (25.3)	1.10 (18.0)
C_{max}, IU/dL	41.1 (12.7)	69.3 (18.7)	82.0 (19.7)	47.3 (25.3)	54.8 (18.0)
$AUC_{0\text{-}inf}$, IU*h/dL	4658 (36)	7670 (22)	9345 (20)	1330 (18)	1503 (31)
CL[c], mL/h/kg	0.574 (31.1)	0.682 (22.3)	0.836 (19.8)	3.87 (18.3)	3.56 (30.9)
Vss[c], dL/kg	0.856 (31.6)	0.923 (17.4)	1.20 (22.6)	1.25 (20.9)	0.975 (17.2)
$t_{1/2}$, h	118 (38.0)	100 (21.1)	104 (17.7)	22.4 (19.8)	19.6 (14.9)
MRT, h	153 (23.8)	138 (17.1)	144 (13.7)	32.8 (20.4)	28.3 (15.7)

Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve from time 0 extrapolated to infinity; C_{max}, maximum plasma concentration; CL, clearance; CV, coefficient of variation; FIX, factor IX; IR, incremental recovery; MRT, mean residence time; n, number of subjects; pdFIX, plasma-derived factor IX; PK, pharmacokinetic; rFIX, recombinant factor IX; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; $t_{1/2}$, terminal half-life; Vss, volume of distribution at steady state.

[a] n = 6 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[b] Incremental recovery is defined as maximum (peak) FIX activity (IU/dL) obtained through 30 minutes following injection, per dose of (IU/kg) injection.

[c] Clearance and Vss are normalized for body weight.

Note: All values are baseline-uncorrected, with the exception of IR and C_{max}, which are baseline-corrected.

Source: Study 2001 CSR Tables 14.2.2.1.1 and 14.2.2.1.2.

A summary of the FIX activity in plasma time course is presented in Table 3:

Table 3 Study 2001: Summary of FIX Activity Concentrations (IU/dL) over time following a single Injection of 25, 50, or 75 IU/kg rIX-FP (PK Population)

	Day 1 (Predose)	Day 1 (30 minutes)	Day 7 (168 h)	Day 10 (240 h)	Day 14 (336 h)
25 IU/kg rIX-FP					
n	7	7	7	4	3
Mean (SD)	1.21 (1.17)	41.9 (5.15)	8.63 (3.31)	5.03 (1.75)	2.97 (2.37)
Median	0.700	40.5	8.70	4.60	2.30
Min, Max	0.100, 3.40	37.1, 50.0	4.60, 14.1	3.60, 7.30	1.00, 5.60
50 IU/kg rIX-FP					
n	13	13	13	13	5
Mean (SD)	1.26 (1.17)	68.6 (13.7)	14.7 (2.95)	8.89 (2.81)	5.86 (2.07)
Median	0.700	64.5	14.4	9.00	5.50
Min, Max	0.100, 3.00	52.2, 97.8	10.7, 18.7	3.70, 14.2	3.50, 8.70
75 IU/kg rIX-FP					
n	8	8	8	8	8
Mean (SD)	0.638 (0.590)	82.6 (14.4)	18.0 (4.67)	10.8 (2.79)	6.65 (2.30)
Median	0.450	85.9	17.3	10.9	5.95
Min, Max	0.100, 1.60	53.7, 101	12.1, 27.0	6.30, 15.0	3.90, 10.2

Abbreviations: FIX, factor IX; Max, maximum; Min, minimum; n, number of subjects; PK, pharmacokinetic; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; SD, standard deviation.

Note: All values are baseline-uncorrected.

Source: Study 2001 CSR Table 14.2.1.1.2.

Study 2004

This phase 1 / 2 study evaluated the safety, PK, and efficacy of rIX-FP as both prophylaxis and on-demand therapy. 13 subjects (aged 15 to 46 years) received 25 IU/kg rIX-FP as a single intravenous (IV) injection for PK-evaluation. Dose was applied at least 4 days after administration of their previously given FIX product. Blood samples for PK assessment were taken before injection of rIX-FP and at the following time points after injection of rIX-FP: 30 minutes, and 3, 24, 48, 72, 120, 168, 240, and 336 hours. The study recorded incremental recovery, in vivo half-life ($t_{1/2}$), area under the curve (AUC) and clearance (CL). All subjects completed the PK-part of the study.

A summary of the rIX-FP PK parameters after a single injection of 25 IU/kg rIX-FP is provided in Table 4:

Table 4 Study 2004: Summary of Mean (CV%) FIX Activity PK Parameters following a single injection of 25 IU/kg rIX-FP (PK Population)

Parameter, Units	rIX-FP 25 IU/kg (n = 13)
IR[a], (IU/dL)/(IU/kg)	1.45 (8.30)
C_{max}, IU/dL	36.1 (8.02)
$AUC_{0\text{-}inf}$, IU*h/dL	3414 (13)
CL[b], mL/h/kg	0.744 (13.2)
Vss[b], dL/kg	0.923 (26.1)
$t_{1/2}$, h	94.8 (37.5)
MRT, h	127 (30.2)

Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve at time 0 extrapolated to infinity; CL, clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; FIX, factor IX; IR, incremental recovery; MRT, mean residence time; n, number of subjects; PK, pharmacokinetic; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; $t_{1/2}$, terminal half-life; Vss, volume of distribution at steady state.

[a] Incremental recovery is defined as maximum (peak) FIX activity (IU/dL) obtained through 30 minutes following injection, per dose of (IU/kg) injection.

[b] Clearance and Vss are normalized for body weight.

Note: All values are baseline-uncorrected, with the exception of IR and C_{max}, which are baseline-corrected.

Source: Study 2004 CSR Tables 14.2.7.1 and 14.2.7.2.

A summary of the FIX activity time-profile in plasma is presented in Table 5:

Table 5 Study 2004: Summary of FIX Activity Concentrations (IU/dL) over time following a single injection of 25 IU/kg rIX-FP (PK Population)

	Day 1 (Predose)	Day 1 (30 minutes)	Day 7 (168 h)	Day 10 (240 h)	Day 14 (336 h)
rIX-FP 25 IU/kg Overall					
n	13	13	13	13	3
Mean (SD)	1.83 (1.32)	38.0 (3.91)	5.58 (0.993)	3.88 (1.02)	2.90 (0.458)
Median	1.70	37.0	5.60	3.80	3.00
Min, Max	0.1, 4.1	32.6, 44.7	3.1, 7.2	2.1, 6.2	2.4, 3.3

Abbreviations: FIX, factor IX; Max, maximum; Min, minimum; PK, pharmacokinetics; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; SD, standard deviation.

Note: All values are baseline-uncorrected.

Source: Study 2004 CSR Table 14.2.6.2.

Study 3001

This pivotal phase 2 / 3 study evaluated safety, efficacy, and PK of rIX-FP as both routine prophylaxis, and on-demand treatment for the control and prevention of bleeding episodes in subjects with hemophilia B (FIX activity ≤ 2%). A total of 63 subjects were enrolled in the study including 40 subjects in the prophylaxis arm (Arm 1) and 23 subjects in the on-demand arm (Arm 2). Of subjects who never received rIX-FP before, PK-evaluation with their previous FIX-product was done. Repeat PK was done in 15 subjects after approximately 6 months. An additional subset of subjects had a PK assessment with a dose of 75 IU/kg at approximately 6 months prior to switching to the 10- or 14-day treatment regimen.

The PK data presented herein focus on FIX activity levels and PK parameters derived from FIX activity data. Blood samples were collected for PK analysis prior to injection, and at 30 minutes, 3, 24, 48, 72,

120, 168, 240 hours after injection of both 25 and 50 IU/kg rIX-FP. For the 50 IU/kg rIX-FP dose and repeat PK, blood samples were also collected at 336 hours.

A summary of the plasma FIX activity PK parameters for 50 IU/kg rIX-FP and previous FIX product are presented in Table 6:

Table 6 Study 3001: Summary of Mean (CV%) FIX Activity PK Parameters after 50 IU/kg rIX-FP and 50 IU/kg of previous FIX product (PK Population)

	rIX-FP	Previous FIX		
Parameter, Units	50 IU/kg (n = 45)[a]	50 IU/kg rFIX (n = 8)[b]	50 IU/kg pdFIX (n = 4)	Total (n = 12)[c]
IR[d], (IU/dL)/(IU/kg)	1.27 (23.9)	0.834 (18.1)	1.27 (25.3)	0.980 (30.6)
C_{max}, IU/dL	63.9 (23.4)	41.7 (18.0)	63.7 (25.3)	49.1 (30.5)
$AUC_{0\text{-}inf}$, IU*h/dL	7176 (30)	1396 (35)	1408 (27)	1400 (31)
CL[e], mL/h/kg	0.769 (33.5)	4.03 (38.2)	3.75 (26.4)	3.93 (33.5)
Vss[e], dL/kg	1.02 (18.7)	1.35 (23.0)	0.893 (17.9)	1.18 (29.0)
$t_{1/2}$, h	102 (21.8)	24.2 (19.7)	17.0 (20.3)	21.6 (25.5)
MRT, h	140 (19.5)	35.3 (20.6)	24.4 (16.1)	31.3 (26.1)

Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve at time 0 extrapolated to infinity; CL, clearance; C_{max}, maximum plasma concentration; CV, 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; $t_{1/2}$, terminal half- life; Vss, volume of distribution at steady state.

[a] n = 43 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[b] n = 7 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[c] n = 11 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[d] Incremental recovery is defined as maximum (peak) FIX activity (IU/dL) obtained through 30 minutes following injection, per dose of (IU/kg) injection.

[e] Clearance and Vss are normalized for body weight.

Note: All values are baseline-uncorrected, with the exception of IR and C_{max}, which are baseline-corrected.

Source: Study 3001 CSR Tables 14.3.7.1, 14.3.7.2, 14.3.9.1, 14.3.9.2, 14.3.9.3, 14.3.9.4, 14.3.9.5, and 14.3.9.6.

When comparing the PK parameters for 50 IU/kg rIX-FP with those of 50 IU/kg rFIX, mean IR (baseline-corrected) was 52% higher (1.27 vs 0.834 [IU/dL]/[IU/kg]), mean $t_{1/2}$ was 4.2-fold longer (102 vs 24.2 hours), mean plasma MRT was 4-fold longer (140 vs 35.3 hours), mean plasma $AUC_{0\text{-}inf}$ was 5.1-fold larger (7176 vs 1396 IU*h/dL), and mean CL was 81% lower (0.769 vs 4.03 mL/h/kg) (Table 7). IR and c_{max} of pd FIX were similar to rIX-FP.

After administration of 25 IU/kg rIX-FP, mean IR (baseline-corrected) was 1.29 (IU/dL)/(IU/kg), mean $t_{1/2}$ was 90.0 hours, mean c_{max} was 33.6 IU/dl, mean MRT was 134 hours, mean plasma $AUC_{0\text{-}inf}$ was 4253 IU*h/dL, and mean CL was 0.665 mL/h/kg (n = 6). After administration of 75 IU/kg rIX-FP, mean baseline-corrected IR was 1.04 (IU/dL)/(IU/kg) and C_{max} was 77.3 IU/dL (n = 5).

After administration of a single IV injection of 50 IU/kg rIX-FP, mean FIX activity remained above 5% through Day 14, which supports the feasibility of a dosing interval once up to every 2 weeks.

Table 7 Study 3001: Summary of FIX Activity Concentrations (IU/dL) over time following a single injection of 50 IU/kg rIX-FP (PK Population)

	Day 1 (Predose)	Day 1 (30 min)	Day 2 (48 h)	Day 7 (168 h)	Day 10 (240 h)	Day 14 (336 h)
n	45	45	40	44	38	35
Mean (SD)	2.35 (2.55)	65.8 (15.5)	35.8 (7.88)	13.8 (4.73)	9.59 (4.14)	6.10 (3.29)
Median	1.80	64.3	35.9	13.5	10.2	5.30
Min, Max	0.0, 14.1	41.2, 125	22.1, 53.1	4.9, 24.5	3.4, 24.8	1.9, 19.7

Abbreviations: FIX, factor IX; Max, maximum; Min, minimum; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; SD, standard deviation.

Note: All values are baseline-uncorrected.

Source: Study 3001 CSR Table 14.3.2.1.

A subset of 15 subjects on prophylaxis treatment underwent an initial PK assessment with 50 IU/kg rIX-FP and a repeat PK assessment with 50 IU/kg rIX-FP approximately 6 months on prophylaxis later with similar results.

Table 8 Study 3001: Summary of Mean (CV%) FIX activity PK parameters following initial and repeat dose of 50 IU/kg rIX-FP (Adults 12 to ≤ 65 Years Old) (PK Population)

Parameter, Units	rIX-FP 50 IU/kg Initial PK (n = 14)[b]	rIX-FP 50 IU/kg Repeat PK[a] (n = 15)[c]
IR[d], (IU/dL)/(IU/kg)	1.28 (16.7)	1.40 (19.5)
C_{max}, IU/dL	64.7 (15.8)	71.0 (19.4)
$AUC_{0\text{-}inf}$, IU*h/dL	7904 (23)	9979 (25)
CL[e], mL/h/kg	0.666 (24.5)	NC
Vss[e], dL/kg	1.01 (17.4)	1.43 (23.8)
$t_{1/2}$, h	112 (15.1)	128 (26.8)
MRT, h	156 (15.2)	172 (25.7)
AR based on AUC	1.15 (13.1)	
LI	0.775 (12.3)	

Abbreviations: AR, accumulation ratio; AUC, area under the concentration-time curve; $AUC_{0\text{-}inf}$, AUC at time 0 extrapolated to infinity; C_{max}, maximum plasma concentration; CL, clearance; CV, coefficient of variation; FIX, factor IX; IR, incremental recovery; LI, linear index; MRT, mean residence time; NC, not calculated; PK, pharmacokinetic; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; $t_{1/2}$, terminal half-life; Vss, volume of distribution at steady state.

[a] Performed approximately 6 months after the initial PK assessment.

[b] n = 13 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[c] n = 14 for AR and n = 13 for LI.

[d] Incremental recovery is defined as maximum (peak) FIX activity (IU/dL) obtained through 30 minutes following injection, per dose of (IU/kg) injection.

[e] Clearance and Vss are normalized for body weight.

Note: All values are baseline-uncorrected, with the exception of IR and C_{max}, which are baseline-corrected.

Source: Study 3001 CSR Tables 14.3.7.5 and 14.3.7.6.

Plasma FIX activity observed during the repeat 50 IU/kg rIX-FP assessment was not substantially different from the plasma FIX activity observed during the initial 50 IU/kg PK assessment. Mean FIX activities measured throughout the duration of the 14-day PK sample collection period were slightly higher during the repeat PK assessment than those measured during the initial PK assessment:

Table 9 Study 3001: Summary of FIX activity concentrations (IU/dL) over time following initial and repeat doses of 50 IU/kg rIX-FP

	Day 1 (Predose)	Day 1 (30 min)	Day 2 (48 h)	Day 7 (168 h)	Day 10 (240 h)	Day 14 (336 h)
rIX-FP 50 IU/kg Initial PK						
n	14	14	14	14	14	13
Mean (SD)	3.40 (3.60)	67.5 (10.2)	36.9 (6.45)	15.9 (4.08)	10.7 (4.86)	7.62 (4.11)
Median	2.30	68.8	36.7	14.9	10.3	6.30
Min, Max	0.0, 14.1	49.0, 85.8	26.9, 48.6	10.6, 24.5	4.6, 24.8	4.0, 19.7
rIX-FP 50 IU/kg Repeat PK[a]						
n	15	15	14	15	14	14
Mean (SD)	11.1 (6.59)	73.4 (12.1)	41.9 (9.02)	19.9 (5.18)	13.3 (4.40)	8.13 (3.45)
Median	9.80	73.6	40.9	19.6	12.7	8.05
Min, Max	2.1, 27.4	53.9, 96.3	26.8, 60.6	10.8, 28.9	3.6, 22.7	2.0, 14.8

Abbreviations: FIX, factor IX; Max, maximum; Min, minimum; PK, pharmacokinetics; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; SD, standard deviation.

[a] Performed approximately 6 months after the initial PK assessment.

Note: All values are baseline-uncorrected.

Source: Study 3001 CSR Table 14.3.2.5.

*

Special populations

Elderly

No subjects over the age of 65 were enrolled in any of the clinical studies. Therefore, no PK / exposure data in the elderly were generated.

Children: Paediatric study 3002

27 Pediatric subjects under 12 years of age (12 subjects < 6 years and 15 subjects 6 to < 12 years) were enrolled into study 3002. 11 adolescent subjects (12 to < 18 years) were included in studies 2001 (1 subject), 2004 (3 subjects), and 3001 (7 subjects).

Plasma FIX activity was measured before injection and then at 30 minutes, and 3, 24, 48, 72, 120, 168, 240, and 336 hours after injection of rIX-FP. A PK evaluation of previous FIX product was also conducted in a subset of subjects with no historical PK data of their previous FIX product. Plasma FIX activity of a subject's previous FIX product was measured before injection and then at 30 minutes, and 10, 24, and 48 hours after injection of the previous FIX product.

A summary of the plasma FIX activity PK parameters are presented in Table 10:

Table 10 Study 3002: Summary of mean (CV%) FIX activity PK parameters after 50 IU/kg dose of rIX-FP and previous FIX product, stratified by age group (PK Population)

	rIX-FP 50 IU/kg			Previous FIX 50 IU/kg		
Parameter, Unit	0 to < 6 years (n = 12)[a]	6 to < 12 years (n = 15)[b]	Total (n = 27)[c]	0 to < 6 years (n = 8)[d]	6 to < 12 years (n = 9)	Total (n = 17)[e]
IR[f], (IU/dL)/(IU/kg)	0.951 (21.5)	1.06 (22.6)	1.01 (22.5)	0.676 (20.7)	0.793 (29.3)	0.738 (26.8)
C_{max}, IU/dL	48.3 (19.0)	52.9 (23.2)	50.9 (21.8)	34.0 (21.4)	39.3 (30.2)	36.8 (27.3)
$AUC_{0\text{-}inf}$, IU*h/dL	4583 (33)	5123 (31)	4894 (32)	886 (70)	890 (21)	888 (47)
CL[g], mL/h/kg	1.18 (27.8)	1.06 (28.5)	1.11 (28.2)	7.16 (39.0)	5.81 (23.7)	6.40 (33.5)
Vss[g], dL/kg	1.42 (24.1)	1.32 (19.7)	1.36 (21.8)	1.77 (24.8)	1.43 (20.5)	1.58 (24.7)
$t_{1/2}$, h	89.6 (12.5)	92.8 (20.5)	91.4 (17.5)	19.9 (40.3)	17.7 (25.6)	18.6 (33.0)
MRT, h	123 (14.2)	129 (19.0)	126 (17.1)	27.7 (40.9)	25.2 (21.2)	26.3 (31.4)

Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve at time 0 extrapolated to infinity; CL, clearance; C_{max}, maximum plasma concentration; CV, 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; $t_{1/2}$, terminal half -life; Vss, volume of distribution at steady state.

[a] n = 11 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[b] n = 14 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[c] n = 26 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[d] n = 7 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[e] n = 16 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[f] Incremental recovery is defined as maximum (peak) FIX activity (IU/dL) obtained through 30 minutes following injection, per dose of (IU/kg) injection.

[g] Clearance and Vss are normalized for body weight.

Note: All values are baseline-uncorrected, with the exception of IR and C_{max}, which are baseline-corrected.

Source: Study 3002 CSR Tables 14.2.13.1 and 14.2.13.2.

In both age groups (0 to < 6 years and 6 to < 12 years), the plasma FIX activity was higher after injection of 50 IU/kg rIX-FP compared with 50 IU/kg previous FIX product. Mean and median plasma FIX activities after a single dose of 50 IU/kg of rIX-FP were above 2% at Day 14, regardless of age.

Table 11 Study 3002: Summary of FIX activity concentrations (IU/dL) over time after 50 IU/kg injection of rIX-FP, stratified by age group (PK Population)

	Day 1 (Predose)	Day 1 (30 min)	Day 2 (48 h)	Day 7 (168 h)	Day 10 (240 h)	Day 14 (336 h)
rIX-FP 50 IU/kg 0 to < 6 years						
n	12	12	7	11	10	8
Mean (SD)	2.56 (2.15)	50.0 (11.2)	19.1 (3.14)	8.35 (3.88)	5.33 (2.66)	2.45 (0.941)
Median	1.90	50.0	18.7	6.60	5.10	2.10
Min, Max	0.7, 8.3	34.7, 72.3	15.6, 23.8	2.9, 16.2	1.9, 11.7	1.5, 4.2
rIX-FP 50 IU/kg 6 to < 12 years						
n	15	15	12	15	14	7
Mean (SD)	2.09 (2.24)	55.0 (12.4)	26.9 (5.65)	9.51 (3.34)	6.41 (2.99)	3.23 (1.45)
Median	1.60	51.8	26.4	9.80	5.80	2.90
Min, Max	0.3, 9.4	36.5, 74.7	17.1, 34.5	4.8, 14.6	3.1, 11.7	2.2, 6.4
rIX-FP 50 IU/kg Total						
n	27	27	19	26	24	15
Mean (SD)	2.30 (2.17)	52.8 (12.0)	24.0 (6.16)	9.02 (3.55)	5.96 (2.85)	2.81 (1.23)
Median	1.60	51.4	23.8	8.65	5.30	2.40
Min, Max	0.3, 9.4	34.7, 74.7	15.6, 34.5	2.9, 16.2	1.9, 11.7	1.5, 6.4

Abbreviations: FIX, factor IX; Max, maximum; Min, minimum; PK, pharmacokinetic; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; SD, standard deviation.

Note: All values are baseline-uncorrected.

Source: Study 3002 CSR Table 14.2.12.1.

Population pharmacokinetic analysis

Population PK analysis was conducted in 104 subjects to further characterize the PK of rIX-FP in adults, adolescents and children with hemophilia, as well to describe and to identify determinants (demographic and clinical covariates) of rIX-FP PK variability and to subsequently undertake simulations of FIX activity-time profiles for various dosing regimens of rIX-FP.

Observed FIX activity levels were modeled as the sum of the endogenous baseline level (with a limit of ≤ 2%), any residual contribution from the previous FIX product and the FIX activity levels attributed to rIX-FP administration. Where subjects had an observed FIX activity value above 2% prior to the first dose of rIX-FP, this was assumed to reflect residual contribution of the previous FIX product in addition to the true endogenous FIX activity levels.

The final FIX activity population PK model for rIX-FP was used to simulate activity-time profiles following single and steady-state dosing of different rIX-FP dosing scenarios in adolescent, adult and pediatric populations. The simulated exogenous FIX age-related activity-time profile after single injections of 25, 40, 50, and 75 IU/kg rIX-FP is shown in Table 12 The simulated steady-state trough exogenous FIX activity levels are summarized in Table 13.

Table 12 Summary of the simulated durations that exogenous FIX activity was maintained above 1%, 3%, and 5% following a single dose of 25, 40, 50, and 75 IU/kg rIX-FP

	Simulated Duration (Days)[a]				
Simulated rIX-FP Dose FIX Activity	Age 0 to < 6 years	Age 6 to < 12 years	Age 12 to < 18 years	Age ≥ 12 years	Age ≥ 18 years
25 IU/kg					
> 1%	9.5 (8)	12 (10)	14.5 (12.5)	16 (13.5)	16.5 (13.5)
> 3%	6 (5)	7.5 (6)	9 (7.5)	10 (8.5)	10 (8.5)
> 5%	4 (3.5)	5 (4.5)	6.5 (5.5)	7 (6)	7 (6)
40 IU/kg					
> 1%	12.5 (10.5)	15.5 (13)	19 (16)	20.5 (17)	20.5 (17)
> 3%	8 (6.5)	10 (8.5)	12.5 (10.5)	13.5 (11.5)	14 (11.5)
> 5%	6 (5)	7.5 (6.5)	9.5 (8)	10.5 (8.5)	10.5 (9)
50 IU/kg					
> 1%	14 (11.5)	17 (14.5)	21 (17.5)	23 (19)	23 (19.5)
> 3%	9 (7.5)	11.5 (9.5)	14 (12)	15.5 (13)	16 (13)
> 5%	7 (6)	9 (7.5)	11 (9.5)	12.5 (10)	12.5 (10.5)
75 IU/kg					
> 1%	17 (14)	21 (17.5)	25.5 (21.5)	27.5 (23)	28 (23.5)
> 3%	12 (10)	15 (12.5)	18 (15)	19.5 (16.5)	20 (16.5)
> 5%	9.5 (8)	12 (10)	14.5 (12.5)	16 (13.5)	16 (13.5)

Abbreviations: FIX, factor IX; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin
[a] Values represent median (25th percentile).
Source: Population PK Report Addendum, Table 4-5.

Table 13 Summary of the simulated trough exogenous FIX activity following multiple doses of 25, 40, 50, and 75 IU/kg rIX-FP

	Trough Exogenous FIX Activity (IU/dL)				
Simulation	Age 0 to < 6 years	Age 6 to < 12 years	Age 12 to < 18 years	Age ≥ 12 years	Age ≥ 18 years
25 IU/kg weekly					
Median	2.6	4.3	6.4	7.5	7.7
25th percentile	1.7	3.0	4.6	5.4	5.5
90% PI	0.8 - 6.0	1.6 - 9.4	2.7 - 13.1	3.2 - 15.0	3.3 - 15.2
40 IU/kg weekly					
Median	4.9	7.9	11.6	13.6	13.9
25th percentile	3.4	5.6	8.5	9.9	10.2
90% PI	1.7 - 10.7	3.2 - 16.5	5.1 - 22.7	6.0 - 26.0	6.2 - 26.3
50 IU/kg every 10 days					
Median	2.9	5.1	7.9	9.4	9.6
25th percentile	1.8	3.3	5.4	6.6	6.7
90% PI	0.8 - 7.4	1.6 - 12.1	2.9 - 16.7	3.6 - 19.7	3.7 - 20.0
50 IU/kg every 14 days					
Median	1.1	2.1	3.7	4.5	4.6
25th percentile	0.5	1.2	2.3	2.9	3.0
90% PI	0.2 - 3.6	0.4 - 6.2	1.0 - 9.3	1.4 - 11.1	1.4 - 11.2
75 IU/kg every 14 days					
Median	2.1	3.9	6.6	8.0	8.2
25th percentile	1.1	2.3	4.2	5.3	5.4
90% PI	0.4 - 6.3	0.9 - 10.6	1.9 - 15.8	2.6 - 18.5	2.7 - 18.8
75 IU/kg every 21 days					
Median	0.4	1.1	2.1	2.8	2.8
25th percentile	0.2	0.5	1.1	1.6	1.6
90% PI	0.04 - 2.3	0.1 - 4.5	0.4 - 6.7	0.6 - 8.4	0.6 - 8.5

Abbreviations: FIX, factor IX; PI, prediction interval; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin.

Source: Population PK Report Addendum, Table 4-6.

Overall, the population PK simulation supports the dose regimens of 25 to 40 IU/kg weekly, 50 IU/kg every 10 days, and 50 to 75 IU/kg every 14 days in all ages. Alternatively, the dose regimens can be selected according to the desired FIX activity troughs based on the simulated FIX activity-time profile; in all age groups, a fixed monthly FIX consumption may be used to effectively provide the desired FIX activity troughs, with the understanding that a lower dose combined with shorter treatment interval may offer a higher trough than a higher dose combined with longer treatment interval.

Comparison and Analyses of Results across studies

The pooled PK population consists of all subjects for whom a PK parameter was derived for the respective individual studies.

Pharmacokinetic parameters after a single injection of rIX-FP

The prolonged $t_{1/2}$ and higher IR values resulting from a single injection of rIX-FP demonstrate the improved PK compared with previous FIX products. When comparing 50 IU/kg rIX-FP with 50 IU/kg rFIX, mean IR was 1.4-fold higher, mean $t_{1/2}$ was 4.4-fold longer, and mean CL was 81% lower.

Table 14 Summary of mean (CV%) single injection PK parameters (adults 18 to ≤ 65 years) (Pooled PK Population)

	rIX-FP			Previous FIX		
Parameter, Unit	25 IU/kg (n = 19)[a]	50 IU/kg (n = 47)[b]	75 IU/kg (n = 3)	50 IU/kg rFIX (n = 15)[c]	50 IU/kg pdFIX (n = 8)	Total (n = 23)[d]
IR[e], (IU/dL)/(IU/kg)	1.47 (14.6)	1.30 (23.8)	0.994 (31.8)	0.904 (22.0)	1.19 (22.4)	1.00 (25.7)
C_{max}, IU/dL	36.8 (14.7)	66.6 (26.7)	74.7 (31.1)	45.2 (22.0)	59.3 (22.4)	50.1 (25.7)
$AUC_{0\text{-inf}}$, IU*h/dL	3662 (25)	7482 (28)	8285 (20)	1396 (25)	1455 (25)	1418 (25)
CL[f], mL/h/kg	0.715 (23.9)	0.731 (26.8)	0.933 (19.5)	3.81 (26.8)	3.66 (27.9)	3.75 (26.6)
Vss[f], dL/kg	0.934 (28.3)	1.02 (27.9)	1.27 (34.4)	1.26 (20.6)	0.934 (17.0)	1.14 (24.2)
$t_{1/2}$, h	102 (43.3)	104 (25.4)	88.6 (12.6)	23.4 (19.0)	18.3 (17.4)	21.5 (21.7)
MRT, h	134 (30.8)	143 (22.7)	133 (16.2)	34.2 (19.8)	26.3 (16.3)	31.4 (22.4)

Abbreviations: $AUC_{0\text{-inf}}$, area under the concentration-time curve at time 0 extrapolated to infinity; C_{max}, maximum plasma concentration; CL, clearance; CV, coefficient of variation; FIX, factor IX; IR, incremental recovery; MRT, mean residence time; pdFIX, plasma-derived FIX; PK, pharmacokinetic; rFIX, recombinant FIX; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; $t_{1/2}$, terminal half-life; Vss, volume of distribution at steady state.

[a] n = 18 for $AUC_{0\text{-inf}}$, CL, Vss, $t_{1/2}$, and MRT.

[b] n = 46 for CL.

[c] n = 14 for $AUC_{0\text{-inf}}$, CL, Vss, $t_{1/2}$, and MRT.

[d] n = 22 for $AUC_{0\text{-inf}}$, CL, Vss, $t_{1/2}$, and MRT.

[e] Incremental recovery is defined as maximum (peak) FIX activity (IU/dL) obtained through 30 minutes following injection, per dose of (IU/kg) injection.

[f] Clearance and Vss are normalized for body weight.

Note: All values are baseline-uncorrected, with the exception of IR and C_{max}, which are baseline-corrected.

Source: Pooled PK Tables 14.2.1.1, 14.2.1.2, 14.2.1.5, 14.2.1.6, 14.2.1.9, 14.2.1.10, 14.2.2.1, and 14.2.2.2.

Body Weight: Body weight had a statistically significant influence on CL, and both central and peripheral volumes of distribution (V1 and V2); the CL of FIX activity on a per kg body weight basis was higher in younger subjects. However, weight was not a significant covariate on CL within the weight range for adult / adolescent age group (ie, ≥ 12 years).

Age: Consistent with ontogeny and observations from other available FIX replacement products, the PK of rIX-FP is similarly influenced by age. This is reflected by decreased $t_{1/2}$ and MRT, as well as increased values of CL in subjects 0 to < 12 years of age. The CL values in pediatric subjects (mean 1.18 mL/h/kg for subjects 0 to < 6 years and 1.06 mL/h/kg for subjects 6 to < 12 years) were higher than those observed in adults (0.765 mL/h/kg for subjects ≥ 12 to 65 years).

The mean IR values for rIX-FP were lower in the 0 to < 6 year age group (mean 0.95 [IU/dL]/[IU/kg]) than in the 12 to ≤ 65 year age group (1.28 [IU/dL]/[IU/kg]) (Table 15).

The population PK analysis examined the potential effect of age on CL, in addition to body weight; age did not provide any significant improvement on the model fitting, and no additional effect of age on other PK parameters was identified. The apparent lack of an age effect is likely to result from the strong correlation between age and total body weight in the pediatric population.

Other Factors: In the population PK report, BMI, AST and ALT levels, and creatinine clearance were analyzed in 104 subjects, and no relevant effects were observed.

Table 15 Mean (CV%) FIX activity PK parameters after a single injection of 50 IU/kg rIX-FP - Stratified by age (Pooled PK Population)

Parameter, Unit	0 to < 6 years (N = 12)	6 to < 12 years (N = 15)	12 to < 18 years (N = 8)	18 to ≤ 65 years (N = 69)	12 to ≤ 65 years (N = 77)
IR[a], (IU/dL)/(IU/kg)					
n	12	15	5	47	52
Mean (CV%)	0.951 (21.5)	1.06 (22.6)	1.11 (27.7)	1.30 (23.8)	1.28 (24.3)
C_{max}, IU/dL					
n	12	15	5	47	52
Mean (CV%)	48.3 (19.0)	52.9 (23.2)	55.3 (28.1)	66.6 (26.7)	65.5 (27.1)
$AUC_{0\text{-}inf}$, IU*h/dL					
n	11	15	5	47	52
Mean (CV%)	4583 (33)	5123 (31)	5347 (48)	7482 (28)	7276 (31)
CL[b], mL/h/kg					
n	11	15	5	46	51
Mean (CV%)	1.18 (27.8)	1.06 (28.5)	1.08 (39.3)	0.731 (26.8)	0.765 (31.9)
Vss[b], dL/kg					
N	11	15	5	47	52
Mean (CV%)	1.42 (24.1)	1.32 (19.7)	1.16 (14.0)	1.02 (27.9)	1.03 (26.8)
$t_{1/2}$, h					
n	11	15	5	47	52
Mean (CV%)	89.6 (12.5)	92.8 (20.5)	87.3 (35.7)	104 (25.4)	103 (26.4)
MRT, h					
n	11	15	5	47	52
Mean (CV%)	123 (14.2)	129 (19.0)	119 (31.2)	143 (22.7)	141 (23.7)

Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve at time 0 extrapolated to infinity; CL, clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; FIX, factor IX; IR, incremental recovery; MRT, mean residence time; N, total number of subjects; n, number of subjects with sufficient data to derive PK parameters; PK, pharmacokinetic; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; $t_{1/2}$, terminal half-life; Vss, volume of distribution at steady state.

[a] Incremental recovery is defined as maximum (peak) FIX activity (IU/dL) obtained through 30 minutes following injection, per dose of (IU/kg) injection.

[b] Clearance and Vss are normalized for body weight.

Note: All values are baseline-uncorrected, with the exception of IR and C_{max}, which are baseline-corrected.

Source: Pooled PK Tables 14.2.2.1 and 14.2.2.2.

For descriptive comparison of PK-results in all included studies, Table 16 summarizes such data:

Table 16 Summary of mean (CV%) FIX activity PK parameters from rIX-FP Clinical Studies (PK Population)

		Parameter, Unit							
Study	**Treatment, Dose**	**n**	**IR[a], (IU/dL)/(IU/kg)**	**C_{max}, IU/dL**	**$AUC_{0\text{-}inf}$, IU*h/dL**	**CL[b], mL/h/kg**	**Vss[b], dL/kg**	**$t_{1/2}$, h**	**MRT, h**
2001	rIX-FP 25 IU/kg	7[c]	1.65 (11.3)	41.1 (12.7)	4658 (36)	0.574 (31.1)	0.856 (31.6)	118 (38.0)	153 (23.8)
	rIX-FP 50 IU/kg	13	1.38 (20.1)	69.3 (18.7)	7670 (22)	0.682 (22.3)	0.923 (17.4)	100 (21.1)	138 (17.1)
	rIX-FP 75 IU/kg	8	1.08 (19.8)	82.0 (19.7)	9345 (20)	0.836 (19.8)	1.20 (22.6)	104 (17.7)	144 (13.7)
	rFIX 50 IU/kg	8	0.945 (25.3)	47.3 (25.3)	1330 (18)	3.87 (18.3)	1.25 (20.9)	22.4 (19.8)	32.8 (20.4)
	pdFIX 50 IU/kg	4	1.10 (18.0)	54.8 (18.0)	1503 (31)	3.56 (30.9)	0.975 (17.2)	19.6 (14.9)	28.3 (15.7)
2004	rIX-FP 25 IU/kg	13	1.45 (8.30)	36.1 (8.02)	3414 (13)	0.744 (13.2)	0.923 (26.1)	94.8 (37.5)	127 (30.2)
3001	rIX-FP 25 IU/kg	6	1.29 (21.5)	33.6 (22.9)	4253 (36)	0.665 (42.6)	0.831 (22.3)	90.0 (20.9)	134 (21.7)
	rIX-FP 50 IU/kg	45[d]	1.27 (23.9)	63.9 (23.4)	7176 (30)	0.769 (33.5)	1.02 (18.7)	102 (21.8)	140 (19.5)
	rIX-FP 75 IU/kg	5	1.04 (12.1)	77.3 (12.4)	NC	NC	NC	NC	NC
	Previous FIX 50 IU/kg	12[e]	0.980 (30.6)	49.1 (30.5)	1400 (31)	3.93 (33.5)	1.18 (29.0)	21.6 (25.5)	31.3 (26.1)
	rFIX 50 IU/kg	8[f]	0.834 (18.1)	41.7 (18.0)	1396 (35)	4.03 (38.2)	1.35 (23.0)	24.2 (19.7)	35.3 (20.6)
	pdFIX 50 IU/kg	4	1.27 (25.3)	63.7 (25.3)	1408 (27)	3.75 (26.4)	0.893 (17.9)	17.0 (20.3)	24.4 (16.1)
3002	rIX-FP 50 IU/kg	27[g]	1.01 (22.5)	50.9 (21.8)	4894 (32)	1.11 (28.2)	1.36 (21.8)	91.4 (17.5)	126 (17.1)
	Previous FIX 50 IU/kg	17[h]	0.738 (26.8)	36.8 (27.3)	888 (47)	6.40 (33.5)	1.58 (24.7)	18.6 (33.0)	26.3 (31.4)
	rFIX 50 IU/kg	12[i]	0.731 (25.0)	36.4 (25.7)	916 (53)	6.36 (36.5)	1.64 (26.4)	19.7 (31.8)	27.6 (32.0)
	pdFIX 50 IU/kg	5	0.756 (33.6)	37.8 (33.6)	828 (29)	6.48 (30.0)	1.45 (18.6)	16.3 (36.2)	23.6 (29.3)

Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve at time 0 extrapolated to infinity; C_{max}, maximum plasma concentration; CL, clearance; CV, coefficient of variation; FIX, factor IX; IR, incremental recovery; MRT, mean residence time; NC, not calculated; pdFIX, plasma-derived factor IX; PK, pharmacokinetic; rFIX, recombinant factor IX; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; $t_{1/2}$, terminal half-life; Vss, volume of distribution at steady state.

[a] Incremental recovery is defined as maximum (peak) FIX activity (IU/dL) obtained through 30 minutes following injection, per dose of (IU/kg) injection.

[b] Clearance and Vss are normalized for body weight.

[c] n = 6 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[d] n = 43 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[e] n = 11 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[f] n = 7 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[g] n = 26 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[h] n = 16 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

[i] n = 11 for $AUC_{0\text{-}inf}$, CL, Vss, $t_{1/2}$, and MRT.

Note: All values are baseline-uncorrected, with the exception of IR and C_{max}, which are baseline-corrected.

Source: Study 2001 CSR Tables 10 and 14.2.2.1.2; Study 2004 CSR Tables 14.2.7.1 and 14.2.7.2; Study 3001 CSR Tables 14.3.6.2, 14.3.7.2, 14.3.8.2, 14.3.9.2, 14.3.9.4, 14.3.9.6, 14.3.6.1, 14.3.7.1, 14.3.8.1, 14.3.9.1, 14.3.9.3 and 14.3.9.5; Study 3002 CSR Tables 11-5 and 11-6.

Table 17 Study 2001: Summary of Population PK Parameter by Dose and Endogenous FIX Activity Levels

Parameter, Unit	25 IU/kg		50 IU/kg		75 IU/kg	
	Endogenous FIX < 1% N = 8[a]	Endogenous FIX 1 to 2% N = 0	Endogenous FIX < 1% N = 11[b]	Endogenous FIX 1 to 2% N = 1	Endogenous FIX < 1% N = 4[c]	Endogenous FIX 1 to 2% N = 1
IR, (IU/dL)/(IU/kg)						
Median	1.49	ND	1.35	1.01	0.923	1.03
Min, Max	1.21, 1.64	ND	1.08, 2.11	NC	0.729, 1.29	NC
C_{max}, IU/dL						
Median	37.2	ND	67.3	51.3	54.8	79.8
Min, Max	26.3, 41.1	ND	56.6, 98.9	NC	32.2, 70.2	NC
$AUC_{0\text{-}inf}$, IU*h/dL						
Median	4161	ND	7224	7557	6887	9098
Min, Max	3466, 5576	ND	5483, 10745	NC	4009, 8040	NC
CL[d], mL/h/kg						
Median	0.555	ND	0.526	0.425	0.622	0.504
Min, Max	0.428, 0.706	ND	0.385, 0.842	NC	0.550, 0.709	NC
$t_{1/2}$, h						
Median	99.1	ND	102	125	102	96.3
Min, Max	86.0, 119	ND	80.7, 133	NC	98.2, 118	NC
Vss[d], dL/kg						
Median	0.888	ND	0.965	1.22	1.26	1.33
Min, Max	0.829, 1.02	ND	0.690, 1.46	NC	0.992, 1.61	NC

2.4.3. Pharmacodynamics

Mechanism of action

No studies on mechanism of action are submitted.

Primary and Secondary pharmacology

No dedicated studies on primary and secondary pharmacodynamics are submitted.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics assessment in adult and adolescent subjects with Haemophilia B covers 3 clinical studies (2001, 2004 and 3001) with dose-escalation (50, 25, 75 IU/kg) with complete PK-evaluation and investigation covering 3 dosages (including a reduced dose of 25 IU/kg), comparison with previous products and repeat PK. Population PK analysis identified potential demographic and clinical covariates of rIX-FP and simulated FIX activity-time profiles for various dosing regimens of rIX-FP. In addition, PK-evaluation in paediatric subjects <12 years of age has been provided in study 3002.

When using an in vitro thromboplastin time (aPTT)-based one stage clotting assay for determining Factor IX activity in patients' blood samples, plasma factor IX activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. Measurement with a one-stage clotting assay using a kaolin based aPTT reagent or Actin FS aPTT reagent will likely result in an underestimation of activity level. This is of importance particularly when changing the laboratory and/or reagents used in the assay. The challenge of the use of different aPTT reagents has been stated in section 4.2 of the SmPC.

The Clinical Guideline has been met, in general, i.e. in terms of number of subjects at least 12; PK parameters [Incremental recovery, in vivo half-life, AUC, Clearance], wash-out-period of 4 days, dose suggestion of the Guideline (50-75 IU/kg); number of lots used; sampling intervals amended when needed in accordance with the extended half-life.

In study 2001, a dose-escalation PK-study covering 25, 50 and 75 IU/kg (7, 13 and 8 subjects, respectively) and comparison with standard recombinant and plasma-derived FIX for the 50 IU/kg dose has been performed (4 and 8 subjects, respectively). For rIX-FP, sampling points have been adapted to the assumed extended half-life (10-15 min and 1h p.i. has been replaced by 30 min; 50h has been deleted, additional samples at 120, 168, 240 and 336 hours have been added). "True" c_{max} and incremental recovery might have been missed by this schedule between 30 minutes and 3 hours p.i.; the other samples are considered to be extensive and adequate. Comparison with well-known plasma-derived and recombinant FIX is acknowledged. However, sampling points for these "previous" products have been reduced, (baseline, 25-35 min, 1-3, 8-12, 20-26 and 32-48h post infusion). Reliability of the comparison of such different data-sets (comparator: sampling up to 32-48h p.i., rFIX-FP up to 336h) as linked due to ethical reasons (use of well-known product in a clinical trial). Minimum activities were above 4.6 IU/dl at day 7 for 25 IU/kg, above 3.7 IU/dl at day 10 for 50 IU/dl and above 3.9 IU/dl for 75IU/dl at day 14. Maximum activity concentrations did not exceed 100 IU/dl even in the 75 IU/kg group.

Results show significantly extended half-life of rIX-FP compared with pdFIX and rFIX and dose-dependent factor activity levels. However, median IR decreased with increasing dose which does not support dose-linearity.
In Study 2004 PK-evaluation covered 13 subjects and the dose of 25 IU/kg. Calculated PK parameters included Incremental recovery, in vivo half-life, AUC, and Clearance, the chosen dose of 25 IU/kg is significantly lower than suggested in the Clinical Guideline (50-75 IU/kg) but adapted to the assumed extended half-life. According to the Clinical Guideline, samples should be taken at baseline, 10-15, 30 minutes,1 hour, 3, 6, 9, 24, 48, and 50 hours post-infusion with a 72 hours optional sample. In study 2004, samples were taken before injection and 30 minutes, and 3, 24, 48, 72, 120, 168, 240, and 336 hours after the injection. Thus, sampling has been adapted to the assumed extended half-life, which is considered to be acceptable with the exception of the early phase up to 3 hours p.i.as for study 2001. Baseline-corrected AUC, CL and $t_{1/2}$ relevantly differ from baseline-uncorrected values: $AUC_{0-\infty}$: 2698 h*IU/dl (compared with 3414), $t_{1/2}$: 69,1 h (compared with 94.8), CL: 0.96 ml/h/kg (compared with 0.74) whereas IR and c_{max} are similar. However, population-PK analysis takes into account confounding factors. In vivo recovery data after first use of the commercial scale batch were similar to previous data.

In Study 3001 calculated PK parameters of overall 63 subjects included incremental recovery, in vivo half-life, AUC, and Clearance. Dosages cover 25, 50 and 75 IU/kg and sampling has been adapted to the assumed extended half-life, which is considered to be acceptable. Repeat PK shows an increase of IR (baseline-corrected from 1.28 to 1.40 (IU/dl) / (IU/kg), c_{max} (68.1 to 74.3 IU/dl), $AUC_{0-\infty}$ (7904 to 9979 IU*h/dl) and $t_{1/2}$ (112.1 to 128 h).

Study 3002 design follows the Guideline requirements in terms of numbers enrolled (27 subjects ; 12 <6 years, 15 > 6 years (requirement for at least 20 children <12 years and 10 in each group below and above 6 years of age being met); PK parameters [Incremental recovery, in vivo half-life, AUC, Clearance], wash-out-period of 4 days) studied. Demography data reflect male subjects less than 12 years of age with a majority of subjects being White (26/27 subjects, 96.3%) and non-Hispanic (25/27 subjects, 92.6%). Other parameters are considered to reflect average population.

In both age groups (0 to < 6 years and 6 to < 12 years), the plasma FIX activity was higher after injection of 50 IU/kg rIX-FP compared with 50 IU/kg of previous FIX product. Mean plasma FIX activity levels were numerically lower in the younger age group (ie, 0 to < 6 years) than the older age group (ie, 6 to < 12 years). Disregarding above discussed methodical aspects, mean and median plasma FIX activities after a single dose of 50 IU/kg of rIX-FP were above 2% at Day 14.

The results of Study 3002 demonstrate that the PK parameters of the younger pediatric age group (ie, 0 to < 6 years) are similar to those of the older pediatric age group (ie, 6 to < 12 years), though CL was marginally higher. However, results differ from the adult population,. Documented median activity levels of >2 IU/dl at day 14 support prolonged treatment interval for prophylaxis, in children <12 years of age.

FIX activity was well described by a 2-compartment population PK model with body weight and weight-adjusted dose being the only significant covariates. The estimated endogenous FIX activity levels were consistent with levels observed in patients with hemophilia B and FIX activity ≤ 2%. FIX antigen was well described by a 2-compartment population PK model with allometric scaling. The FIX antigen model confirmed PK linearity of the rIX-FP protein.

Using the final FIX activity population PK model to perform simulations, the median peak FIX activity after a single 50 IU/kg injection of rIX-FP was predicted to be at least 40 IU/dL (age ≥ 12 years: ~55 IU/dL; age 6 to < 12 years: ~45 IU/dL; age 0 to < 6 years: ~40 IU/dL). In all age groups, the simulated median trough FIX activity between injections exceeded ~3% for rIX-FP dosing regimens of 25 IU/kg or 40 IU/kg weekly, and 50 IU/kg every 10 days. In the adult / adolescent age group and the older pediatric age group (ie, 6 to < 12 years), the simulated median trough FIX activity between injections exceeded ~2% with a rIX-FP dosing regimen of 50 IU/kg every 14 days. In the younger pediatric age group (ie, 0 to < 6 years), a rIX-FP dose of 75 IU/kg every 14 days was required to maintain median trough FIX activity levels between injections above 2%.). Extended half-life and consequential reduction of treatment frequency has been presented within the Population-PK-Modelling. Furthermore, dose-dependent posology and age-adjusted dosage has been presented. Overall, the approach supports the suggested decrease of injection frequency as well as the potential of reduced dosage in adults and children (See discussion on clinical efficacy).

Considerable inter-individual PK-variability is known to be challenging for Haemophilia B. Therefore, when generating representative data, most homogenous patient group of severely affected individuals should be chosen and for this Population PK analysis, stratification for true severe Hemophilia (endogenous activity <1%) and truly followed wash-out-period was performed. Overall, 19 of 83 subjects had non-severe haemophilia. Numbers within each study and treatment-group are considered to be low. However, these data show that especially half-life and AUC might be relevantly increased for patients with less severe type of haemophilia. Furthermore, stratified analysis covering severe haemophilia and true washout as requested by the Clinical Guideline presents lower values than those without stratification. These findings are considered to be plausible and support the concern of patient-selection having at least contributed to the incongruence of encouraging PK-results and efficacy results. Data were reflected in the SmPC section 5.2.

When analyzing the results of the pooled analysis, the assumed half-life extension of rIX-FP even in "lower" dosages (25 IU/kg) in comparison with standard FIX has been elaborated and is considered to offer relevant options for treatment-adaptation. Overall numbers of subjects as well as developmental approaches are acknowledged. However, methodological points need to be taken into account according to the above mentioned points: Sampling for previous FIX has been substantially reduced and comparison might therefore be challenging; missing early phase sampling between 30 min and 3 hours p.i. remains open; patient population of 75 IU/kg dosing-group is constituted of 3 subjects – which is considered to be low. Non-severe hemophilia and increased pre-dose activities are not in table 14; correction of early-phase results (e.g IR and c_{max}) for carry-over effects and late- or whole-phase results (e.g. $t_{1/2}$ and AUC) for non-severe haemophilia.

Age-dependent results support the need for dose-adjustments in the paediatric age-group. Dose-dependency as well as age-dependency is evident but not surprising; differences of PK-results between studies with similar doses are considered to be interesting and might be reason for further considerations.

The PK-data-package is considered to support the assumption of clinically relevant half-life-extension of rIX-FP. 50 IU/kg has been used as target-dosage for PK-evaluation, which is covered by the clinical guideline, representing the lower range. Even a significantly lower dose (25 IU/kg) than suggested by the Guideline has been shown to induce protective FIX-levels. Maximum activity levels remain below 100 IU/dl, which is considered to be relevant for assumed thrombogenic potential. In addition, PK-comparison of previous treatment with rIX-FP is acknowledged. Details as true wash-out-periods and the gap in sampling between 30 min and 3 hours for rIX-FP, representing the early PK-phase and cmax, require further elucidation. Implications for PK-Modelling and reflection in the SmPC depend on the results of such discussion. An increased targeted trough-level of 5-10% FIX activity can explain increased dosage and dose-guidance (See SmPC).

Pharmacokinetic data in elderly subjects beyond 60 years of age have not been provided and such data are not requested by the Clinical Guideline. However, information on the elderly will be needed to bridge a potential gap with the aging haemophilia community; it will be provided on an ongoing basis at post-authorisation phase (See RMP).

No clinical evaluation has been provided for *impaired renal* or *hepatic function*. Population PK modelling has been performed for adults, adolescents and paediatric subjects. PK-result-stratification with regard to severity of haemophilia and correctly met wash-out period has been provided. Justification provided for increased dosages includes increased target trough-levels of FIX-activity: In general, trough levels of 1% are aimed at; in clinical studies with albutrepenonacog alfa 5-10% was targeted. Simulated PK-results for such increased levels roughly match the documented dosages within the efficacy studies (See also discussion on clinical efficacy). See Section 5.2 of the SmPC.

Recommendation for up to 14-days extended treatment-interval is based on clinical efficacy data (See also discussion on clinical efficacy) from 26 selected patients have been switched from once-weekly to extended intervals (10 days or 14 days) meeting selection criteria reflecting lower bleeding risk and 21 Subjects switched to a 14-days interval.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics data in adults support a clinically relevant half-life-extension of rIX-FP and the posology as recommended in the SmPC.

PK results support half-life extension in children. Age-dependent results support the need for dose-adjustments in the paediatric age-group. PK results have been appropriately reflected in the SmPC.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

2.5.2. Main study(ies)

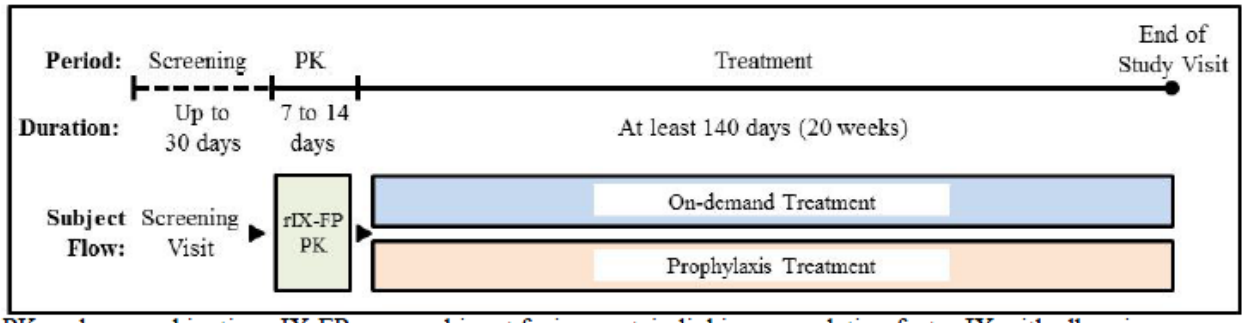
Study 2004: Safety, PK and Efficacy study for Prophylaxis and Treatment of Bleeding Episodes

This prospective, open-label, phase 1 / 2 study was designed to evaluate the safety, PK, and efficacy of rIX-FP for both prophylaxis and on-demand treatment of bleeding episodes in patients with hemophilia B (FIX activity of ≤ 2%).

Methods

The study consisted of a screening period of up to 30 days, a PK evaluation period of 7 to 14 days, and a treatment period of at least 20 weeks. (Figure 4) During the treatment period, subjects were administered rIX-FP as prophylaxis and / or on-demand treatment.

Figure 1: Study Design of Study 2004



PK = pharmacokinetics; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin.

Study Participants

Relevant criteria for inclusion into the study were: Male between 12 to 65 years old, Previously documented severe hemophilia B (FIX activity ≤ 2%) or confirmed at screening by the central laboratory, received FIX products (pdFIX and / or rFIX) for > 150 exposure days (EDs) and no confirmed prior history of FIX inhibitor formation.

Relevant criteria to be not eligible for inclusion into the study were: Known hypersensitivity (allergic reaction or anaphylaxis) to any FIX product or hamster protein, Any known congenital or acquired coagulation disorder other than congenital FIX deficiency, Confounding medicinal conditions or treatments, use of any investigational medicine product (IMP) other than FIX products within 4 weeks prior to the first rIX-FP administration, On-demand subjects experiencing less than 12 or 6 non-trauma induced bleeding episodes requiring treatment with a FIX product during the previous 6 or 3 months, respectively.

Treatments

Prophylaxis Treatment

Subjects in the prophylaxis treatment group administered a single IV infusion of rIX-FP once a week (ie, 7-day treatment interval) at a dose of 15 to 35 IU/kg, or at a dose determined by the investigator. The initial rIX-FP dose was based on the subject's PK profile, determined during the PK evaluation period and / or the phase 1 study (2001), and the subject's bleeding phenotype. The dose was adjusted up to 75 IU/kg to maintain the trough FIX activity level > 1% between infusions.

Subjects in the prophylaxis treatment group could also administer rIX-FP for the control of bleeding episodes (ie, on-demand treatment) or the prevention of bleeding prior to activity.

On-demand Treatment of Bleeding Episodes

Subjects receiving on-demand treatment were administered 1 or more IV infusions of rIX-FP at a dose of at least 25 IU/kg to treat minor, moderate or major bleeding episodes. The dose of rIX-FP was calculated by the investigator, based on the subject's PK profile determined during the PK evaluation period and / or the phase 1 study (2001), and the dose and / or maintenance dose required to achieve and maintain the FIX activity level recommended by the World Federation of Hemophilia.

Minor and moderate bleeding episodes were treated by the subject or their caregiver. Major bleeding episodes including life-threatening bleeding episodes and severe bleeding into a joint or muscle, were treated at a hemophilia center.

Duration of treatment for subjects receiving prophylaxis treatment with rIX-FP was approximately 9 to 11 months and for subjects receiving on-demand treatment of bleeding episodes was approximately 4 to 6 months.

Objectives

The primary objective of the study was to evaluate the safety of intravenous rIX-FP. Safety was evaluated by the nature and incidence of adverse events (AEs), laboratory changes over time, inhibitor formation and antibody development against rIX-FP.

The secondary objectives of the study were to evaluate the PK of rIX-FP and to evaluate the clinical response of routine prophylaxis with rIX-FP with respect to the prevention of bleeding episodes.

Outcomes / endpoints

Primary Endpoints represent Safety endpoints.

Secondary PK Endpoints represent PK-endpoints and the number of breakthrough bleeding episodes in subjects receiving a prophylaxis treatment regimen with rIX-FP during the last 12 weeks (eg, from Week 9 to Week 20) in the per-protocol population.

Exploratory Endpoints: rIX-FP consumption during the last 12-week period (eg, from Week 9 to Week 20) compared to previous FIX consumption during the 12 weeks prophylactic therapy prior to screening; proportion of prophylaxis subjects on weekly routine prophylactic treatment on Week 20 or at end of the study; rIX-FP consumption per infusion, while maintaining weekly prophylactic treatment interval during routine prophylaxis on Week 20 or at end of the study; proportion of bleeding episodes requiring one or two infusions of rIX-FP to achieve hemostasis; Investigator's overall clinical assessment of haemostatic efficacy for treatment of bleeding episodes, based on a four point ordinal scale (excellent, good, moderate, poor/ none).

Sample size

It was planned to include up to 22 subjects into this phase I/II study. Up to 22 subjects, aged 12 to 65 years old, were to be enrolled in the study; approximately 12 of these subjects were to be administered rIX-FP as prophylaxis treatment.

Randomisation

N/A

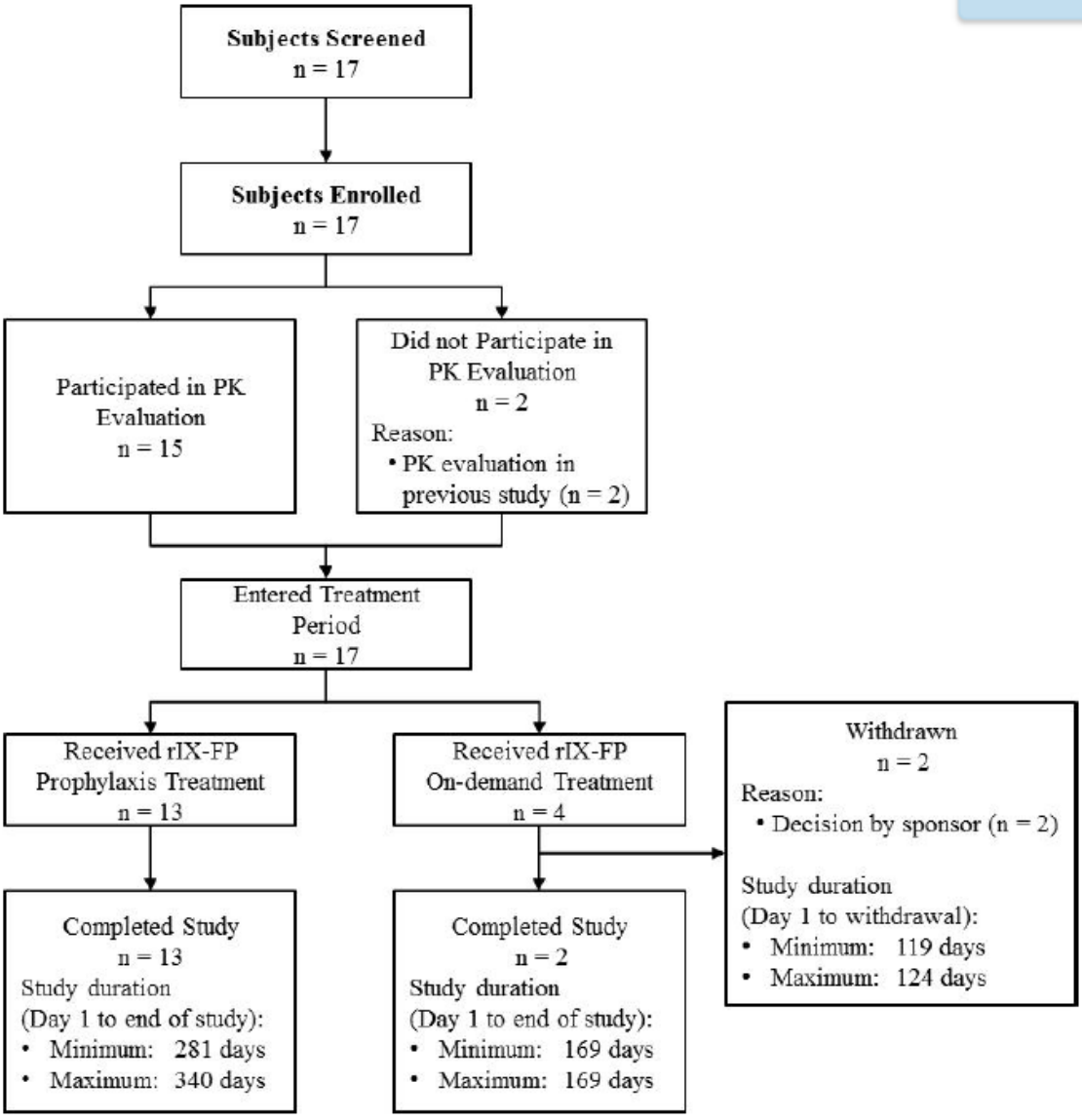
Blinding (masking)

N/A

Results

Participant flow

Figure 2:



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

Source:

Recruitment

17 subjects were treated in the study and comprised both the Safety and Efficacy populations; 13 subjects participated in the prophylaxis treatment group (duration of treatment: 281 to 340 days) and 4 subjects participated in the on-demand treatment group (duration of treatment: 119 to 169 days). Most subjects (15/17 subjects, 88.2%) completed the study.

Conduct of the study

The original protocol (dated 21 December 2010) and the first protocol amendment (dated 12 May 2011) were issued before the enrolment of the first subject on 17 July 2011. There was 1 additional protocol amendment during the course of the study (dated 13 October 2011).

Amendment 1, dated 12 May 2011:

Change to the PK blood sample time points after rIX-FP infusion: removal of optional 9- hour time point and addition of 120 ± 6 hours (Day 5) time point; addition of collection of retained sample for CHO cell antibody testing at Day 1 and the End of Study Visit; removal of rIX-FP antibody and FIX inhibitor testing at Weeks 8 and 16; clarification that a subject must be withdrawn from the study if the subject experiences a life-threatening bleeding episode, except if the subject meets the conditions listed in Section 7.5 of the protocol; clarification that a major bleeding episode is classified as a bleeding episode for which a subject is required to seek treatment recommendations at the hemophilia center from the treating physician; Clarification that use of any IMP other than FIX products within 4 weeks prior to the first rIX-FP administration on Day 1 is an exclusion criteria; clarification that a bleeding episode that occurs as a result of the subject's unchanged, pre-existing hemophilia condition should not be documented as an AE.

Amendment 2, dated 13 Oct 2011:

Increase in the number of subjects from approximately 15 to approximately 20 (up to 22) subjects.; Change in the rIX-FP IV infusion duration from 10 to 15 minutes to 5 to 15 minutes; study subjects may receive a single dose of 25 or 50 IU/kg rIX-FP, whichever dose is closer to the estimated treatment dose, for PK assessment; addition of an additional PK evaluation period for subjects in the prophylaxis treatment group before being treated with the GMP commercial-scale rIX-FP for the first time; clarification that for the on-demand treatment of a bleeding episode, the study subject's PK data from this study and / or PK data from the phase 1 study may be utilized for calculating the initial treatment doses for the treatment of bleeding episodes as recommended by the WFH and also local treatment protocol / practice; clarification that the assessment of pain relief at the 16 and 24 hours after infusion time points are optional.

Protocol deviations

There were 70 protocol deviations documented for 16 of 17 subjects during the study. All protocol deviations related to minor infringements and none of these protocol deviations resulted in subject withdrawal from the study or exclusion from the analysis populations.

Baseline data

The mean total bleeding episodes experienced by subjects in the 12 months before study entry was 14.0 in the prophylaxis group (n = 13) compared with 27.0 in the on-demand group (n = 4). Ten of 13 subjects in the prophylaxis group previously received prophylaxis treatment and experienced a mean of 5.2 bleeding episodes in the 12 months before study entry, compared with a mean of 43.3 bleeding episodes in the 3 subjects in the prophylaxis group who had previously received only on-demand treatment.

All subjects were male and of white race. The majority (14/17; 82.4%) of subjects were ≥ 18 years old; in the prophylaxis treatment group, there were 3 subjects < 18 years old (ages: 13, 15, and 16 years) (Table 19). All subjects had been diagnosed with hemophilia B and had been previously treated with an FIX product (ie, pdFIX or rFIX).

In the prophylaxis treatment group, there were 3 subjects < 18 years old. Other baseline characteristics were similar between the 2 treatment groups.

All subjects had been diagnosed with hemophilia B and were previously treated with a FIX product (ie, pdFIX or rFIX). A total of 10 subjects had received prophylaxis therapy before study entry; all of these subjects were in the prophylaxis treatment group.

The per-protocol population consisted of the 15 subjects who completed the study without any major protocol violations or deviations; 2 subjects (50010003 and 50010004) did not complete the protocol due to a decision by the sponsor to enroll these subjects in another rIX-FP study (3001).

Table 18 Demographic and baseline characteristics (safety population)

	Prophylaxis Treatment Group N = 13	On-demand Treatment Group N = 4	Total N = 17
Gender [n (%)]			
Male	13 (100)	4 (100)	17 (100)
Race [n (%)]			
White	13 (100)	4 (100)	17 (100)
Country [n (%)]			
Israel	13 (100)	0	13 (76.5)
Bulgaria	0	4 (100)	4 (23.5)
Age in years at screening			
Mean (SD)	23.2 (9.4)	35.8 (9.7)	26.1 (10.7)
Median	19.0	35.0	25.0
Min, Max	13,42	27,46	13, 46
Age at screening [n (%)]			
< 18 years	3 (23.1)	0	3 (17.6)
≥ 18 years	10 (76.9)	4 (100.0)	14 (82.4)

Max = maximum; Min = minimum; PK = pharmacokinetics; SD = standard deviation.

The weight and body mass index of subjects (mean ± SD) was 66.8 ± 13.5 kg (min: 36.0 kg, max: 93.0 kg) and 21.8 ± 3.5 kg/m2 (min: 16.4 kg/m2, max: 31.4 kg/m2), respectively. There was no notable difference in weight, height and body mass index between the 2 treatment groups.

Numbers analysed

The efficacy population consisted of 17 subjects who participated in the efficacy portion of the study and received at least 1 dose of rIX-FP; 13 subjects were in the prophylaxis treatment group (all from the study center in Israel) and 4 subjects were in the on-demand treatment group (all from the study center in Bulgaria).

Outcomes and estimation

Efficacy was evaluated based on the number and type of bleeding episodes, rIX-FP consumption, the number of infusions required to achieve hemostasis, the investigator's assessment of efficacy, the dose of rIX-FP administered, changes to the treatment regimen, and the time of the most recent infusion of rIX-FP and the start of a spontaneous bleeding episode (ie, for subjects in the prophylaxis treatment group). These efficacy evaluations were determined from the data collected in the treatment period only, and not the PK evaluation period, unless otherwise indicated. Similar results for all efficacy parameters were obtained for the efficacy and PP populations.

The outcome measures that support efficacy for the indication of routine prophylaxis include annualized spontaneous bleeding rate (AsBR) and consumption.

In both the prophylaxis and on-demand treatment groups, subjects experienced either spontaneous or traumatic bleeding episodes; there were no post-surgery bleeding episodes reported for either group. In the prophylaxis treatment group, 5/13 subjects (38.5%) did not experience a bleeding episode requiring treatment during the treatment period. The other 8/13 subjects (61.5%) in this treatment group experienced at least 1 bleeding episode requiring treatment during the treatment period. In the on-demand treatment group, all subjects (4/4; 100%) experienced at least 1 bleeding episode

requiring treatment. In both treatment groups, all bleeding episodes were either minor or moderate in severity.

Spontaneous and traumatic bleeding episodes were collected and compared:

Table 19 Annualized Bleeding Rate: Total, Spontaneous and Traumatic Bleeding episodes

	Prophylaxis Treatment Group (n = 13)	On-demand Treatment Group (n = 4)
Total bleeding episodes, bleeds/year		
Mean	4.4 (4.7)	26.8 (2.7)
Median	2.3	26.9
Min, Max	0.0, 14.0	23.6, 29.9
Spontaneous bleeding episodes, bleeds/year		
Mean (SD)	1.3 (1.5)	21.7 (4.0)
Median	1.1	22.2
Min, Max	0.0, 4.5	16.6, 25.9
Traumatic bleeding episodes, bleeds/year		
Mean	3.1 (3.9)	5.1 (6.4)
Median	2.3	3.5
Min, Max	0.0, 12.7	0.0, 13.3

Max = maximum; Min = minimum; SD = standard deviation.

Consumption of rIX-FP During Weekly Prophylaxis

During the treatment period, all 13 subjects in the prophylaxis treatment group administered (mean ± SD) 4.4 ± 0.1 infusions per subject per month for weekly prophylaxis, with an rIX-FP prophylaxis dose per infusion (mean ± SD) of 55.1 ± 13.9 IU/kg. The total dose of rIX-FP administered per subject per month (mean ± SD) as weekly prophylaxis was 243.2 ± 36.8 IU/kg per month.

The 10 subjects in the prophylaxis treatment group, who had received prophylaxis treatment with a different FIX replacement product before study entry, administered a lower total weekly dose of rIX-FP compared with the weekly dose of the FIX replacement product previously used for prophylaxis treatment. During the last 12 weeks of the treatment period these subjects administered a total dose (mean ± SD) of rIX-FP of 58.6 ± 10.7 IU/kg as routine prophylaxis. During the 12-week period before study entry, these same 10 subjects administered a total dose (mean ± SD) of other FIX replacement product of 87.7 ± 45.8 IU/kg.

Table 20 Consumption rIX-FP and Previous Factor IX Product

	rIX-FP [a] (n = 10)	Previous FIX product [b] (n = 10)
IU/kg per subject per week [a]		
Mean (SD)	58.6 (10.7)	87.7 (45.8)
Median	53.8	73.2
Min, Max	47.7, 75.0	32, 154

FIX = factor IX; Max =maximum; Min = minimum; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin; SD = standard deviation.
[a] Dose of rIX-FP consumed during last 12 weeks of the study
[b] Dose of factor IX product consumed during the 12 weeks before study entry.

Assessment of Haemostatic Efficacy

The investigator's overall clinical assessment of haemostatic efficacy of rIX-FP for each bleeding episode was based on the subject's assessment of pain relief and the number of infusions needed to establish hemostasis.

The investigator's assessment of haemostatic efficacy of rIX-FP, reported for all 85 minor or moderate bleeding episodes requiring treatment, was either excellent or good for the majority of bleeding episodes (excellent: 53/85 bleeding episodes, 62.4%; good: 29/85 bleeding episodes, 34.1%); haemostatic efficacy was assessed as moderate for the other 3 bleeding episodes (3.5%). There were no major bleeding episodes reported during the study.

Table 21 Investigator's Assessment of Haemostatic Efficacy for Treatment of Minor and Moderate Bleeding episodes (Efficacy Population)

	Time after start of bleeding episode			
	< 4 hours	≥ 4 hours and < 8 hours	≥ 8 hours and < 16 hours	≥ 16 hours
Subjects assessed, n	11	6	5	2
Bleeding episodes assessed, n	58	13	9	5
Assessment, n (%) [a]				
Excellent	44 (75.9)	5 (38.5)	2 (22.2)	2 (40.0)
Good	14 (24.1)	8 (61.5)	5 (55.6)	2 (40.0)
Moderate	0 (0)	0 (0)	2 (22.2)	1 (20.0)
None	0 (0)	0 (0)	0 (0)	0 (0)

[a] Percentages for assessments are based on the total number of bleeding episodes assessed.

Dose and Dose Adjustment

All subjects in the prophylaxis treatment group were assigned a treatment schedule of once every week, which was maintained for the duration of the treatment period. These 13 subjects were prescribed an initial weekly prophylaxis rIX-FP dose (mean ± SD) of 30.4 ± 3.2 IU/kg (min: 25.0 IU/kg, max: 35.0 IU/kg)

At the end of the treatment period, the dose (mean ± SD) of rIX-FP prescribed for weekly prophylaxis was 61.9 ± 11.5 IU/kg (min: 50.0 IU/kg, max: 75.0 IU/kg). The dose of rIX-FP administered per infusion over the treatment period was 55.0 ± 13.9 IU/kg.

The initial dose (mean ± SD) of rIX-FP prescribed for the on-demand treatment of bleeding episodes was 33.3 ± 2.4 IU/kg (n = 17). Subjects in the prophylaxis treatment group were prescribed a slightly higher initial dose of rIX-FP for the on-demand treatment of bleeding episodes than subjects in the on-demand treatment group. At the end of the treatment period, the dose of rIX-FP prescribed for the on-demand treatment of bleeding episodes was 57.4 ± 15.9 IU/kg; the dose prescribed for subjects in the prophylaxis treatment group (50 to 75 IU/kg) was higher than the dose prescribed for subjects in the on-demand treatment group (26.5 to 30.0 IU/kg).

Table 22 Dose of rIX-FP for on-demand treatment at the beginning and end of the treatment period

	Treatment Group [a]		
	Prophylaxis N = 13	On demand N = 4	Total N = 17
Initial prescribed dose			
Mean (SD)	34.3 (1.7)	30.0 (0.0)	33.3 (2.4)
Median	35.0	30.0	35.0
Min, Max	30.0, 35.0	30.0, 30.0	30.0, 35.0
Final prescribed dose			
Mean (SD)	61.9 (11.5)	28.3 (2.5)	57.4 (15.9)
Median	60.0	28.3	55.0
Min, Max	50.0, 75.0	26.5, 30.0	26.5, 75.0
Actual dose administered			
Mean (SD)	66.7 (31.0)	31.3 (8.2)	50.9 (29.5)
Median	59.2	30.0	45.5
Min, Max	30.8, 151.1	19.9, 68.6	19.9, 151.1

Max = maximum; Min = minimum; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin; SD = standard deviation

Table 23 Summary of efficacy for trial 2004

Title: A Phase 1/2 Open-label, Multicenter, Safety and Efficacy Study of a Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B				
Study identifier	CSL654-2004			
Design	This prospective, open-label study was designed to evaluate the safety, PK, and efficacy of rIX-FP for both prophylaxis and on-demand treatment of bleeding episodes in patients with hemophilia B. The study consisted of a screening period of up to 30 days, a PK evaluation period of 7 to 14 days, and a treatment period of at least 20 weeks. During the treatment period, subjects were administered rIX-FP as either prophylaxis and / or on-demand treatment.			
	Duration of main phase:	11 months		
	Duration of Run-in phase:	not applicable		
	Duration of Extension phase:	not applicable		
Hypothesis	Exploratory: For all efficacy outcome measures descriptive statistics were presented.			
Treatments groups	Prophylaxis treatment	Prophylactic treatment with rIX-FP for at least 140 days (20 weeks), N=13		
	On-demand treatment	On-demand treatment with rIX-FP for at least 140 days (20 weeks), N=4		
Endpoints and definitions	Prophylaxis	NB12	number of breakthrough bleeding episodes in subjects receiving a prophylaxis treatment regimen with rIX-FP during the last 12 weeks	
	Prophylaxis	ABR	Bleeds/year	
	Prophylaxis	TTSBE	time of the most recent infusion of rIX-FP and the start of a spontaneous bleeding episode	
	Consumption	FPD	Final prescribed dose per infusion	
	Haemostatic efficacy	NINF	proportion of bleeding episodes requiring 1 or 2 infusions of rIX-FP to achieve hemostasis	
	Haemostatic efficacy	HAEF	Investigator's overall clinical assessment of hemostatic efficacy for treatment of bleeding episodes, based on a 4-point ordinal scale (excellent, good, moderate, poor / none)	
Database lock	28 June 2012			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Prophylaxis	On-demand	All
	Number of subject	13	4	17
	NB12	0.8	6.8	NA
	SD	±1.2	±1.3	NA
	ABR	4.4	26.8	NA

	SD, min, max	4.7, 0.0, 14.0	2.7, 23.6, 29.9	NA
	TTSBE	101.4 ±40.1hours	313.3 ±163.1hours	NA
	FPD	61.9 (11.5) IU/kg	28.3 (2.5) IU/kg	57.4 (15.9) IU/kg
	NINF 1 2 more	NA	NA	 76 (89.4%) 9 (10.6%) 0
	HAEF Excellent Good Moderate None/Poor	NA	NA	 53/85 (62.4%) 29/85 (34.1%) 3/85 (3.5%) 0

Ancillary analyses

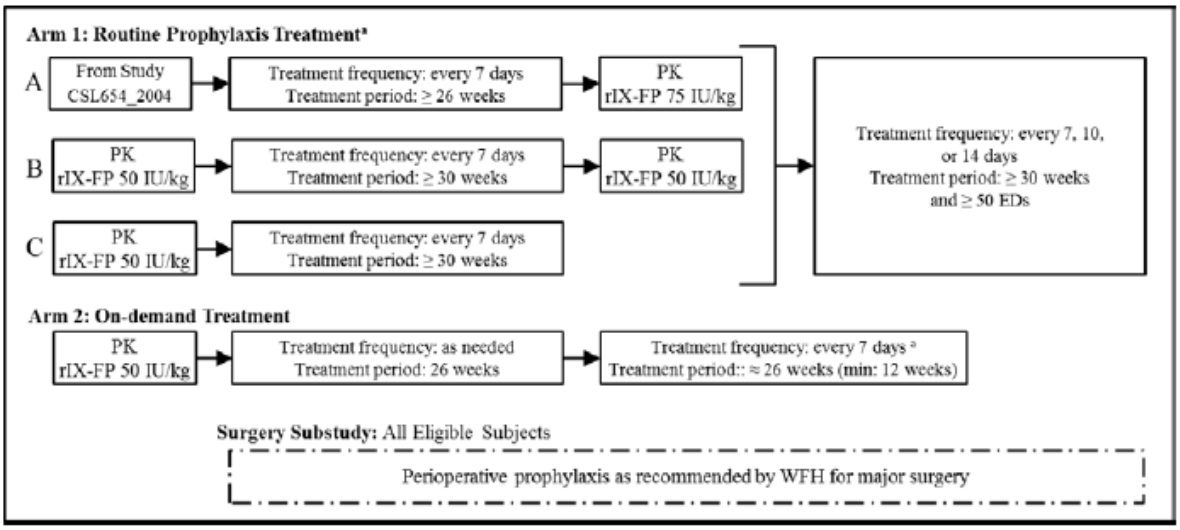
N/A

Study 3001: Safety, PK and Efficacy study for Prophylaxis and Treatment of Bleeding Episodes

This prospective, open-label, phase 2 / 3 study was designed to evaluate the efficacy of rIX-FP in preventing bleeding episodes (prophylaxis), safety of rIX-FP with respect to the development of inhibitors against factor IX (FIX) in subjects with hemophilia B (FIX activity of ≤ 2%) and the efficacy of rIX-FP in the prevention and control of bleeding during surgical procedures.

The study consisted of a 1-month screening period, a PK evaluation period of up to 14 days, and a treatment period lasting between 12 and 14 months. During the treatment period, subjects were administered rIX-FP as prophylaxis and / or on-demand treatment. Any subject requiring nonemergency surgery during the course of the study could be enrolled in the surgery substudy.

Figure 3: Study Design of Study 3001



Abbreviations: ED, exposure day; PK, pharmacokinetic; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; WFH, World Federation of Hemophilia.

[a] During prophylaxis treatment, rIX-FP could also be administered on demand to treat bleeding episodes or as prevention, as needed.

Methods

Study participants

Inclusion criteria

Subjects who met the following criteria were eligible for inclusion in the study:

- Male subjects, 12 to 65 years of age
- Documented severe hemophilia B (FIX activity of ≤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, ie, 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

For *on-demand subjects* only:

- Experienced a minimum average of 2 spontaneous (nontrauma-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

In addition, subjects who also met the following criteria were eligible for inclusion in the *surgical substudy*:

- Required nonemergency surgery
- Written informed consent for substudy participation obtained before undergoing any substudy-specific procedures

Exclusion criteria

Subjects who met any of the following criteria were to be excluded from the study:

- 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 (ie, at study entry) receiving IV immunomodulating agents such as immunoglobulin or chronic systemic corticosteroid treatment
- Platelet count <100,000/µL at Screening
- HIV positive subjects with a CD4 (lymphocyte) count <200/mm3. 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 × upper limit of normal (ULN) at Screening
- Serum creatinine concentration >2 × 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 IMP other than rIX-FP within 4 weeks prior to the first rIX-FP administration on Day 1
- Concurrent nonhemophiliac inflammatory joint disease or other medical condition that, in the Investigator's judgment, could confound study results
- Suspected inability (eg, language problem or mental condition) or unwillingness to comply with study procedures or history of noncompliance

For *on-demand subjects* only:

- Had active synovitis
- Routinely received FIX infusion prior to activity (ie, sports) as a preventative measure more than 2 times per month

Treatments

The main study consisted of a PK period, and an active treatment period for all subjects. Any subjects requiring nonemergency surgery during the course of the study could be enrolled in the surgical substudy. The surgical substudy included a PK period, if required, and an active treatment period after which subjects resumed their assigned treatment plan in the main study.

To evaluate both the treatment (control and prevention) of bleeding episodes and the prophylaxis treatment regimen, subjects who were receiving on-demand treatment with FIX and subjects who were receiving prophylaxis therapy with FIX were both enrolled into the study. All subjects received rIX-FP and were assigned to treatment groups (prophylaxis [Arm 1] or on-demand [Arm 2]) based on their history of use with FIX products. Subjects in the prophylaxis treatment arm were further stratified into 1 of 3 treatment blocks: Block A (prophylaxis subjects who completed Study CSL654_2004), Block B (first 15 non-CSL654_2004 subjects), or Block C (remaining subjects who enrolled in the study).

Subjects in Arm 2 received on-demand treatment for 26 weeks and then the number of bleeding episodes was recorded in order to calculate the ABR. Subjects then switched to a 7 day prophylaxis regimen for approximately 26 weeks (minimum of 12 weeks), and the ABR on prophylaxis was compared to on-demand treatment. This design allowed subjects to serve as their own control in measuring the difference in the ABR between the on-demand and prophylaxis treatments.

The PK of 50 IU/kg of rIX-FP was evaluated at the beginning of the study in all subjects except the subjects who had a PK assessment performed in study 2004. The PK of 25 IU/kg of rIX-FP was also assessed in 6 subjects who received an initial dose of 25 IU/kg under the original protocol.

The recommended doses for each arm in this study (prophylaxis [Arm 1] and on-demand [Arm 2]) were selected based on group PK data from a previous Phase 1 study (2001). The desired FIX activity level for the treatment of a bleeding episode for subjects in both treatment arms was based on the recommendation of the World Federation of Hemophilia (WFH). The calculated dose should have been in the range of 35 to 50 IU/kg. If a subject had a low recovery rate and/or experienced a more severe bleeding episode, the dose could exceed 50 IU/kg up to a maximum of 75 IU/kg.

Prophylaxis dosing for Arm 1:

Subjects in the prophylaxis treatment group (Arm 1) received a weekly prophylaxis dose of 35 to 50 IU/kg rIX-FP for 26 to 30 weeks, after which subjects could switch to a 10-day or 14-day prophylaxis regimen at a dose of 75 IU/kg rIX-FP for an additional ≥ 30 weeks, if specified criteria were met.

If a subject experienced at least 1 spontaneous hemorrhage during any 28-day period of prophylaxis treatment, the dose of rIX-FP could be increased, up to a maximum dose of 75 IU/kg rIX-FP with a target of maintaining the trough FIX activity level above 1% between doses, while maintaining a treatment interval of 7 days. The dose could also be decreased during the weekly prophylaxis period based on clinical outcome and FIX trough levels.

To change to a new dose and dosing regimen, a subject must have met all of the following criteria: was on a stable dose in the previous month (no dose adjustment); did not experience a spontaneous bleeding episode in the previous month; was currently on a weekly prophylaxis dose of ≤ 50 IU/kg rIX-FP; was willing to switch to a longer treatment interval.

Subjects whose current weekly dose was ≤ 40 IU/kg rIX-FP could switch to a 14-day interval at a dose of 75 IU/kg rIX-FP. Subjects whose current weekly dose was > 40 to ≤ 50 IU/kg rIX-FP could switch to a 10-day interval at a dose of 75 IU/kg rIX-FP. Subjects whose current weekly dose was > 50 IU/kg rIX-FP were to maintain their current dose.

If a subject was receiving the 14-day treatment regimen and experienced 2 spontaneous hemorrhages at any location during a 2-month period of prophylaxis treatment, the treatment interval could be reduced to 10 days. If a subject was receiving the 10-day treatment regimen and experienced 2 spontaneous hemorrhages at any location during a 2-month period of prophylaxis treatment, the treatment interval could be reduced to 7 days and the stable 7-day regimen dose prior to the regimen switch was to be resumed.

Subjects who did not meet the criteria to switch or did not wish to switch were to continue on the 7-day treatment interval at the current dose for the remainder of the study.

Prophylaxis dosing for Arm 2:

On-demand subjects switched to a 7-day prophylaxis regimen of 35 to 50 IU/kg rIX-FP after either completing 26 weeks (minimum of 12 weeks) of on-demand treatment with rIX-FP or experiencing at least 12 spontaneous bleeding episodes, whichever occurred first. On-demand subjects maintained the 7-day prophylaxis treatment interval for the remainder of the study.

During the first 4 weeks of prophylaxis treatment, the dose of rIX-FP could be increased from an initial dose of 35 to 50 IU/kg to a maximum dose of 75 IU/kg, if needed, while maintaining a treatment interval of 7 days. The dose prescribed after 4 weeks of prophylaxis treatment was maintained for the remainder of the study.

On-demand dosing for all subjects:

For the on-demand treatment of a bleeding episode, the subject's PK data from this study was utilized for calculating the initial treatment doses for the treatment of bleeding episodes as recommended by the WFH, with a minimum dose of 35 IU/kg of rIX-FP. After hemostasis was achieved, maintenance dose(s) of rIX-FP may have been prescribed at the discretion of the Investigator. During the prophylaxis treatment period, subjects were to maintain the prophylaxis treatment schedule, if possible, while receiving on-demand treatment for a bleeding episode.

Surgical dosing:

Dosing and treatment during the surgical period, as recommended by the WFH for surgery, was dependent on the type of surgery. During the preoperative treatment period, the dose was selected based on the subject's individual PK parameters in the range of 50 to 75 IU/kg, in order to increase the FIX activity levels to 60% to 80%. During the intraoperative treatment period, the subject could receive doses of rIX-FP depending on the FIX activity levels, type of surgery, and local standard of care. The trough FIX activity level was to be maintained at 60% to 80% during the major surgical procedure. The subject received postoperative doses of rIX-FP from 1 to 14 days depending on the FIX activity levels and type of surgery as recommended by the WFH. FIX activity levels were to be measured prior to repeat dosing during the intraoperative and postoperative treatment periods.

Efficacy and safety assessments were performed at the study center on a monthly basis.

Objectives

The primary objectives of the study were to evaluate the efficacy of rIX-FP in preventing bleeding episodes (prophylaxis) in subjects with severe hemophilia B (FIX activity of ≤2%).

The primary objective of the surgical substudy was to evaluate the efficacy of rIX-FP in the prevention and control of bleeding in subjects with severe hemophilia B (FIX activity of ≤2%) during surgical procedures.

The secondary objectives of the study were to evaluate the PK of a single dose of rIX-FP and the clinical response to rIX-FP for the prevention and treatment of bleeding episodes. Further secondary objective was the evaluation of the efficacy of rIX-FP in surgical prophylaxis (primary objective of the surgical substudy)

The secondary objective of the surgical substudy was to evaluate the safety of rIX-FP during the intraoperative and postoperative periods.

Outcomes/endpoints

Primary Endpoint:

The primary efficacy endpoint was the annualized spontaneous bleeding rate (AsBR) for treated bleeding episodes during on-demand treatment compared with that during routine prophylaxis treatment.

Secondary Endpoints:

Secondary efficacy endpoints were the number of infusions to achieve hemostasis; investigator's overall clinical assessment of haemostatic efficacy for the treatment of bleeding episodes, based on a four point ordinal scale (excellent, good, moderate, poor/none); rIX-FP consumed per month while maintaining assigned prophylaxis; AsBR among Arm 1 subjects who switched treatment regimens; investigator's (or surgeon's) overall clinical assessment of haemostatic efficacy for surgical prophylaxis, based on a four point ordinal scale (excellent, good, moderate, poor/none).

Additional Endpoints:

Additional efficacy endpoints were: time from last dose to onset of spontaneous bleeding episodes; annualized bleeding rates; monthly consumption of rIX-FP for routine prophylaxis treatment compared with previous FIX treatment.

Additional endpoints collected during the surgical substudy were: occurrence of related AEs to rIX-FP during the intraoperative and postoperative periods; occurrence of FIX inhibitors; occurrence of antibodies against rIX-FP; comparison of predicted and intraoperative estimated blood loss; comparison of predicted and actual transfusion requirements; change in hemoglobin levels between baseline, intraoperatively and postoperatively.

If a second infusion of rIX-FP was required for the treatment of a bleeding episode (eg, as a maintenance dose to maintain the FIX activity level for multiple days, as recommended by WFH), the FIX activity level was tested before administration of the second rIX-FP infusion (if feasible).

Sample size

It was planned to include 35 subjects into the prophylaxis treatment arm (arm 1) and 25 subjects into the on demand treatment arm (arm 2). The number of subjects in arm 1 was not based on statistical considerations. Regarding the number of subjects for arm 2 a mean spontaneous bleeding rate for on demand treatment of 24 bleeds per year was assumed compared to a mean spontaneous bleeding rate of 12 bleeds per year following the switch to prophylaxis treatment. Anticipating a standard deviation of 14 it was calculated that with 21 subjects a one sample t-test with alpha = 0.05 (2-sided) would archive 95% power to detect such effect. To account for potential dropouts, approximately 25 subjects were to be enrolled in arm 2.

Randomisation

n/a

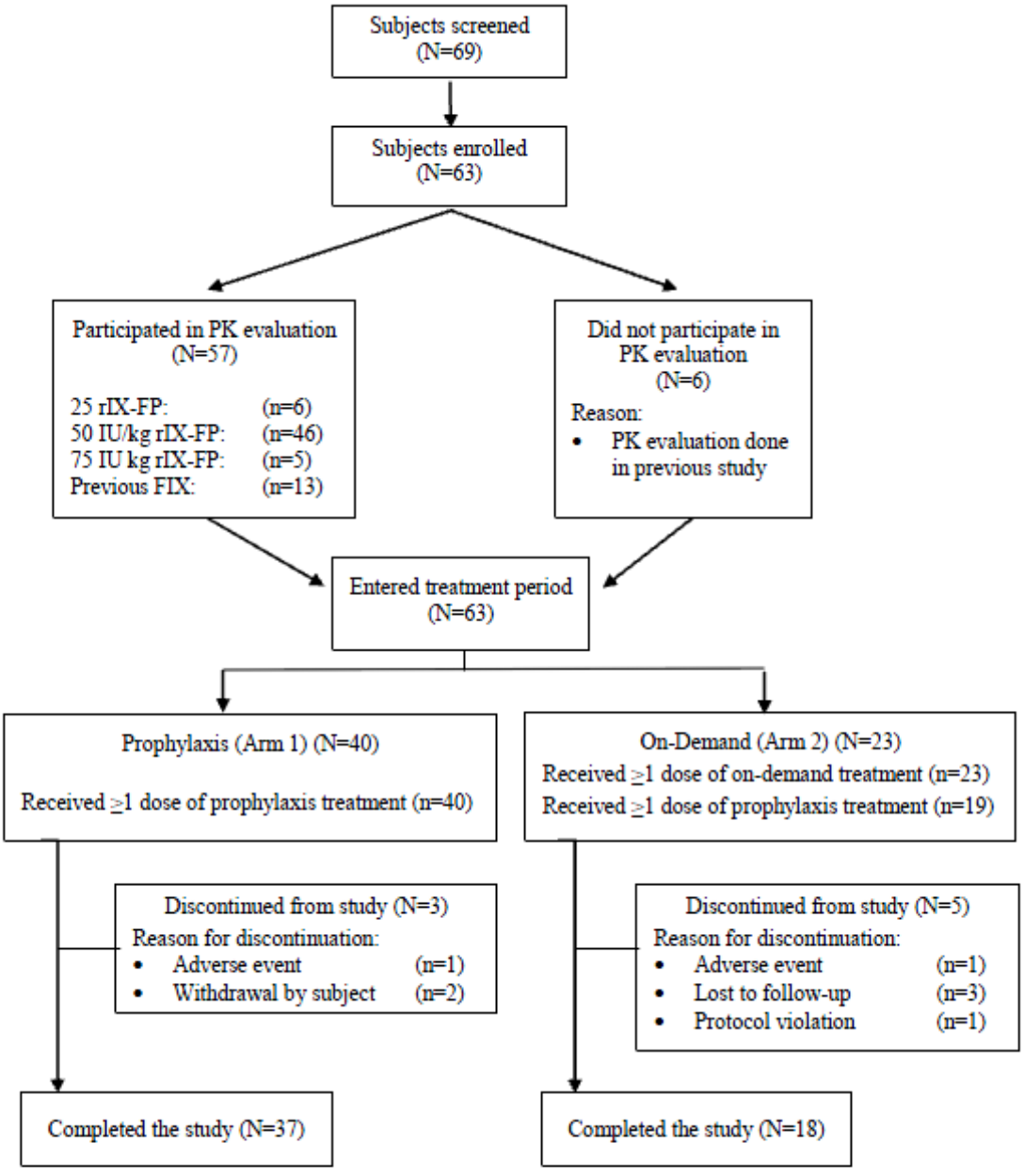
Blinding (masking)

n/a

Results

Participant flow

Figure 4: Subject Disposition (Study 3001)



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

Recruitment

Subjects were enrolled from 32 sites in 10 countries. 69 subjects provided informed consent and were screened for study participation. Of these, 63 subjects were enrolled and treated with rIX-FP (40 subjects in the prophylaxis treatment group [Arm 1] and 23 subjects in the on-demand treatment group [Arm 2]). Four subjects, 3 in the prophylaxis treatment group and 1 in the on-demand treatment group, also participated in the surgical substudy. Overall, 55/63 (87.3%) subjects completed the study (37/40 [92.5%] in the prophylaxis treatment group and 18/23 [78.3%] in the on-demand treatment group). Subject disposition is illustrated below in Figure 6.

Conduct of the study

The original Clinical Study Protocol (dated 14 June 2011) and Amendment 1 (dated 30 November 2011) were issued before the enrollment of the first subject on 23 February 2012. There were 2 additional protocol amendments issued during the course of the study (Amendment 2, dated 18 October 2012, and Amendment 3, dated 27 February 2014).

Summarized key changes in Amendments 1, 2, and 3 is provided below:

Amendment 1, 30 November 2011

Change of the secondary endpoint “number of subjects with FIX inhibitors” to the primary safety endpoint; addition of an efficacy evaluation algorithm for the Investigator rating of bleeding episodes for clarification; update of treatment groups and assigned doses; addition of criteria for dose adjustment and treatment regimen switching; as well as an algorithm for the new dose interval; update of the statistical methodology section.

Amendment 2, 18 October 2012

Addition for on-demand treatment (Arm 2) that a subject’s prophylaxis dose could only be adjusted during the first 4 weeks, and that the dose prescribed after 4 weeks of prophylaxis treatment was to be maintained for the rest of the study; update of the statistical methodology section with analysis population definitions, additional secondary and exploratory endpoints, and additional details on statistical methods; addition of the comparison of mean ABRs between different prophylaxis regimens as one of the secondary endpoints.

Amendment 3, 27 February 2014

The bleeding episodes that occurred during the 4-week run-in period of prophylaxis therapy for subjects in Arm 2 (on-demand) were no longer to be excluded from analyses of the 26-week treatment period, and the total duration of treatment for Arm 2 was reduced from 30 weeks to 26 weeks, but a minimum of 12 weeks; addition of additional statistical methods to clarify how missing data were handled during the primary efficacy analysis; clarification that the test proposed for the comparison between the 7-day and the 10-day or 14-day prophylaxis regimens was referred to as a non-inferiority test.

Baseline data

Demographic and baseline characteristics

Only male subjects were enrolled in this study. The majority of subjects were white (52/63 subjects, 82.5%) or Asian (10/63 subjects, 15.9%) and non-Hispanic (62/63 subjects, 98.4%).

For the overall study population, subjects had a mean age of 33.0 years (range, 12 to 61 years). Seven subjects were 12 to <18 years of age, all of which were enrolled in the prophylaxis treatment

arm. This contributed to a lower mean age in the prophylaxis treatment arm compared to the on-demand treatment arm (31.6 vs 35.3 years).

Mean BMI was similar between the arms, at 23.0 and 25.7 kg/m2 for prophylaxis and on- demand, respectively. More subjects in the on-demand treatment arm had BMI ≥30 (n=6) than in the prophylaxis treatment arm (n=1).

Numbers analysed

Protocol deviations:

There were no protocol deviations relating to inclusion/exclusion criteria reported during the study. 23 major protocol deviations were reported in 17/63 (27.0%) subjects. In the prophylaxis treatment group, 16 major protocol deviations were reported for 10/40 [25.0%] subjects and 7 major protocol deviations were reported in 7/23 [30.4%] subjects in the on-demand treatment group. Subjects were not excluded from the efficacy analysis population.

Minor protocol deviations were reported for the majority of subjects. The most common minor protocol deviations pertained to visit schedule (eg, visit not performed or out of window), laboratory tests (eg, laboratory parameter not performed or out of window), subject assessment (eg, pain relief assessment not performed), and rIX-FP administration (eg, noncompliance or dosing deviation).

Seven subjects had minor protocol deviations relating to the use of prohibited concomitant medication.

Outcomes and estimation

Response to prophylaxis treatment

Annualized spontaneous bleeding rate in Arm 2 (primary efficacy endpoint) covered the Primary Efficacy analysis set (n=19) of subjects in the on-demand treatment arm (Arm 2) who received on-demand treatment during the first half of the study followed by prophylaxis treatment. The AsBR was significantly reduced when subjects switched from on-demand to weekly prophylaxis treatment with rIX-FP (P <0.0001). The median (Q1, Q3) AsBR was 15.43 (7.98, 17.96) for on-demand treatment and 0.00 (0.00, 0.96) for weekly prophylaxis treatment.

Compilation of bleeding episodes and treatment regimens is presented, below.

Table 24 Annualized Bleeding Rates by Bleeding Category (Efficacy Population)

	Prophylaxis (Arm 1)			On-demand (Arm 2)		
	7-day regimen (N=40)	10-day regimen (N=7)	14-day regimen (N=21)	On-demand regimen (N=23)	Prophylaxis regimen (N=19)	Total 7-day prophylaxis (N=59)
Total bleeding episodes						
Annualized bleeding rate (bleeding episodes/year) per subject						
n	38	7	21	22	18	56
Mean (SD)	1.24 (1.780)	0.82 (1.195)	1.96 (2.653)	20.28 (8.616)	2.87 (4.954)	1.76 (3.209)
Median	0.00	0.00	1.08	18.65	1.19	0.61
Q1, Q3	0.00, 1.87	0.00, 1.78	0.00, 2.70	16.70, 25.53	0.00, 4.06	0.00, 2.57
Min, Max	0.0, 6.0	0.0, 3.0	0.0, 9.1	2.0, 46.1	0.0, 21.1	0.0, 21.1
Spontaneous bleeding episodes						
Annualized bleeding rate (bleeding episodes/year) per subject						
n	38	7	21	22	18	56
Mean (SD)	0.52 (1.116)	0.13 (0.334)	1.07 (2.114)	13.26 (8.613)	0.73 (1.205)	0.59 (1.139)
Median	0.00	0.00	0.00	11.57	0.00	0.00
Q1, Q3	0.00, 0.00	0.00, 0.00	0.00, 1.00	7.69, 17.03	0.00, 0.96	0.00, 0.75
Min, Max	0.0, 4.5	0.0, 0.9	0.0, 7.3	0.0, 39.5	0.0, 4.2	0.0, 4.5

rIX-FP consumption (secondary efficacy endpoint)

Subjects on routine prophylaxis with rIX-FP had lower monthly consumption compared with previous FIX product (mean [SD] total monthly dose per subject was 202.7 [47.92], 201.5 [42.56], and 157.4 [16.34] IU/kg for the 7-, 10-, and 14-day regimens, respectively, vs 320.7 [208.75] IU/kg for previous FIX).

Table 25 Monthly consumption of rIX-FP during routine prophylaxis compared to previous product (efficacy population)

	Prophylaxis (Arm 1)			
	7-day regimen (N=40)	10-day regimen (N=7)	14-day regimen (N=21)	Previous FIX (N=40)
Number of subjects on routine prophylaxis treatment, n (%)	40 (100.0)	7 (100.0)	21 (100.0)	28 (70.0)
Prophylaxis dose administered per subject per month (IU/kg)				
n	40	7	21	28
Mean (SD)	202.679 (47.9217)	201.499 (42.5566)	157.439 (16.3435)	320.721 (208.7529)
Median	194.693	222.483	162.280	256.545
Q1, Q3	167.412, 215.043	149.029, 224.733	158.642, 164.214	208.714, 365.250
Min, Max	139.86, 321.52	131.57, 238.86	111.76, 179.12	65.22, 978.35

Abbreviations: FIX factor IX; Max maximum; Min minimum; Q quartile; rIX-FP recombinant fusion protein linking coagulation factor IX with albumin; SD standard deviation.

Note: Only subjects receiving rIX-FP prior to study entry are included.

Source: Table 14.2.4.5.

Table 26 Monthly consumption of rIX-FP during routine prophylaxis (efficacy population)

	Prophylaxis (Arm 1)			On-demand (Arm 2)	Total 7-day prophylaxis (N=59)
	7-day regimen (N=40)	10-day regimen (N=7)	14-day regimen (N=21)	Prophylaxis regimen (N=19)	
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
Mean prophylaxis dose (IU/kg)					
n	40	7	21	19	59
Mean (SD)	47.828 (10.759)	70.596 (9.560)	71.900 (7.866)	45.519 (11.197)	47.085 (10.860)
Median	47.495	73.630	74.151	40.319	46.137
Q1, Q3	39.435, 50.655	72.048, 75.000	73.500, 75.096	37.594, 50.594	38.450, 50.594
Min, Max	34.15, 74.06	49.28, 77.49	50.00, 79.03	34.01, 74.39	34.01, 74.39

Abbreviations: Max maximum; Min minimum; Q quartile; rIX-FP recombinant fusion protein linking coagulation factor IX with albumin; SD standard deviation.

Subjects were required to achieve a stable dose of 40 IU/kg or less to transition from a 7- to 14-day regimen. The total monthly consumption (IU/kg) of rIX-FP during routine prophylaxis was similar across the 7-day and 10-day treatment regimens in Arm 1 (mean [SD] total monthly dose per subject 202.7 [47.92] and 201.5 [42.56] IU/kg, respectively) and the prophylaxis regimen in Arm 2 (191. 7 [36.33] IU/kg), and was slightly lower in the 14- day treatment regimen in Arm 1 (157.4 [16.34] IU/kg). Weekly consumption was higher in the Middle East (Israel) than in Europe or Asia (249.9 IU/kg/month vs 184.6 and 186.1 IU/kg/month, respectively).

Control of bleeding episodes

Number of infusions of rIX-FP to achieve hemostasis (secondary efficacy endpoint)

358 bleeding episodes required treatment. Of these, 353 bleeding episodes (98.6%) [95% CI 96.2% to 99.5%] were treated successfully with 1 or 2 infusions.

The results were similar in the prophylaxis and on-demand treatment groups. Overall, 93.6% of bleeding episodes were successfully treated with 1 infusion with similar rates observed across all treatment regimens. Overall, the mean (SD) first dose of rIX-FP used to treat bleeding episodes was 47.717 (13.3855) IU/kg.

The results of the PP analysis support the conclusions obtained in the Efficacy population

Excluding bleeds experienced during the surgical substudy, 4 subjects (all on on-demand treatment) had 5 bleeding episodes that required >2 infusions to achieve hemostasis. Of these 5 bleeding

episodes, 3 were not treated per protocol within 4 hours of the start of the bleed (and 2 were added; therefore these bleeds were excluded from the PP population.

Investigator's overall clinical assessment of haemostatic efficacy for the treatment of bleeding episodes (secondary efficacy endpoint)

The Investigator's assessment of haemostatic efficacy of rIX-FP reported that treatment was effective for most bleeding episodes (94.1%) ie, was rated excellent in 297/358 (83.0%) or good in 40/358 (11.2%) bleeding episodes. Haemostatic efficacy of rIX-FP was assessed as moderate for 9/358 (2.5%) bleeding episodes, the majority of which were joint bleeds (7/9) and were treated with 1 infusion (5/9). One bleeding episode (1/358 [0.3%]) was assessed as poor/no response for technical reasons.

There were no major (life-threatening) bleeding episodes in this study. However, there were 5 iliopsoas bleeding episodes occurring in 4 subjects. Four of the 5 bleeds required only 1 dose of rIX-FP to achieve hemostasis.

The results of the PP analysis support the conclusions obtained in the Efficacy population.

Table 27 Investigator's overall clinical assessment of haemostatic 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)

Surgical sub-study

4 subjects reported 6 surgeries during the study, 2 of which were related to hemophilia. At the time of surgery, the FIX activity was above 60% for all subjects, as required by WFH guidelines (World Federation of Hemophilia, 2012). Individual plasma FIX activity measurements, along with sampling times have been presented, in addition. Haemostatic efficacy for surgical prophylaxis was rated as excellent or good for all surgeries at wound closure, 72 hours post-surgery, and at the end of the surgery sub-study (Day 14).

The estimated actual intraoperative blood loss and transfusion requirements were within the range predicted by the Investigator/ Surgeon prior to surgery. No additional haemostatic interventions or transfusion support were required for any subject. Acceptable FIX levels were achieved before, during, and after surgery.

Hemoglobin levels were maintained throughout the surgical period and at levels not unexpected for the type of surgeries performed. Levels below the lower limit of normal were few and returned to within

normal limits within 24 hours. One subject had a clinically significant low hemoglobin value (112 g/L) 24 hours after surgery, which was recorded as an AE of anemia.

All surgical subjects received 1 dose of rIX-FP prior to surgery; no doses were administered intraoperatively. During the 14-day postoperative period, subjects received a range of 2 to 7 infusions of rIX-FP, depending on the type of surgery. Overall, a total of 25 doses of rIX-FP were administered for the 6 surgeries throughout the 14-day surgical sub-study. Mean total consumption of rIX-FP during the surgical period was 239.9 IU/kg (range 106 - 380 IU/kg).

Table 28 Perioperative Hemostasis Response

Surgical Procedures	Subject Number	Assessment of Hemostasis Response			Number of rIX-FP infusions Days 1-14 [b]	Blood Transfusions	Estimated Actual Blood Loss (mL)	
		Wound closure (0 hr)	72 Hours/ Discharge[a]	EOS/ POD 14			Intra-operative	Post operative
Double Mastectomy Liposuction after sterile adrenalized saline solution - Under nipple incision and periareolar deepidermisation - Glandular resection and cutaneous envelope decrease		Excellent	Excellent	Excellent	3 [c]	None	55	0
Installation of Left Knee total prosthesis with medial collateral ligament suture on anchor		Excellent	Excellent	Excellent	7 [d]	None	500	610
Installation of Right Knee total prosthesis with medial collateral ligament suture on anchor		Excellent	Excellent	Excellent	7	None	450	600
Ligature of stage IV hemorrhoidal prolapse. Hemorrhoidal ligation and rectopexy (Doppler - HAL RAR)		Excellent	Excellent	Excellent	2	None	3	0
Wisdom tooth extraction (1)		Excellent	Good	Excellent	4[e]	None [f]	-- [g]	-- [g]
Tooth extraction (Supernumerary #13 tooth)		Excellent	-- [g]	Excellent	2	None	0	0

Abbreviations: EOS End of study; hr hours; POD postoperative day; rIX-FP recombinant fusion protein linking coagulation factor IX with albumin

[a] 72 hours or hospital discharge, if prior to 72 hr evaluation.

[b] Surgery is counted as Day 1. All doses, including preoperative dose, and routine prophylaxis doses after surgery are counted for the 14 days following surgery.

[c] One preoperative dose, then subject returned to weekly prophylaxis 5 days after surgery.

[d] Subject had second total right knee replacement 5 days after total L knee replacement, includes doses for both surgeries through Day 14 following 1st surgery.

[e] The number of infusions includes the preoperative dose on Day -1 (recorded as routine prophylaxis administration) through routine prophylaxis on postoperative Day 14.

[f] Subject used tranexamic acid (1000 mg every 8 hrs) following surgery for 4 days.

[g] Not reported.

Table 29 Consumption (IU/kg) during surgery

Site - Subject ID	Surgery Identifier	Surgery	Number of infusions	Total consumption (IU kg)
	1	Double Mastectomy Liposuction after sterile adrenalized saline solution - Under nipple incision and periareolar deepidermisation - Glandular resection and cutaneous envelope decrease.	3	178.81
	2	Installation of Left Knee total prosthesis with medial collateral ligament suture on anchor [1]	7	380.41
	3	Installation of Right Knee total prosthesis with medial collateral ligament suture on anchor	7	339.57
	4	Ligature of stage IV hemorrhoidal prolapse. Hemorrhoidal ligation and rectopexy (Doppler - HAL RAR)	2	180.75
	5	tooth extraction	4	253.79
	6	Supernumerary #13 tooth extraction	2	106.21

Table 30 Summary of efficacy for trial 3001

Title: A Phase 2/3 Open-label, Multicenter, Safety and Efficacy Study of a Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B		
Study identifier	CSL654_3001	
Design	This was a prospective, open-label study to evaluate the efficacy, PK, and safety of rIX-FP, which is being developed for the prophylaxis and treatment (control and prevention) of bleeding episodes in patients with congenital FIX deficiency (hemophilia B). The main study design consisted of a screening period, a PK period, and an active treatment period for all subjects. Any subjects requiring nonemergency surgery during the course of the study could be enrolled in the surgical substudy.. To evaluate both the treatment (control and prevention) of bleeding episodes and the prophylaxis treatment regimen, subjects who were receiving on-demand treatment with FIX and subjects who were receiving prophylaxis therapy with FIX were both enrolled into the study. All subjects received rIX-FP and were assigned to treatment groups (prophylaxis [Arm 1] or on-demand [Arm 2]) based on their history of use with FIX products. Subjects in the prophylaxis treatment arm were further stratified into 1 of 3 treatment blocks: Block A (prophylaxis subjects who completed Study CSL654_2004), Block B (first 15 non-CSL654_2004 subjects), or Block C (remaining subjects who enrolled in the study). Subjects in Arm 2 received on-demand treatment for 26 weeks and then the number of bleeding episodes was recorded in order to calculate the ABR. Subjects then switched to a 7 day prophylaxis regimen for approximately 26 weeks (minimum of 12 weeks), and the ABR on prophylaxis was compared to on-demand treatment. This design allowed subjects to serve as their own control in measuring the difference in the ABR between the on-demand and prophylaxis treatments.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	approx. 29 months not applicable not applicable
Hypothesis	Continuous data were summarized using descriptive statistics including mean, standard deviation (SD), median, minimum, and maximum. Primary efficacy analysis: The AsBR with on-demand treatment, with prophylaxis treatment, and the percent reduction in AsBR with prophylaxis treatment were summarized using descriptive statistics. The AsBR was analyzed using the Wilcoxon signed-rank test. A test of null hypothesis that the ratio of AsBR (prophylaxis/on-demand) was $\geqslant$0.50 was conducted at the 1-sided 0.025 level. The ratio was based on the original scale. Comparison of annualized spontaneous bleeding rate between the 7-day and >7-day prophylaxis regimens: To show that the extended prophylaxis regimen was non-inferior to the 7-day prophylaxis regimen, 50% of the 7-day treatment effect was to be maintained. The null and alternative hypotheses were as follows: H0: μ7-day – μextended $\leqslant$ -6 H1: μ7-day – μ extended > -6 The lower confidence limit of the 95% CI, based on a 1-sample (paired) t-test for the difference between the 2 means, must be greater than -6.	
Treatments groups	Prophylaxis treatment (Arm 1)	weekly prophylaxis dose of 35 to 50 IU/kg rIX-FP for 26 to 30 weeks, after which subjects could switch to a 10-day or 14-day prophylaxis regimen at a dose of 75 IU/kg rIX-FP for an additional $\geqslant$30 weeks, if specified criteria were met; N=40

	On-demand treatment (Arm 2)		On-demand subjects switched to a 7-day prophylaxis regimen of 35 to 50 IU/kg rIX-FP after either completing 26 weeks (minimum of 12 weeks) of on-demand treatment with rIX-FP or experiencing at least 12 spontaneous bleeding episodes, whichever occurred first; N=23
Endpoints and definitions	Primary EP	ABRpr-od	Comparison of AsBR between on-demand and prophylaxis treatment in Arm 2
	Prophylaxis	7d-ext	Comparison of AsBR during once weekly treatment regimen with that during extended (10-day or 14-day) treatment regimen
	Prophylaxis /On-demand	ABR	Bleeds/year
	Prophylaxis /On-demand	TTSBE	time of the most recent infusion of rIX-FP and the start of a spontaneous bleeding episode
	Consumption	MD	Mean dose
	Haemostatic efficacy	NINF	proportion of bleeding episodes requiring 1 or 2 infusions of rIX-FP to achieve hemostasis
	Haemostatic efficacy	HAEF	Investigator's overall clinical assessment of haemostatic efficacy for treatment of bleeding episodes, based on a 4-point ordinal scale (excellent, good, moderate, poor / none)
Database lock	21 July 2014		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Efficacy population Primary EP: primary efficacy population			
Descriptive statistics and estimate variability	Treatment group	Prophylaxis	On-demand	Total 7-day prophylaxis
	Number of subject	7day: N=40 10-day: N=7 14-day: N=21	On-demand: N=23 7-day: N=19	59
	ABR	7-day: 1.24 10-day: 0.82 14-day: 1.96	On-demand: 20.28 7-day: 2.87	1.76
	TTSBE	7-day: 105.00 14-day: 207.07	NA	99.72hours
	MD	7-day: 47.828 IU/kg 10-day: 70.596 IU/kg 14-day: 71.900 IU/kg	On-demand: 44.155 IU/kg 7-day: 45.519 IU/kg	47.085 IU/kg
	NINF 1 2 More 1 2 more	 93 (92.1%) 8 (7.9%) 0	OD 208 (94.5%) 9 (4.1%) 3 (1.4%) PROPH 34 (91.9%) 1 (2.7%) 2 (5.4%)	Overall N=63 335 (93.6%) 18 (5.0%) 5 (1.4%)

	HAEF Excellent Good Moderate None/Poor Missing	72 (71.3%) 21 (20.8%) 3 (3.0%) 0 5 (5.0%)	225 (87.5%) 19 (7.4%) 6 (2.3%) 1 (0.4%) 6 (2.3%)	Total N= 63 297 (83.0%) 40 (11.2%) 9 (2.5%) 1 (0.3%) 11 (3.1%)
Effect estimate per comparison	ABRpr-od	Comparison groups	Arm 2: AsBR on-demand treatment vs. once weekly prophylactic treatment	
		Percent reduction in AsBR with prophylaxis treatment (%)	95.96	
		SD	5.539	
		P-value	<0.0001	
	7d-ext	Comparison groups	Arm 1: AsBR during 7-day regimen vs. extended regimen (10-day or 14-day)	
		AsBR 7-day/AsBR extended	0.33	
		95% CI	0.073, 1.449	
		P-value	NA	

Ancillary analyses

n/a

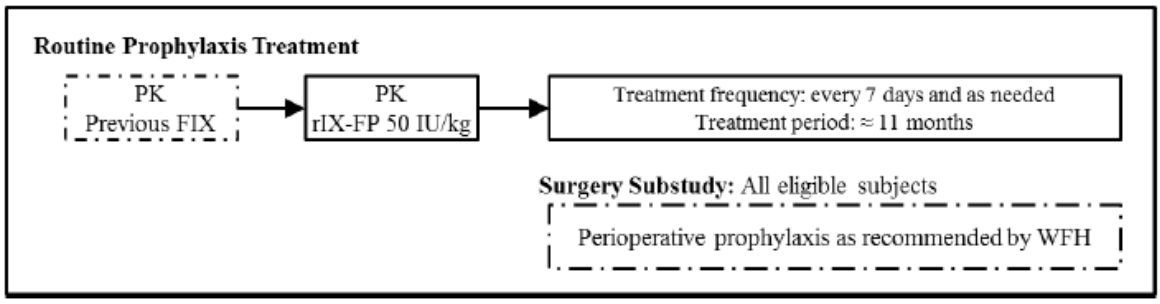
Study 3002: Pharmacokinetics, Safety, and Efficacy Study in Previously Treated Children with Hemophilia B

This was a prospective, open-label study in subjects < 12 years of age to evaluate the efficacy, PK, and safety of rIX-FP, which is being developed for the prophylaxis and treatment (control and prevention) of bleeding episodes in patients with congenital FIX deficiency (hemophilia B).

The main study design consisted of a screening period, a PK period, and an active treatment period of weekly prophylaxis therapy with rIX-FP for all subjects. If a subject required a minor, nonemergency surgical procedure during the study, the subject could be treated with rIX-FP for surgical prophylaxis. Subjects were to be withdrawn from the study if a major or emergency surgical procedure was required.

Efficacy and safety assessments were performed at the study center on a monthly basis.

Figure 5: Study Design of Study 3002



Abbreviations: PK, pharmacokinetics; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; WFH, World Federation of Hemophilia.

Methods

Study participants

29 subjects provided informed consent and were screened for study participation. Of these, 27 subjects were enrolled and treated with rIX-FP (12 subjects < 6 years of age and 15 subjects 6 to < 12 years of age).

Male subjects, < 12 years of age and with body weight ≥ 10 kg, with documented severe hemophilia B (FIX activity of ≤ 2%), who had no prior history of FIX inhibitor formation and who were currently receiving FIX replacement therapy and had FIX products ≥ 150 exposure days (EDs) (6 to < 12 years of age) or ≥ 50 EDs (< 6 years of age) were eligible for inclusion in the study.

Treatments

The main study design consisted of a screening period, a PK period, and an active treatment period of weekly prophylaxis therapy with rIX-FP for all subjects. If a subject required a minor, nonemergency surgical procedure during the study, the subject could be treated with rIX-FP for surgical prophylaxis. Subjects were to be withdrawn from the study if a major or emergency surgical procedure was required.

Pharmacokinetic analyses covered PK of 50 IU/kg of rIX-FP at the beginning of the study in all subjects and PK of 50 IU/kg of the previous FIX product at limited time points at the beginning of the study in a subset of subjects who had no historical PK data of their previous FIX product.

The recommended doses for prophylaxis treatment were selected based on group PK data and treatment experience from Phase 1and Phase 1/2 (studies 2001 and 2004) studies. The desired FIX activity level for the treatment of a bleeding episode was based on the recommendation of the World Federation of Hemophilia (WFH), with a minimum dose of 35 IU/kg. The appropriate dose and dosing regimen of rIX-FP for both prophylaxis and on-demand treatment of bleeding episodes were prescribed by the Investigator.

Prophylaxis dosing for all subjects:

Subjects were initially treated with a weekly prophylaxis dose of 35 to 50 IU/kg rIX-FP, which could be adjusted up to a maximum dose of 75 IU/kg, based on the subject's PK data from this study as well as the PK data from the previous rIX-FP study 2001, the subject's previous prophylaxis dose with another FIX product, the treatment dose/efficacy data from previous rIX-FP studies 2004 and 3001, the subject's bleeding phenotype, and the subject's physical activity level.

If a subject experienced at least 1 spontaneous breakthrough hemorrhage due to an inadequate treatment dose, the dose of rIX-FP could be increased by an increment of 5 to 15 IU/kg, up to a maximum dose of 75 IU/kg of rIX-FP with a target of maintaining the trough FIX activity level above 3% to 5% between doses, while maintaining a treatment interval of 7 days. The prophylaxis treatment dose could also be adjusted to a lower weekly dose due to an unnecessarily high trough FIX activity level.

On-demand dosing for all subjects:

For the on-demand treatment of a bleeding episode, the subject's PK data from this study, the subject's previous treatment dose with another FIX product, the treatment dose / efficacy data from previous rIX-FP studies 2004 and 3001, and the type, location, and severity of the bleeding episode were utilized for calculating / selecting the treatment doses, with an initial dose of 35 to 50 IU/kg, that could be adjusted up to a maximum of 75 IU/kg.

The study center was to be contacted if hemostasis was not achieved after the first rIX-FP administration. If a bleeding episode required a maintenance dose of rIX-FP (to maintain the FIX activity level after achieving hemostasis for multiple days as recommended by WFH), the FIX activity level was to be tested prior to the second rIX-FP administration, if feasible, and administered at least 24 hours after the first treatment dose. After hemostasis was achieved, a lower maintenance dose(s) of rIX-FP could be prescribed at the discretion of the Investigator.

Subjects were to maintain the prophylaxis treatment schedule, if possible, while receiving on-demand treatment for a bleeding episode.

Surgical dosing:

If a subject required a minor, nonemergency surgical procedure during the study, the subject could receive rIX-FP for surgical prophylaxis as recommended by the WFH for surgery.

During the preoperative treatment period (approximately 1 to 3 hours prior to the start of the scheduled surgery), the subject received a single bolus dose of rIX-FP in order to increase the FIX activity levels to 60% to 80%. During the intraoperative treatment period, additional bolus doses of rIX-FP could be administered, if needed, based on the individual subject's possible variation in recovery and/or clearance, or FIX activity levels. Blood samples for the determination of FIX activity levels were collected prior to and 30 minutes following administration of additional doses of rIX-FP. During the postoperative period, defined as starting at wound closure, additional dosing of rIX-FP could be prescribed at the Investigator's discretion at 3- to 7-day treatment intervals to maintain a required trough FIX activity level as recommended by the WFH.

Duration of treatment:

The main study design consisted of a < 1-month screening period and up to a 14-day PK period, followed by an active treatment period of about 11 months. Thus, the duration of the study for an individual subject was expected to be approximately 12 months. A subject could continue in the study if a Phase 3 extension study was not yet enrolling at the time of the subject's planned End-of-study visit.

Objectives

*Primary Objectives w*ere to evaluate the pharmacokinetics (PK) of a single dose of rIX-FP and to evaluate the safety of rIX-FP with respect to the development of inhibitors to factor IX (FIX) in patients with severe hemophilia B (FIX activity of ≤ 2%).

*Secondary Objectives w*ere to evaluate the safety of rIX-FP, based on adverse events (AEs) and the development of antibodies to rIX-FP; to evaluate the clinical response to rIX-FP for the prevention of bleeding episodes; to evaluate the clinical response to rIX-FP in the treatment of bleeding episodes.

Outcomes/endpoints

Primary Endpoint:

Primary endpoints were PK- and safety-endpoints.

Secondary Endpoints:

Secondary efficacy endpoints included the consumption of rIX-FP (expressed as number of infusions and IU/kg per month and per year, as well as IU/kg per event), and the proportion of bleeding episodes that required 1, 2, or > 2 infusions of rIX-FP to achieve hemostasis.

Other Endpoints:

Other endpoints included the Investigator's overall clinical assessment of haemostatic efficacy for treatment of bleeding episodes based on a 4 point ordinal scale, the Investigator's overall clinical assessment of haemostatic efficacy for surgical prophylaxis based on a 4 point ordinal scale (if applicable), annualized bleeding rate (ABR) during the routine prophylaxis treatment period, and quality of life assessed by subjects and their parents/caregivers.

Sample size

In line with the requirements for the clinical investigation of FIX products in children < 12 years of age (EMA/CHMP/BPWP/144552/2009) enrolment of up to 24 subjects was planned.

Randomisation

n/a

Blinding (masking)

n/a

Results

Participant flow

All Subjects received weekly (7-day) routine prophylaxis treatment with an initial weekly dose of 35 to 50 IU/kg rIX-FP, which may have been adjusted. On-demand treatment in this study refers specifically to treatment of bleeding episodes as needed while subjects were receiving prophylaxis treatment.

Recruitment

Of the 18 sites that were activated, subjects were enrolled from 17 sites in 10 countries. Of the 29 subjects screened, 27 subjects were enrolled and treated with rIX-FP (12 subjects <6 years of age and 15 subjects 6 to <12 years of age). Two subjects (both 6 to <12 years of age) participated in the surgical substudy. No subject discontinued from the study.

Conduct of the study

There was 1 non-substantial amendment to the original protocol (dated 08 November 2013) to clarify the visit schedule and correct typographical errors in the Schedule of Assessments tables. There were no changes in the conduct of the study and/or the planned statistical analysis.

Baseline data

Demographic and baseline characteristics

All subjects were male and <12 years of age. The majority of subjects were White (26/27 subjects, 96.3%) and non-Hispanic (25/27 subjects, 92.6%). Subjects had an overall mean (SD) age of 5.9 (2.93) years. 12 Subjects were < 6 years of age and 15 subjects were 6 to < 12 years of age. Subjects < 6 years of age had a mean (SD) age of 3.2 (1.70) years (range, 1 to 5 years) and a mean (SD) BMI of 15.61 (1.727) kg/m^2 (range, 13.6 to 19.1 kg/m^2). Subjects 6 to < 12 years of age had a mean (SD) age of 8.1 (1.41) years (range, 6 to 10 years) and a mean (SD) BMI of 17.64 (3.766) kg/m^2 (range, 12.7 to 26.9 kg/m^2).

All subjects had been diagnosed with hemophilia B and had a FIX activity level ≤2%.

Previous treatment

In the 12 months prior to study entry, subjects experienced a mean (SD) of 7.0 (11.89) total, 3.0 (4.44) trauma-induced, and 3.9 (9.18) spontaneous bleeding episodes with similar proportions in the 2 age groups. The number of unknown bleeding episodes (mean [SD]) was low (0.3 [0.59] overall).

Target joints (defined as 3 or more spontaneous bleeds into a single joint within a consecutive 6-months period) were reported in 3 subjects (2 subjects <6 years of age and 1 subject 6 to <12 years of age group) prior to study entry.

As a requirement for study enrollment, all subjects had received previous FIX products (pdFIX or rFIX) for ≥150 EDs (6 to <12 years of age) or ≥50 EDs (<6 years of age). Overall, the majority of subjects received previous FIX as routine prophylaxis treatment prior to study entry (24/27 subjects, 88.9%), while 3/27 (11.1%) subjects received previous FIX only for on-demand treatment of bleeding episodes. All 3 subjects who received previous FIX as on-demand treatment prior to study entry (1 subject <6 years of age and 2 subjects 6 to <12 years of age) were from the same site).

The mean weekly consumption for routine prophylaxis prior to study entry was 107 IU/kg; for subjects <6 years of age, the mean weekly consumption prior to study entry was 139 IU/kg, and for subjects 6 to <12 years of age, it was 80 IU/kg. The majority of subjects (20/24) received routine prophylaxis treatment more frequently than once weekly.

Table 31 Weekly consumption for routine prophylaxis prior to study entry (Safety Population)

	Age <6 years (N=12)	Age 6 to <12 years (N=15)	Total (N=27)
n	11	13	24
Weekly Consumption			
Mean (SD)	138.667 (123.8274)	80.339 (47.2500)	107.073 (93.3422)
Median	100.000	60.000	86.000
Q1, Q3	60.000, 150.000	43.080, 100.000	50.500, 136.667
Min, Max	50.000, 490.00	35.00, 182.00	35.00, 490.00
Prophylaxis treatment interval			
2 times per week	8	7	15
3 times per week	0	2	2
Every 3 days	1	1	2
Every other day	1	0	1
Every week	1	3	4

Abbreviations: Max = maximum; Min = minimum; Q = quartile; SD = standard deviation.
Note: 'n' represents then number of subjects who received routine prophylaxis prior to study entry;

Protocol deviations:

There was no protocol deviations relating to inclusion/exclusion criteria reported during the study.

3 Major protocol deviations were reported in 3 of 27 (11.1%) subjects; 1 in subjects <6 years of age (signed information sheet not submitted to the IEC; this protocol deviation did not influence the efficacy assessment; therefore, this subject was included in the analyses of the PP population) and 2 in subjects 6 to <12 years age of age: the screening laboratory samples were collected prior to signing of the ICF but the subject was included in the analyses of the PP population and in a subject who underwent a major surgery for a fractured arm, treatment during the surgery period was excluded from analyses of the Efficacy and PP populations.

All remaining protocol deviations were minor. The most common minor protocol deviations pertained to procedures, IMP administration, visit schedule, and Laboratory tests.

Outcomes and estimation

Response to prophylaxis treatment

The ABR during routine prophylaxis treatment was calculated per subject and summarized for total, spontaneous (AsBR), and joint bleeds overall and by age category.

23 Subjects had bleeding episodes that required treatment in the Efficacy population (11 subjects <6 years of age and 12 subjects 6 to <12 years of age).

In the Efficacy population, the overall median ABR for total bleeding episodes during prophylaxis treatment was 3.12. The ABRs in the 2 age groups were comparable, with differences in median ABRs between the 2 age groups of <1 bleeding episode per year (median in subjects <6 years of age vs subjects 6 to <12 years of age: 2.64 vs 3.39). More than half of the subjects (51.9%) in the Efficacy population reported no spontaneous bleeding episodes during the study

For the 3 subjects who received previous FIX as on-demand treatment prior to study entry the AsBRs in the study were 0.00, 2.36, and 3.55, These AsBRs of all 3 subjects were markedly reduced in the study when compared with the number of spontaneous bleeding episodes these subjects reported in the last 12 months prior to study entry (15 spontaneous bleeds for one Subject, 34 for a second Subject, and 31 for a third Subject). Similar differences were also seen for the ABRs of these subjects in the study vs the total number of bleeding episodes these subjects reported in the last 12 months prior to study entry (1.18 vs 19,: 4.73 vs 42, and 5.91 vs 39). The median ABR at the joints was 0.99 overall in the Efficacy population and was comparable between the 2 age groups (differences in median ABRs between the 2 age groups <1 bleeding episode per year).

Table 32 Annualized Bleeding Rates by Bleeding Category (Efficacy Population)

	Age <6 years (N=12)	Age 6 to <12 years (N=15)	Total (N=27)
Total bleeding episodes			
Number of subjects with at least 1 bleeding episode requiring treatment, n (%)	11 (91.7)	12 (80.0)	23 (85.2)
Annualized bleeding rate (bleeding episodes/year/ subject)			
n	12	15	27
Mean (SD)	4.22 (3.561)	3.44 (3.178)	3.78 (3.311)
Median	2.64	3.39	3.12
Q1, Q3	2.00, 6.48	0.76, 5.91	0.91, 5.91
Min, Max	0.0, 10.7	0.0, 9.5	0.0, 10.7
Spontaneous bleeding episodes			
Number of subjects with at least 1 bleeding episode requiring treatment, n (%)	1 (8.3)	9 (60.0)	10 (37.0)
Annualized bleeding rate (bleeding episodes/year/ subject)			
n	12	15	27
Mean (SD)	0.08 (0.287)	0.96 (1.103)	0.57 (0.942)
Median	0.00	0.78	0.00
Q1, Q3	0.00, 0.00	0.00, 1.99	0.00, 0.91
Min, Max	0.0, 1.0	0.0, 3.5	0.0, 3.5

Target joints were reported in 3 subjects prior to study entry. Two of the subjects had no bleeds at the location of their previous target joint, whereas 1 subject had 2 bleeds (only 1 treated) at his previous target joint location Because there were fewer than 3 bleeds in 6 months at previously identified target joints, all target joints were considered resolved during the study.

The overall median ABR and AsBR in the study were similar to the median (Q1, Q3) number of bleeding episodes (3.0 [1.0, 6.0]) and spontaneous bleeding episodes (0.0 [0.0, 2.0]), respectively, reported in the last 12 months prior to study entry.

Time between the most recent prophylaxis infusion and spontaneous bleeding episode

In the Efficacy population, the overall median (Q1, Q3) time between the most recent prophylaxis infusion and a spontaneous bleeding episode was 132.2 (100.0, 148.6) hours. The time between the most recent prophylaxis infusion and a spontaneous bleeding episode was >72 hours for all episodes. Of the 16 bleeding episodes assessed, the time between the most recent prophylaxis infusion and a spontaneous bleeding episode was more than 6 days (>144 hours) for 7 bleeding episodes (6 bleeding episodes >144 to ≤168 hours; 1 bleeding episode >168 hours). The data were similar in the analysis of the PP population.

rIX-FP consumption

In the Efficacy population, the mean number of prophylaxis infusions per month was 4.31 overall, was comparable between the 2 age groups (4.32 in subjects <6 years of age and 4.29 in subjects 6 to <12 years of age), and was in accordance with the study schedule of weekly prophylaxis therapy with rIX-FP.

The mean total prophylaxis dose per month was 205 IU/kg overall, 214 IU/kg in subjects <6 years of age, and 198 IU/kg in subjects 6 to <12 years of age. The mean total prophylaxis dose per year was 2461 IU/kg overall, 2562 IU/kg in in subjects <6 years of age, and 2380 IU/kg in in subjects 6 to <12 years of age. The mean weekly prophylaxis dose was 47 IU/kg overall, 49 IU/kg in subjects <6 years of age, and 46 IU/kg in subjects 6 to <12 years of age. Of note, the mean weekly prophylaxis dose in this study (47 IU/kg) was considerably lower than the weekly consumption for routine prophylaxis prior to study entry (107 IU/kg).

The mean total prophylaxis dose per infusion was 47 IU/kg overall and was slightly higher in subjects <6 years of age than in subjects 6 to <12 years of age (49 vs 45 IU/kg). Only 1 subject n the subjects <6 years of age group) received doses above the recommended maximum treatment dose of 75 IU/kg (doses of 76.36 to 77.48 IU/kg).

The data presented for the PP population were identical to the ones for the Efficacy population for the analysis of rIX-FP consumption.

A summary of dose adjustments has been provided.

Table 33 Consumption of rIX-FP During Routine Prophylaxis (Efficacy Population)

	Age <6 years (N=12)	Age 6 to <12 years (N=15)	Total (N=27)
Total prophylaxis dose per year (IU/kg)			
n	12	15	27
Mean (SD)	2562.200 (532.6176)	2379.773 (462.8311)	2460.852 (493.8598)
Median	2545.472	2222.253	2385.208
Q1, Q3	2336.523, 2933.166	2107.843, 2659.389	2120.278, 2910.356
Min, Max	1516.70, 3612.27	1611.08, 3178.11	1516.70, 3612.27
Total prophylaxis dose per infusion (IU/kg)			
n	571	900	1471
Mean (SD)	49.030 (11.1418)	45.179 (8.9768)	46.674 (10.0469)
Median	49.876	43.253	45.957
Q1, Q3	44.333, 54.205	39.895, 50.000	40.000, 51.010
Min, Max	15.06, 77.48	26.03, 66.87	15.06, 77.48

Abbreviations: Max = maximum; Min = minimum; Q = quartile; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin; SD = standard deviation.

Control of bleeding episodes

Number of infusions of rIX-FP to achieve hemostasis (secondary efficacy endpoint)

Of the 106 bleeding episodes that required treatment in the Efficacy population, 41 occurred at joints, 18 at muscles, and 47 at other locations. When analyzed by type of bleeding episodes, 16 episodes were spontaneous, 73 traumatic, 1 post-surgical, and 16 of unknown nature in the Efficacy population. 103 were treated successfully with 1 or 2 infusions. Successful treatment with 1 or 2 infusions was reported for all bleeding episodes in subjects < 6 years of age and for 58 of 61 bleeding episodes in subjects 6 to < 12 years of age.

3 Subjects (all 6 to <12 years of age) had 3 bleeding episodes that required >2 infusions to achieve haemostasis . These bleeding episodes were minor/moderate, occurred at the joints, and were traumatic (2 episodes) or spontaneous (1 episode).

Investigator's overall clinical assessment of haemostatic efficacy for the treatment of bleeding episodes (secondary efficacy endpoint)

Treatment was effective for the vast majority of minor/moderate bleeding episodes (75.0% rated excellent; 21.2% rated good), and for both of the major bleeding episodes (100%) according to the Investigator's assessment.

Table 34 Investigator's Overall Clinical Assessment of Haemostatic Efficacy for the Treatment of Bleeding Episodes (Efficacy Population)

Bleeding Severity Assessment	Age <6 years (N=12)	Age 6 to <12 years (N=15)	Total (N=27)
Minor/moderate bleeding episodes			
Number of bleeding episodes requiring treatment	43	61	104
n (%)[a]			
Excellent	36 (83.7)	42 (68.9)	78 (75.0)
Good	6 (14.0)	16 (26.2)	22 (21.2)
Moderate	0	1 (1.6)	1 (1.0)
Poor/no response	0	0	0
Missing	1 (2.3)	2 (3.3)	3 (2.9)
Major bleeding episodes			
Number of bleeding episodes requiring treatment	2	0	2
n (%)[a]			
Excellent	0	0	0
Good	2 (100.0)	0	2 (100.0)
Moderate	0	0	0
Poor/no response	0	0	0
Missing	0	0	0

[a] n (%) corresponds to the number and percentage of bleeding episodes; percentages are based on the number of bleeding episodes requiring treatment.

Bleeding episodes not requiring treatment

20 Bleeding episodes in the Efficacy population did not require treatment (17 of these episodes occurred in subjects <6 years of age). Six events were spontaneous, 11 traumatic, and 3 of unknown type. The location of these episodes were: nasal (11 episodes), multiple, oral, right elbow, right knee, (1 episode in each category), and other (5 episodes).

Surgical substudy

2 Subjects reported 2 surgeries during the study, neither of which were related to hemophilia

Haemostatic efficacy for surgical prophylaxis was rated as excellent or good for both surgeries at wound closure (0 hours) and/or 7 days following surgery (168 hours).

No haemostatic interventions or transfusion support were required for any subject, and no estimated actual intraoperative blood loss was recorded. There were no surgical evacuations needed and no hematomas. No re-bleeding occurred within 72 hours. All surgical subjects received 1 dose of rIX-FP prior to surgery; no doses were administered intra-operatively. Consumption during the post-operative period was not unexpected for the type of surgery performed. The mean consumption of rIX-FP was 45.1 IU/kg for the pre-surgical dose.

Table 35 Perioperative response

Surgical Procedures	Subject Number	Assessment of Hemostasis Response		Number of rIX-FP infusions Days 1 - 14[a]
		Wound closure (0 h)	EOS/ POD 7	
Extraction of 2 teeth		Excellent	Excellent	2[c]
Extraction of 4 teeth after tooth abscess		--[b]	Good	4[d]

Abbreviations: EOS = end of study; POD = post-operative day; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin.

[a] Surgery is counted as Day 1. All doses, including preoperative dose, and routine prophylaxis doses after surgery are counted for the 14-days following surgery.

[b] Not reported.

[c] Preoperative dose on Day 1 prior to surgery, and routine prophylaxis dose on POD 9.

[d] Preoperative dose on Day 1 prior to surgery, routine prophylaxis doses on POD 3 and 10, and an additional dose on POD 6.

Ancillary analyses

n/a

Table 36 Summary of efficacy for trial 3002

Title: A Phase 3 Open-label, Multicenter, Pharmacokinetics, Safety, and Efficacy Study of a Recombinant Fusion Protein Linking Coagulation Factor IX with Albumin (rIX-FP) in Previously Treated Children with Hemophilia B				
Study identifier	CSL654_3002			
Design	This was a prospective, open-label study in subjects <12 years of age to evaluate the efficacy, PK, and safety of rIX-FP, which is being developed for the prophylaxis and treatment (control and prevention) of bleeding episodes in subjects with congenital FIX deficiency (hemophilia B). The main study design consisted of a screening period, a PK period, and an active treatment period of weekly prophylaxis therapy with rIX-FP for all subjects. If a subject required a minor, nonemergency surgical procedure during the study, the subject could be treated with rIX-FP for surgical prophylaxis.			
	Duration of main phase:	Approx. 21 months		
	Duration of Run-in phase:	not applicable		
	Duration of Extension phase:	not applicable		
Hypothesis	Exploratory: For all efficacy outcome measures descriptive statistics were presented.			
Treatments groups	<6 years of age	Once weekly prophylactic treatment, N=12		
	6-<12 years of age	Once weekly prophylactic treatment, N=15		
Endpoints and definitions	Prophylaxis	ABR	Bleeds/year	
	Consumption	MD	Mean total prophylaxis dose	
	Prophylaxis	TTSBE	time of the most recent infusion of rIX-FP and the start of a spontaneous bleeding episode	
	Haemostatic efficacy	NINF	proportion of bleeding episodes requiring 1 or 2 infusions of rIX-FP to achieve hemostasis	
	Haemostatic efficacy	HAEF	Investigator's overall clinical assessment of haemostatic efficacy for treatment of bleeding episodes, based on a 4-point ordinal scale (excellent, good, moderate, poor / none)	
Database lock	05 October 2014			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Efficacy Population			
Descriptive statistics and estimate variability	Treatment group	<6 years of age	6-<12 years of age	Total
	Number of subject	12	15	27
	ABR	4.22	3.44	3.78
	MD	49.030 IU/kg	45.179 IU/kg	46.674 IU/kg
	TTSBE	NA	NA	132.2hours

	NINF 1 2 More	 40 (88.9%) 5 (11.1%) 0	 54 (88.5%) 4 (6.6%) 3 (4.9%)	 94 (88.7%) 9 (8.5%) 3 (2.8%)
	HAEF minor/moderate BE Excellent Good Moderate None/Poor Missing HAEF major BE Excellent Good Moderate None/Poor Missing	 36 (83.7%) 6 (14.0%) 0 0 1 (2.3%) 0 2 (100.0%) 0 0 0	 42 (68.9%) 16 (26.2%) 1 (1.6%) 0 2 (3.3%) 0 0 0 0 0	 78 (75.0%) 22 (21.2%) 1 (1.0%) 0 3 (2.9%) 0 2 (100.0%) 0 0 0

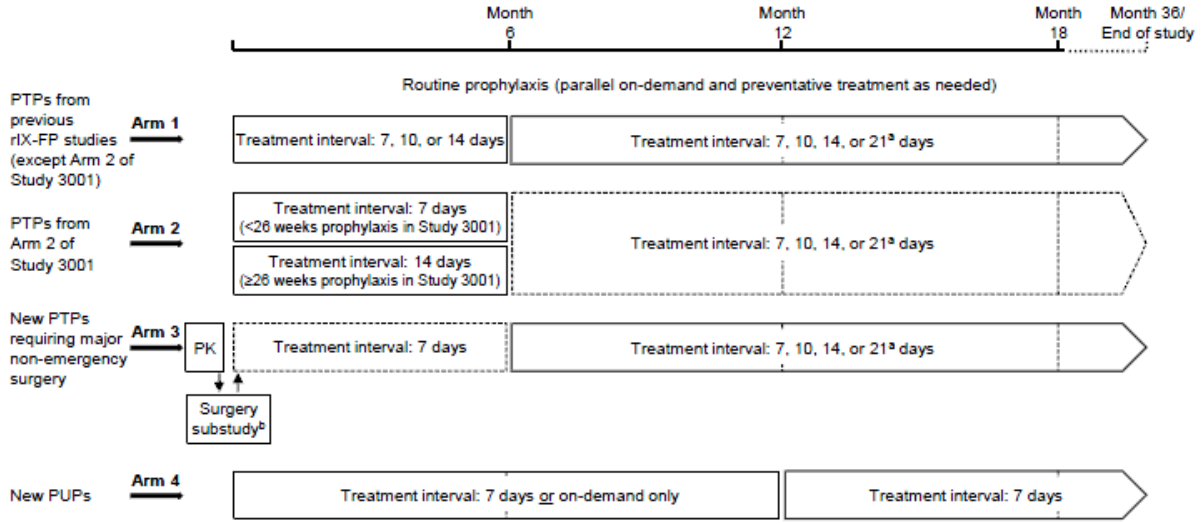
Supportive Studies

<u>Study 3003: Safety and Efficacy Extension Study in subjects with Hemophilia B</u> (Abbreviated Clinical Study Report)

This is an ongoing, multicenter, open-label, phase 3b study to investigate the long-term safety and efficacy of rIX-FP for the routine prophylaxis and on-demand treatment of bleeding episodes in subjects with hemophilia B. The study includes a surgery substudy to investigate the efficacy of rIX-FP in the prevention and control of bleeding in subjects with hemophilia B during surgical procedures. As of the data cut-off date (09 January 2015), subjects have been enrolled at 39 centers in 15 countries.

Subjects are allocated to 4 treatment arms as per the following diagram.

Figure 6: Overview of Study Design 3003



IU = International Unit(s); PK = pharmacokinetic(s); PTP = previously treated patient; PUP = previously untreated patient; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin.

[a] Only subjects ≥18 years of age with ≥6 months of prophylaxis treatment with a 14-day treatment interval may switch to a 21-day treatment interval, after PK evaluation with a single dose of 100 IU/kg rIX-FP.

[b] Subjects from Arms 1 and 2 who require minor or major non-emergency surgery and subjects from Arm 4 who require minor non-emergency surgery may also participate in the surgery substudy.

Methods

Study participants

Number of subjects planned: Approximately 115 male subjects are planned to be enrolled in Study 3003. At least 5 subjects and 10 major surgeries are planned across all CSL Behring rIX-FP lead-in studies and Study 3003 (ie, combined).

Number of subjects analyzed: At the time of data cut-off, 83 subjects were screened, 81 subjects were enrolled, and 80 subjects were treated with rIX-FP (24 subjects < 12 years of age). Overall, 7 subjects had participated in the surgery substudy.

Male subjects with documented severe hemophilia B (FIX activity of ≤2%), who had no history of FIX inhibitor formation. Criteria for Inclusion were completion of a previous rIX-FP study for arms 1 and 2, subjects 12 to 70 years of age scheduled to have a major non-emergency surgery for Arm 3 (excluding subjects from France), and previously untreated subjects up to 18 years of age for Arm 4.

If a subject requires non-emergency surgery during the study, the subject may be treated with rIX-FP for surgical prophylaxis in the surgery substudy.

Treatments

Routine prophylaxis dosing: The dose is based on the subjects' previous experience and/or the targeted FIX activity trough level (target FIX activity level >2%, but optimally between 5% and 15%). In Arms 1, 2, and 3, the treatment interval ranges between 7 and 14 days for the first 6 months and may generally only be changed at each 6 month follow-up assessment (up to 21 days for subjects ≥18 years of age who received rIX-FP prophylaxis at 14-day intervals for 6 months and had a PK evaluation with 100 International Units [IU]/kg rIX-FP).

On-demand dosing: On-demand treatment is used for all bleeding episodes requiring treatment. The dose (35 to 75 IU/kg) is determined by the Investigator, based on the effective on demand treatment dose used in the lead in study and/or the subject's PK data.

Preventative dosing: Preventative treatment may be administered before vigorous physical activity or physical therapy. The dose (35 to 50 IU/kg) is determined by the Investigator, based on the effective on demand treatment dose used in the lead in study and/or the subject's PK data.

Surgical dosing was based on recommendations for surgery by the World Federation of Hemophilia. During the pre-operative treatment (approximately 3 hours before the start of the surgery), a single bolus injection of 50 to 100 IU/kg (or higher) are applied. During surgery, intraoperative doses depend on the FIX activity levels, type of surgery, and local standard of care. Postoperative injections of rIX-FP are administered for 1 to 14 days (or longer, if needed) depending on FIX activity levels and type of surgery.

Duration of the study for an individual subject is expected to be approximately 3 years or the time it takes to achieve a total of 100 exposure days (EDs) during the subject's enrollment in any CSL Behring-sponsored rIX-FP studies (for subjects in Arms 1 or 2). The overall study duration (ie, first subject's first visit to last subject's End-of-study visit) is expected to be approximately 3 years.

For the surgery substudy, the active treatment period is 1 to 14 days (or longer, if needed) depending on the type of surgery and local standard of care. After completing the surgery substudy, subjects will return to the treatment plan of the main study, or start routine prophylaxis with rIX-FP, if enrolled as a new subject (Arm 3).

Table 37 Dose Guidelines for routine prophylaxis

	Dose in IU/kg by treatment interval			
	7 days	10 days [a]	14 days	21 days
Suggested dose	25 - 50	50 - 75	75	100
Maximum dose	50 [b]	75	75	100

IU = International Unit(s).

[a] The 10-day treatment interval may be based on a schedule of once every 10 calendar days or 3 times per month (eg, 1st, 11th, and 21st day of each month).

[b] An rIX-FP dose higher than 50 IU/kg is acceptable if the FIX activity trough level was <5% at Day 7 and a higher trough level is necessary to prevent spontaneous bleeding.

Further details on the selection and timing of doses are provided in Section 9.4.5.1 for routine prophylaxis, in Section 9.4.5.2 for on-demand treatment, in Section 9.4.5.3 for preventative treatment before vigorous physical activity or physical therapy, and in Section 9.4.5.4 for the surgery substudy.

Objectives

*Primary Objectives w*ere to evaluate the safety of rIX-FP as measured by new cases of inhibitors against coagulation factor IX (FIX) in subjects, including previously untreated subjects, with severe hemophilia B and for the *Surgery substudy t*o evaluate the efficacy of rIX-FP in the prevention and control of bleeding in subjects with severe hemophilia B during surgical procedures.

Secondary objectives were to further evaluate the safety of rIX-FP and for the *Surgery substudy t*o evaluate the safety of rIX-FP during the intraoperative and postoperative periods.

Only safety data from the main study and data from the surgery substudy (data cut-off date: 09 January 2015) are reported in the abbreviated CSR and summarized in the dossier. Secondary and

exploratory objectives related to efficacy, pharmacokinetics (PK), and quality of life will be evaluated at the end of the study, and will be reported in the final CSR.

Outcomes/endpoints

Primary efficacy endpoint of the surgery sub-study was the Investigator's overall clinical assessment of haemostatic efficacy for surgical prophylaxis, based on a four point ordinal scale (excellent, good, moderate, poor / none).

Sample size

The choice of sample size for this study is not based on statistical power considerations. Approximately 115 subjects are to be enrolled in this study, including all eligible subjects from rIX-FP lead-in studies, approximately 10 subjects requiring major non-emergency surgery who had not previously received treatment with rIX-FP, and approximately 20 PUPs. The target is at least 50 subjects completing 100 EDs during enrollment in all CSLB-sponsored rIX-FP studies.

Randomisation

n/a

Blinding (masking)

n/a

Results

Participant flow

Refer to Figure 7

Recruitment

The study is planned to be conducted at approximately 40 study centers worldwide. The duration of the study for an individual subject is expected to be approximately 3 years or the time it takes to achieve a total of 100 exposure days (EDs) during the subject's enrollment in any CSLB-sponsored rIX-FP studies (for subjects in Arms 1 or 2). The overall study duration (ie, first subject's first visit to last subject's End-of-study visit) is expected to be approximately 3 years. The target is at least 50 subjects completing 100 EDs during enrollment in all CSLB-sponsored rIX-FP studies,

All 80 subjects were male. The majority of subjects were White (67 subjects, 83.8%) and non Hispanic (77 subjects, 96.3%). For the overall study population, subjects had a mean age of 27.5 years (minimum [min], maximum [max]: 2, 63); 24 subjects were <12 years of age.

A total of 7 subjects underwent 7 surgeries during the surgery substudy at the time of the data cut-off on 09 January 2015 (excision of pigmental nevus, 1 subject; rhinoplasty and submucosal resection with inferior turbenectomy, 1 subject; endoscopic mucosal resection, 1 subject; root canal, 1 subject; right ankle arthroplasty, 1 subject; total knee replacement, 2 subjects).

Conduct of the study

There were 3 amendments to the original protocol (dated 14 May 2013):

Amendment 1 of 17 September 2013 covers the addition of Arm 3 to the study design comprising subjects who had not previously completed a CSLB-sponsored rIX-FP lead-in study and who were scheduled to have a major non-emergency surgery within 8 weeks from the start of the initial rIX-FP

(100 IU/kg) PK evaluation period, Change of the sample size from 85 to 95 and clarification that the exploratory objective relating to QoL is limited to subjects from the lead-in Study 3002.

Amendment 2 of 17 February 2014 (applicable only to study centers in France) was based on requests from the French regulatory agency and included restriction to exclude additional new surgical subjects in France from enrolling in Arm 3, exclusion of French subjects enrolled from the lead-in studies from the 21-day prophylaxis regimen and clarification of treatment of a subject if an inhibitor to FIX was confirmed.

Amendment 3 of 03 June 2014 reflects the addition of Arm 4 covering PUPs, change of the sample size from 95 to 115, to allow for inclusion of at least 20 PUPs and introduction of an IDMC to provide an independent evaluation of Arm 4 of the study.

Baseline data

Demographic and baseline characteristics

Subjects were enrolled from 39 centers in 15 countries. Study enrollment was ongoing at the time of data cutoff (09 January 2015) for this abbreviated CSR. 83 Subjects were screened for study participation. Of these, 81 subjects were enrolled, and 80 subjects were treated with rIX-FP. Overall, 7 subjects had participated in the surgery substudy at the time of data cutoff, 3 in arm 1, 1 in arm2, and 3 in arm3.

Only male subjects were enrolled in this study. The majority of subjects were White (67 subjects, 83.8%) and non-Hispanic (77 subjects, 96.3%). Subjects had an overall mean age of 27.5 years (min, max: 2, 63). As only subjects ≥12 years of age could be enrolled in Arms 2 and 3 of the study according to the inclusion criteria, the mean age, height, and body weight in Arms 2 and 3 were higher than in Arm 1, which included 24 pediatric subjects <12 years of age.

Further details will be presented in the final study report.

Outcomes and estimation

Surgery substudy

At the time of data cutoff (09 January 2015), 7 surgeries had been performed in 7 subjects.

Haemostatic efficacy for surgical prophylaxis was rated as excellent or good at wound closure (0 hours) and at 72 hours or discharge for all surgeries for which assessments were available. The overall hemostasis response was rated as excellent for the 2 surgeries for which an assessment was available.

The desired FIX levels were achieved before, during, and after surgery with a total of 3 to 7 rIX-FP injections during the 14-day surgical period, including a single preoperative dose. A mean dose of 79.0 IU/kg was given preoperatively; hemostasis from the preoperative dose was maintained until the end of surgery for all surgeries. Consumption during the postoperative period (2 to 6 rIX-FP injections) was lower than expected based on using currently marketed FIX replacement products to achieve the recommended FIX activity level. The mean postoperative consumption of rIX-FP was 53.3 IU/kg during the first 72 hours after surgery and 191.4 IU/kg during the first 14 days after surgery.

Estimated actual intraoperative blood loss was below or equal to the maximum predicted blood loss for a non-hemophilic individual undergoing the same type and extent of surgical procedure. One subject received packed red blood cells after a total knee replacement, as planned prior to surgery; however, the amount was less than predicted. Assessments of hemoglobin levels relative to surgery are available for 4 subjects.

Table 38 Perioperative hemostasis response (Surgical Population)

Surgical procedure	Subject number	Assessment of hemostasis response		Number of rIX-FP injections during surgical period [b]
		Wound closure (0 hours)	72 hours or discharge [a]	
Excision of pigmental nevus – lumbal area		Not reported	Excellent	3
Rhinoplasty, submucosal resection, and inferior turbinectomy		Excellent	Excellent	4
Endoscopic mucosal resection		Excellent	Excellent	4
Root canal		Not reported [c]	Not reported [c]	3
Right ankle arthroplasty		Excellent	Excellent	6
Total knee replacement, left		Good	Not reported	6
Total knee replacement, right		Excellent	Excellent	7

rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin.

[a] Whichever occurred first.

[b] All doses, including preoperative dose and doses after surgery are counted for the 14 days (336 hours) following surgery.

[c] Only an overall assessment of hemostasis response (excellent) was reported.

Note: Data based on cutoff of 09 January 2015. Final results will be reported in the final clinical study report.

Source: Table 14.4.1; Listing 16.2.6.4.

- **Ancillary analyses**

n/a

Analysis performed across trials (pooled analyses and meta-analysis)

The comparison and analysis of results are organized according to the indication being sought. Because both studies 2004 and 3001 collected PK and efficacy data relevant to the on-demand treatment of a bleeding episode, these data have been pooled. Pooled data are reported along with presentations of the separate study data as they are relevant to each indication.

Demographics and baseline characteristics

Demographics and baseline characteristics of the populations in studies 2004, 3001, 3002, and 3003 have been presented. Subjects who participated in both studies 2004 and 3001 were counted only once in the pooled efficacy assessment, using their baseline data from Study 2004.

Comparison of Efficacy Results for All Studies

Data supporting efficacy of rIX-FP are presented according to the treatment regimen. Primary support for the use of rIX-FP as routine prophylaxis derives from a prospective analysis of the difference in AsBR for on-demand vs prophylaxis treatment regimens in Study 3001. Study 3001 also included an analysis of ABR for 3 different routine prophylaxis regimens (7-, 10-, and 14-day). Efficacy data from Study 3002 support the use of rIX-FP as routine prophylaxis for the treatment and prevention of bleeding episodes in pediatric patients.

Data supporting use of rIX-FP for perioperative hemostasis derive from studies 3001, 3002, and 3003.

Response to prophylaxis treatment

Subjects ≥ 12 to 65 Years (Adults and Adolescents)

Study 3001 was designed to demonstrate the efficacy of rIX-FP when used as routine prophylaxis. The analysis population included subjects who received on-demand treatment during the first half of the study followed by prophylaxis treatment (Arm 2), thus allowing for a within-subject comparison of spontaneous bleeding rates between on-demand and prophylaxis treatment.

Table 39 Studies 2004 and 3001: Efficacy Assessments Relevant to Prophylaxis Treatment with rIX-FP (Efficacy Population)

	Study 2004		Study 3001	
	On-demand (N = 4)	Weekly Prophylaxis (N = 13)	On-demand (N = 23)	Weekly Prophylaxis (N = 59)
Duration of treatment period (days)				
n	4	13	23	59
Mean (SD)	131.3 (27.50)	314.7 (20.13)	177.4 (41.22)	338.7 (183.32)
Median	132.5	322.0	186.0	284.0
Q1, Q3	107.5, 155.0	315, 323	175.0, 192.0	210.0, 523.0
Min, Max	105, 155	259, 335	77, 278	14, 640
Annualized bleeding rate (bleeding episodes/year/subject)				
n	4	13	22	56
Mean (SD)	26.80 (2.696)	4.352 (4.674)	20.28 (8.616)	1.76 (3.209)
Median	26.88	2.27	18.65	0.61
Q1, Q3	24.74, 28.86	0.00, 8.09	16.70, 25.53	0, 2.57
Min, Max	23.56, 29.88	0, 14.00	2.0, 46.1	0, 21.1

Abbreviations: Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; SD, standard deviation.

Source: Study 2004 CSR Table 14.2.2.1; Study 3001 CSR Tables 14.2.1.2, 14.2.1.3, and 14.2.1.5.

The design of Study 3001 allowed for the extension of the prophylaxis treatment interval to 10 or 14 days in Arm 1 subjects who met the switching criteria of the protocol (ie, subjects were on a stable dose of ≤ 40 IU/kg and had no spontaneous bleeds in the previous month). After approximately 26 weeks on a 7-day regimen, 26/40 subjects switched to a longer regimen. The ABR results for those subjects are shown in Table 41 along with data from subjects participating in both Arms 1 and 2 on a 7-day prophylaxis regimen.

Table 40 Study 3001: Annualized Bleeding Rate of All Prophylaxis Regimens with rIX-FP (Efficacy Population)

	Total 7-day Regimen (Arm 1 + Arm 2) (N = 59)	Arm 1 Intra-subject		
		7-day Regimen (N = 26)	10-day Regimen (N = 7)	14-day Regimen (N = 21)
Annualized spontaneous bleeding rate (bleeding episodes/year/subject)				
n	56	26	7	21
Mean (SD)	0.59 (1.139)	0.23 (0.911)	0.13 (0.334)	1.07 (2.114)
Median (Q1, Q3)	0.00 (0.00, 0.75)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 1.00)
Min, Max	0.0, 4.5	0.0, 4.5	0.0, 0.9	0.0, 7.3
Total annualized bleeding rate (bleeding episodes/year/subject)				
	56	26	7	21
Mean (SD)	1.76 (3.209)	0.67 (1.327)	0.82 (1.195)	1.96 (2.653)
Median (Q1, Q3)	0.61 (0.00, 2.57)	0.00 (0.00, 1.53)	0.00 (0.00, 1.78)	1.08 (0.00, 2.70)
Min, Max	0.0, 21.1	0.0, 6.0	0.0, 3.0	0.0, 9.1

Abbreviations: Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; SD, standard deviation.

Table 41 Study 3001: Total 7-day Prophylaxis Dose per Injection of rIX-FP by Global Region (Efficacy Population)

	Asia[a]	Europe[b]	Middle East[c]	North America[d]
Number of subjects	9	34	11	5
Number of injections	559	1466	707	215
Mean (SD) (IU/kg)	43.46 (9.273)	44.30 (8.809)	63.27 (11.248)	52.48 (12.551)
Median (IU/kg)	41.61	40.00	68.67	50.00
Q1, Q3 (IU/kg)	35.01, 48.57	38.17, 49.73	50.96, 73.86	49.88, 51.40
Min, Max (IU/kg)	32.33, 62.52	2.14, 99.87	39.09, 82.26	25.33, 81.28

Abbreviations: Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; SD, standard deviation.

[a] Asia: Japan.

[b] Europe: Austria, Bulgaria, Germany, Spain, France, Italy, Russia.

[c] Middle East: Israel.

[d] North America: United States.

All subjects who switched to the 14-day prophylaxis regimen fulfilled the switching criteria of maintaining a stable dose of at most 40 IU/kg weekly.

Control and prevention of bleeding episodes.

In both studies 2004 and 3001, 93.0% of bleeding episodes were successfully treated with a single injection. In Study 3001, subjects in the Arm 2 on-demand regimen exhibited a success rate of 98.6% (95% CI: 94.3% to 99.7%) and those in the Arm 2 prophylaxis regimen exhibited a rate of 94.6% (95% CI: 76.9% to 98.9%) Across both studies, the probability of successfully treating a bleeding episode with 2 injections or fewer was 98.9% (95% CI: 96.9% to 99.6%).

Across studies 2004 and 3001, Investigators assessed the efficacy of rIX-FP for the majority of bleeding episodes as excellent or good.

All bleeding episodes in both studies were classified as minor or moderate; none were classified as major (life-threatening) During Study 3001, there were 5 bleeds reported in 4 subjects. While not classified as major by the subject (all 5 bleeds were reported as minor bleeds), 4 / 5 bleeds required only 1 dose of rIX-FP to achieve hemostasis.

Table 42 Studies 2004 and 3001: Efficacy Assessments Relevant to Control and Prevention of Bleeding Episodes with rIX-FP (EfficacyPopulations)

	Study 2004 (N = 17)	Study 3001 (N = 63)	Studies 2004 + 3001 (N = 65)[a]
Bleeding episodes requiring treatment			
Number of bleeding episodes	85	358	443
1 injection, n (%)	76 (89.4)	335 (93.6)	412 (93.0)
2 injections, n (%)	9 (10.6)	18 (5.0)	26 (5.9)
> 2 injections, n (%)	0	5 (1.4)	5 (1.1)
Probability of success[b]	NA	98.6 (CI: 96.2 to 99.5)	98.9 (CI: 96.9 to 99.6)
Assessment of hemostatic efficacy			
Number of subjects	12	63	65
Number of bleeding episodes	85	358	443
Excellent, n (%)	53 (62.4)	297 (83.0)	350 (79.0)
Good, n (%)	29 (34.1)	40 (11.2)	69 (15.6)
Moderate, n (%)	3 (3.5)	9 (2.5)	12 (2.7)
Poor / no response, n (%)	0	1 (0.3)	1 (0.2)
Missing, n (%)	0	11 (3.1)	11 (2.5)

Abbreviations: CI, confidence interval; NA, not assessed; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin.

[a] The pooled efficacy data for studies 2004 and 3001 count subjects participating in both studies only once.

[b] Probability of success is derived from a repeated measures model (expressed as percentages) and is defined as the probability of achieving hemostasis with 1 or 2 injections.

Note: Confidence intervals computed at 95%.

In the paediatric Study 3002, 23/27 subjects experienced 106 bleeding episodes that were treated with rIX-FP; the majority of bleeding episodes (103/106; 97.2%) were successfully treated with 1 or 2 injections of rIX-FP. Investigators assessed the haemostatic efficacy of rIX-FP as excellent or good for the majority of bleeding episodes in Study 3002, regardless of bleeding severity. For the 2 major bleeding episodes reported in the study (both of which were traumatic and occurred at the hip), haemostatic efficacy of rIX-FP was assessed as good. In addition, 2 iliopsoas bleeds were reported in 2 subjects; each required 1 dose of rIX-FP to achieve hemostasis, only.

Table 43 Study 3002: Efficacy Assessments Relevant to Control and Prevention of Bleeding Episodes with rIX-FP (Efficacy Population)

	Age < 6 years (N = 12)	Age 6 to < 12 years (N = 15)	Total (N = 27)
Bleeding episodes requiring treatment			
Number of bleeding episodes	45	61	106
1 injection, n (%)	40 (88.9)	54 (88.5)	94 (88.7)
2 injections, n (%)	5 (11.1)	4 (6.6)	9 (8.5)
> 2 injections, n (%)	0	3 (4.9)	3 (2.8)
Probability of success[a]	NC	95.1 (CI: 86.7 to 98.3)	97.2 (CI: 92.0 to 99.0)
Assessment of hemostatic efficacy: minor / moderate bleeding episodes			
Number of bleeding episodes requiring treatment	43	61	104
Excellent, n (%)	36 (83.7)	42 (68.9)	78 (75.0)
Good, n (%)	6 (14.0)	16 (26.2)	22 (21.2)
Moderate, n (%)	0	1 (1.6)	1 (1.0)
Poor / no response, n (%)	0	0	0
Missing, n (%)	1 (2.3)	2 (3.3)	3 (2.9)
Assessment of hemostatic efficacy: major bleeding episodes			
Number of bleeding episodes requiring treatment	2	0	2
Excellent, n (%)	0	0	0
Good, n (%)	2 (100)	0	2 (100)
Moderate, n (%)	0	0	0
Poor / no response, n (%)	0	0	0
Missing, n (%)	0	0	0

Abbreviations: CI, confidence interval; NC, not calculated; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin.

[a] Probability of success is derived from a repeated measures model (expressed as percentages) and is defined as the probability of achieving hemostasis with 1 or 2 injections.

Perioperative management of bleeding: There were 15 surgeries in the rIX-FP clinical development program, including 12 surgeries in adolescents and adults (studies 3001 and 3003) and 3 surgeries in children < 12 years of age (studies 3002 and 3003).

Table 44 Perioperative Consumption of rIX-FP

Surgical Procedures	[redacted]	Total Number of Injections[a]	Consumption of rIX-FP (IU/kg) During Surgery						
			Pre-surgery	Intra-operative	≤ 72 h Post-surgery	≤ 168 h Post-surgery	> 168 h Post-surgery to ≤ 336 h Post-surgery	≤ 336 h Post-surgery	Total Dose (IU/kg)
Double mastectomy		3	80.85	0	0	47.74	50.23	97.96	178.81
Total knee replacement		7[b]	127.66	0	38.30	109.78	142.97	252.75	380.41
Total knee replacement		7	45.95	0	51.06	142.97	150.64	293.61	339.57
Hemorrhoidectomy		2	139.87	0	0	40.88	0	40.88	180.75
Wisdom tooth (1)[c] extraction		4	75.00	0	0	51.90	126.90	178.79	253.79
Tooth (1) extraction		2	64.89	0	0	0	41.32	41.32	106.21
Teeth (2) extraction		2	40.34	0	0	0	40.34	40.34	80.69
Teeth (4) extraction due to abscess		4	49.80	0	48.98	80.95	48.98	129.93	179.73
Excision of pigmental nevus		3	82.29	0	55.10	110.21	0	110.21	192.50
Rhinoplasty and submucosal resection inferior turbenectomy		4	73.89	0	0	56.30	147.54	203.84	277.72
Right ankle arthroplasty		6	87.20	0	106.25	146.04	106.25	252.29	339.49
Endoscopic mucosal resection		4	70.38	0	77.87	130.08	52.22	182.30	252.68
Total knee replacement		6	105.51	0	53.95	161.85	107.90	269.75	375.25
Total knee replacement		7	80.59	0	26.86	80.59	134.32	214.92	295.51
Root canal		3	53.32	0	53.32	53.32	53.32	106.63	159.95

Abbreviations: rIX FP, recombinant fusion protein linking coagulation factor IX with albumin.
[a] The total number of injections is calculated from injections administered pre-surgery and up to 14 days (336 hours) post-surgery.
[b] Includes 4 doses that were administered for the second knee replacement, which were administered within 14 days after the start of the first knee replacement.
[c] Numbers in parenthesis are number of teeth extracted.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

An extensive clinical investigation programme has been provided. Concept and patient numbers meet the requirements of the Clinical Guideline. Target population of the studies is in accordance with the target population of the MAA. Treatment options (on-demand treatment, prophylaxis, perioperative prophylaxis) meet the intended indication taking into account the assumed extended half-life. Inclusion and exclusion criteria for the efficacy-studies follow currently applied standards.

Annualized (spontaneous) bleeding rates have been introduced as an efficacy parameter which is regarded to be challenging and not reflected in the Clinical Guideline for the following reasons: Such rate might serve as a parameter for efficacy of prophylaxis as it is “countable” and represents an easy-to-understand number. However, lack of definitions for a “bleed”, for “spontaneous” or “traumatic” nature of such bleed and individual evaluation factors are considered to be challenging when comparing numbers. Furthermore, comparison of ABR while on on-demand versus on prophylaxis-regimen is considered to be of highly restricted value: On-demand therapy mainly represents severity of haemophilia (overall bleeding frequency) and not efficacy of a certain product. Furthermore, bleeding episodes might not require treatment (as documented for study 3002) – these are not reflected in the ABR.

The study design of the efficacy-part of study 2004 is based upon PK-evaluation and two parallel arms for on-demand or prophylaxis treatment and meets guideline requirements in terms of treatment interval; the requested number of Exposure Days, patient population and objectives / efficacy endpoints. Suggested treatments comply with the results of the PK-assessment and are considered to reflect the assumed extended half-life of the product. Chosen dosages (prophylaxis: 15-35 IU/kg, on-

demand: not less than 35 IU/kg) follow the current standard treatment (*Core-SmPC: 20-40 IU/kg at intervals of 3 to 4 days*) and adaptation to higher (75 IU/kg) dosages is considered to be acceptable. Demographic data reflect an expected patient population. Number of Exposure days is above 40 (instead of 50) EDs which is considered to be acceptable in the light of the extended treatment interval. BMI as a confounding factor for Recovery is considered to be in a wide-range; treatment of overweight patient is part of the Core SmPC.

The study design of the efficacy-part of study 3001 is based upon PK-evaluation and two parallel arms for on-demand or prophylaxis treatment. Subjects from study 2004 as well as additional subjects were included, repeat PK was done for a subgroup, and prophylaxis-intervals of 7, 10 and 14 days were studied. Duration of prophylaxis-period as suggested by the guideline is covered by the design. As patient population for Haemophilia B overall is limited, such design is acceptable. However, low patient numbers for each sub-population is considered to be challenging. Assignment of subjects to the prophylaxis or on-demand arm according to their previous regimen is a potential cause of bias. Furthermore, criteria for changing prophylaxis treatment regimen, i.e. extending the treatment interval from 7 to 10 or 14 days, apply to subjects with lower bleeding risk.

Initial dosage suggestion for prophylaxis was 35-50 IU/kg once weekly and could be adapted according to clinical experience and factor IX trough levels. The efficacy endpoints regarding individual haemostasis-response for on-demand bleeds, efficacy response for surgical procedures including blood-loss and transfusions, and respective consumption follow the suggestions of the Clinical Guideline. For evaluation of efficacy under prophylaxis, ABR (AsBR) and comparison with the on-demand period has been introduced; the associated challenges with this approach apply accordingly. Demographic data reflect an expected patient population. Body weight and BMI range are considered to be wide. However, no relevant differences between the treatment arms are overt.
The study design of the efficacy-part of paediatric study 3002 is based upon PK-evaluation, individual historical data and clinical experience. All subjects received prophylaxis and on-demand-treatment was offered for bleeding episodes under prophylaxis. Non-emergency surgery was admitted and respective guidance for treatment was proposed. Initial dosage suggestion for prophylaxis was 35-50 IU/kg once weekly and could be adapted stepwise according to clinical effect, breakthrough-bleeds and factor IX trough levels. This dose-finding approach is considered to meet clinical needs. Dosage-recommendation regarding on-demand and perioperative treatment in the study protocol corresponds with the suggestions of the Core-SmPC and has been adapted to the extended half-life which is considered to be adequate. Overall consumption for surgery according to the Guideline has been provided.

Similar to study 3001, the efficacy endpoints regarding individual haemostasis-response for on-demand bleeds, and consumption of FIX were reflected in the secondary efficacy endpoints and follow the Clinical Guideline. Efficacy response for surgical procedures including blood-loss and transfusions, and respective consumption were not part of the study-endpoints, but were recorded, accordingly. For evaluation of efficacy under prophylaxis, ABR (AsBR) and comparison with the on-demand period of previous therapy has been presented. Enrolment of two different age-groups in the paediatric population is reflected by the Clinical Guideline and is considered to be acceptable. Number of subjects meets the suggestions of the Clinical Guideline. Demographic data reflect an expected patient population. Consumption of Previous therapy corresponds with posology of plasma-derived and recombinant FIX-products.

The design of study 3003 aims at supporting treatment intervals of 7 days up to 21 days with increasing doses and at documentation of surgeries. Follow-up of 3 years to achieve 100 Exposure days; efficacy response assessment and documentation of at least 10 surgeries in at least 5 individuals

is in accordance with the requirements of the Clinical Guideline. Blood-loss and transfusions, and respective consumption were not part of the study-endpoints, but were recorded, accordingly which is considered to be acceptable.

Demographic specifications reflect target population (adult/paediatric) and geographic location of the respective studies. For other parameters (height, weight, BMI) distribution with the exception of paediatric subjects is similar. The age-group above 65 years has not been covered although relevant in the light of increasing age of the target population, however, it is not a guideline requirement.

Subjects from studies 3001, 3002, and 3003 who were undergoing *surgery* contributed to the overall evaluation. Efficacy and safety data during and after surgery were recorded, including dosage of rIX-FP, Investigator's assessments of overall efficacy on a 4-point scale, predicted and estimated actual blood loss, predicted and actual transfusion requirements, haematology, concomitant medications, and AEs. There were 15 surgeries in the rIX-FP clinical development program, including 12 surgeries in adolescents and adults (studies 3001 and 3003) and 3 surgeries in children < 12 years of age (studies 3002 and 3003).

Efficacy data and additional analyses

Study 2004: ABR was recorded for on-demand treatment and prophylaxis. A median of 2.3 bleeds in the prophylaxis-group is considered to be acceptable, although a maximum of 14 bleeds seems to be high. ABR in the on-demand treatment group was with a median of 27 and a range of 24-30 bleeds in the assumed area of severe haemophilia.

Median weekly consumption under prophylaxis-regimen was 53,8 IU/kg (range 47.7-75) compared with 73.2 IU/kg (range 21-154). Corresponding numbers are 2800 and 3806 IU/kg per year.

The investigator's assessment of haemostatic efficacy of rIX-FP, was either excellent or good for the majority of bleeding episodes (excellent: 53/85 = 62.4%; good: 29/85 = 34.1%); haemostatic efficacy was assessed as moderate for the other 3 bleeding episodes (3.5%).Presented results are considered to be acceptable.

For this newly developed extended half-life product, link between PK-results, PK-simulations and efficacy results is considered to be crucial as it represents the link between "surrogate" PK-calculations, simulated protective trough levels and clinical efficacy. According to the CSR of study 2004, mean of initial dosage (about 34 IU/kg/week) in the prophylaxis group has been increased to 62 IU/kg/week. This adaptation does not meet the results of the PK-simulations derived from PK-results but reflects higher doses. Similarly, increase of dosage for bleeding episodes under prophylaxis is remarkable: Mean initial dose was 33 IU/kg, at the end of the treatment period it was 57 IU/kg. No dosage-increase was documented in the on-demand treatment-group. Relevant dosage increase under prophylaxis and the gap between PK-results required discussion and adaptations of the SmPC

In study 3001 for the once-weekly regimen, median ABR was 0 (range 0-6), for the 10-days regimen 0 (range 0-3.0) and the 14 days regimen 1.08 (range 0-9.1). Although the numbers are considered to be adequate, maximum of 9 bleeds in the 14-days-regimen and maximum of 21 in the on-demand-arm after switching to weekly prophylaxis, which is considered to be unexpectedly high. Median monthly consumption under prophylaxis-regimen (194, range 139-321 IU/kg) shows reduction when comparing once-weekly with previous prophylaxis (256, range 65-978 IU/kg). Further reduction of consumption can be demonstrated with the 14-days regimen (162, range 112-238).

A subgroup of patients switched to extended treatment intervals (every 10 or 14 days) with a recommended dose of 75 IU/kg and individual adjustments. 21 PTPs remained on the extended 14 day prophylaxis interval for additional treatment duration of 98 to 575 (median 386) days. From those

subjects, 8 (38%) experienced at least one bleeding during the 14 day-prophylaxis, while they had no bleeding events during once weekly prophylaxis. These results provide adequate basis for the posology recommendations in the SmPC section 4.2. as follows: For long-term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are 35 to 50 IU/kg once weekly. Some patients who are well-controlled on a once-weekly regimen might be treated with up to 75 IU/kg on an interval of 10 or 14 days (see sections 4.2 and 5.1 of the SmPC).

The investigator's assessment of haemostatic efficacy of rIX-FP, was either excellent or good for the majority of bleeding episodes (excellent: 297/358 = 83%; good: 40/358 = 34.1%); haemostatic efficacy was assessed as moderate for 9 bleeding episodes (2.5%). Presented results are considered to be acceptable.

Perioperative haemostatic efficacy was rated as excellent or good for all 6 surgical procedures. Consumption for each surgery shows wide range of 106 to 380 IU/kg in accordance with the underlying procedure. Details regarding total consumption specifically for the 3 major orthopaedic surgeries have been provided, in addition

In study 3002 median total ABR was 2.64 (range 0-10) for the age <6 years and 3.39 (range 0-9.5) for the age 6 to <12 years. Such numbers are considered to be acceptable although maximum rates of 10 do not meet an "ideal" ABR of 2 to zero. Furthermore, 20 bleeding episodes did not require treatment and were therefore not counted for the ABR. 6 Events were spontaneous, 11 traumatic and 3 unknown. Prevention of bleeds into previous target joints has been documented for 2 of 3 respective subjects. In overall, efficacy of rIX-FP in prophylaxis in children is demonstrated.

Dosage of the once-weekly prophylaxis regimen has been proposed to be 35-50 IU/kg with an adaptation approach similar to study 3001. Median weekly prophylaxis dose was 49 IU/kg for subjects <6 years with a minimum of 29 and a maximum of 69 IU/kg. For 6 to 12 year old children median dose was 43 IU/kg with a minimum of 31 and a maximum of 61 IU/kg.

Investigator's analysis of consumption shows about 2500 IU/kg/year for both age-groups. Relevant reduction compared with previous therapy (4472 IU/kg) has been documented. Investigator's assessment of haemostatic efficacy in 106 bleeds was "excellent" or "good" in the majority (96%) of bleeding episodes which is considered be acceptable. However, for 20 bleeds no FIX-substitution was required, at all.

Two surgical interventions (Tooth extractions) have been documented. Although these are considered to represent a narrow data-base, haemostatic efficacy has been demonstrated. The Clinical Guideline does not request documentation of surgical procedures in children.

Results of surgery substudy of study 3003 are considered to be preliminary, detailed assessment of efficacy is expected for the final study report however, based upon the available data, haemostatic efficacy of FIX-FP to prevent haemorrhage in and post-surgery, is not doubted.

Trough levels of 5-10% have been targeted in clinical trials for achieving bleeding control while on prophylaxis. PK simulations suggest the time to reach 5% plasma FIX activity following a single injection of 50 IU/kg Idelvion to be 7 days for 1-<6years, 9 days for 6-<12 years and 11 days for 12-<18 years of age).

Analysis across all studies showed that Control of bleeding episodes in paediatric and adult subjects is considered to be adequate. Efficacy assessment in terms of ABR regarding prophylaxis in adults was provided for studies 2004 and 3001. Median results for on-demand and prophylaxis differ between both studies (on-demand: 27 vs 19 bleed per year/subject; prophylaxis: 2.3 vs 0.6; study 2004 vs study 3001). As the dosage has been substantially increased, the results are considered to be

plausible. Efficacy of bleeding control during and after surgical procedures has been documented for rIX-FP. Surgery-related consumption, specifically for the major orthopaedic surgeries has been provided according to the Clinical Guideline.

2.5.4. Conclusions on the clinical efficacy

Clinical efficacy of rIX-FP in terms of successful once-weekly prophylaxis in adults and children, successful treatment of breakthrough bleeds and bleeding episodes in the on-demand setting and perioperative prophylaxis, has been documented.

It is recommended (SmPC section 4.2) that for long-term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are 35 to 50 IU/kg once weekly. Some patients who are well-controlled on a once-weekly regimen might be treated with up to 75 IU/kg on an interval of 10 or 14 days. Results from the clinical trials and available information have been included in section 5.1.

The CHMP considers the following measures necessary to address issues related to efficacy:

Results from the surgery substudy of ongoing clinical trial 3003 evaluating the efficacy of rIX-FP in the prevention and control of bleeding in subjects with severe haemophilia B during surgical procedures will be provided. This study is also expected to provide information with the use of the product in previously untreated patients.

2.6. Clinical safety

Patient exposure

Table 45

Table 1–3 Demographic Characteristics of Subjects in rIX-FP Clinical Studies (Safety Populations) and in the Overall Safety Population

	Study 2001 (N = 25)	Study 2004 (N = 17)	Study 3001 (N = 63)	Study 3002 (N = 27)	Overall Safety Population[a] (N = 107)	Study 3003[b] (N = 80)
Age (years)						
Mean (SD)	35.0 (11.69)	26.1 (10.7)	33.0 (13.91)	5.9 (2.93)	25.7 (16.39)	27.5 (17.96)
Median (min, max)	31.0 (15, 58)	25.0 (13, 46)	30.0 (12, 61)	6.0 (1, 10)	25.0 (1, 61)	27.0 (2, 63)
Age group, n (%)						
< 6 years	0	0	0	12 (44.4)	12 (11.2)	7 (8.8)
≥ 6 to < 12 years	0	0	0	15 (55.6)	15 (14.0)	17 (21.3)
< 12 years	0	0	0	27 (100)	27 (25.2)	7 (8.8)
≥ 12 to ≤ 65 years	25 (100)	17 (100)	63 (100)	0	80 (74.8)	56 (70.0)
≥ 12 to < 18 years	1 (4.0)	3 (17.6)	7 (11.1)	0	9 (8.4)	NC
≥ 18 to ≤ 65 years	24 (96.0)	14 (82.4)	56 (88.9)	0	71 (66.4)	NC

a The Overall Safety population includes subjects from studies 2001, 2004, 3001, and 3002.

b Demographics are presented for 80 subjects in Study 3003 as of the 09 January 2015 cut-off date.

Source: Study 2001 CSR Section 11.2 and Table 14.1.2.1; Study 2004 CSR Section 11.2 and Table 14.1.2.1; Study 3001 CSR Section 11.2 and Table 14.1.3.1; Study 3002 CSR Table 14.1.3.1 and Listing 16.2.4.2; Study 3003 Abbreviated CSR Table 14.1.2 and Listing 16.2.4.2; Pooled Safety Table 14.1.2.1 and 14.3.7.1.

The 107 subjects of the Overall Safety population are ranging in age from 1 to 61 years.

Exposure (in EDs) to rIX-FP is shown in table 46 and – for the subgroup of paediatric patients <12 years of age – additionally in table 47 below.

Table 46

Table 1–2 Exposure to rIX-FP in Clinical Studies (Safety Populations) and in the Overall Safety Population

	Study 2004 (N = 17)	Study 3001 (N = 63)	Study 3002 (N = 27)	Overall Safety Population[a] (N = 107)	Study 3003[b] (N = 80)
Exposure days (EDs)[c]					
Mean (SD)	42.5 (17.28)	64.8 (27.27)	61.9 (12.63)	60.5 (38.64)	22.3 (9.53)
Median (min, max)	50.0 (12, 59)	71.0 (4, 103)	58.0 (42, 94)	63.0 (1, 158)	21.0 (1, 48)
< 50 EDs, n (%)		14 (22.2)	2 (7.4)	32 (29.9)	80 (100.0)
≥ 50 EDs, n (%)	9 (52.9)	49 (77.8)	25 (92.6)	75 (70.1)	0
≥ 75 EDs, n (%)	0	24 (38.1)	0	33 (30.8)	0
≥ 100 EDs, n (%)	0	2 (3.2)	0	16 (15.0)	0
Total number of EDs	722	4080	1672	6471	NC
Study duration (days)					
Mean (SD)	283.1 (81.45)	550.6 (193.96)	397.4 (77.36)	483.4 (291.93)	206.5 (73.11)
Median (min, max)	326.0 (119, 340)	617.0 (42, 844)	382.0 (287, 554)	469.0 (25, 986)	195.5 (44, 338)
Study duration (months)					
Mean (SD)	NC	18.1 (6.37)	13.1 (2.54)	15.9 (9.59)	6.8 (2.40)
Median (min, max)	NC	20.3 (1.4, 27.7)	12.6 (9, 18)	15.4 (0.8, 32.4)	6.4 (1.4, 11.1)
Total subject-years[d]	NC	NC	NC	141.6	NC
Number of injections					
Mean (SD)	NC	NC	61.0 (12.58)	60.6 (38.67)	NC
Median (min, max)	NC	NC	57.0 (41, 93)	63.0 (1, 158)	NC
Total IU administered					
Mean (SD)	NC	247884 (136653.5)	79971 (42796.5)	190257 (185557.3)	82884 (48743.9)
Median (min, max)	NC	253688 (9758.9, 662353.0)	66942 (22332.0, 198491.8)	126810 (1900.0, 999051.4)	86186 (7580.0, 256195.0)
Total IU / injection					
Mean (SD)	NC	NC	1290.6 (580.0)	3146.0 (1653.7)	NC
Median (min, max)	NC	NC	1064.0 (250.0, 3190.0)	3000.0 (138.9, 10570.0)	NC

Abbreviations: ED, exposure day; max, maximum; min, minimum; NC, not calculated; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; SD, standard deviation.

[a] The Overall Safety population includes subjects from studies 2001, 2004, 3001, and 3002. Note: exposure data from Study 2001 are not included as a separate column because the study was a dose-escalation study in which subjects received only 1 (n = 18) or 2 (n = 7) doses of rIX-FP.

[b] Exposure as of the 09 January 2015 cut-off date.

[c] An exposure day is any day that the subject receives an injection of rIX-FP regardless of the number of injections on that day or the number of injections.

[d] Subject-years = (last visit day on study – first injection day) / 365.25.

Source: Study 2004 CSR Section 12.1; Module 2.7.4 Appendix 1, Tables 2 and 3; Study 3001 CSR Section 12.1 and Table 14.1.4; Module 2.7.4 Appendix 1, Table 1; Study 3002, CSR Section 12.1 and Table 14.1.4, Study 3003 Abbreviated CSR Table 14.1.3; Pooled Safety Table 14.2.1 and Table 14.2.2.

Table 12-1 Exposure (Safety Population)

	Age <6 years (N=12)	Age 6 to <12 years (N=15)	Total (N=27)
Time on study (days)			
n	12	15	27
Mean (SD)	347.1 (39.75)	437.6 (77.28)	397.4 (77.36)
Median	356.0	456.0	382.0
Q1, Q3	313.0, 373.5	361.0, 492.0	330.0, 469.0
Min, Max	287, 416	323, 554	287, 554
Time on study (months)			
n	12	15	27
Mean (SD)	11.4 (1.31)	14.4 (2.54)	13.1 (2.54)
Median	11.7	15.0	12.6
Q1, Q3	10.3, 12.3	11.9, 16.2	10.8, 15.4
Min, Max	9, 14	11, 18	9, 18
EDs			
n	12	15	27
Mean (SD)	55.3 (8.88)	67.3 (12.87)	61.9 (12.63)
Median	54.5	67.0	58.0
Q1, Q3	50.0, 57.0	57.0, 72.0	52.0, 69.0
Min, Max	42, 78	51, 94	42, 94
<50 EDs, n (%)	2 (16.7)	0	2 (7.4)
≥50 EDs, n (%)	10 (83.3)	15 (100.0)	25 (92.6)
Total EDs within study	663	1009	1672

Abbreviations: ED = exposure day(s); Max = maximum; Min = minimum; Q = quartile; SD = standard deviation.

Note: Where indicated, table presents number and percentage of subjects (n [%]).

Source: Table 14.1.4.

Time on rIX-FP categorized by age for pooled studies 2001, 2004, 3001 and 3002 is presented as follows:

CSL Behring
CSL654 (rIX-FP)
Response to EMA Day 120 LoQ - Clinical

Study ISS: Table 14.7.1 Time on rIX-FP (Safety Population)

	Age		
Time on rIX-FP	< 12 years (N=27) n (%)	>=12 years (N=80) n (%)	Overall (N=107) n (%)
<= 6 months	0	20 (25.0)	20 (18.7)
> 6 months to <= 12 months	13 (48.1)	9 (11.3)	22 (20.6)
> 12 months to <= 18 months	13 (48.1)	10 (12.5)	23 (21.5)
> 18 months to <= 24 months	1 (3.7)	20 (25.0)	21 (19.6)
> 24 months to <= 30 months	0	10 (12.5)	10 (9.3)
> 30 months to <= 36 months	0	11 (13.8)	11 (10.3)

Adverse events

Of the 107 subjects in the Overall Safety population, 94 subjects (87.9%) reported at least 1 TEAE for a total of 579 AEs.

Eight subjects (7.5%) reported AEs that were considered by the Investigator to be related to treatment:

- In Study 2001, three subjects (12.0%) experienced 4 AEs that were considered by the Investigator to be possibly related to treatment with rIX-FP:
  - 1 subject (25 IU/kg rIX-FP): constipation;
  - 1 subject (50 IU/kg rIX-FP): mild headache and feeling hot;
  - 1 subject (75 IU/kg rIX-FP): injection site erythema.

  All events resolved within 1 day.
- In Study 3001, five subjects experienced 11 AEs that were considered by the Investigator to be related to rIX-FP:
  - rash (5 events),
  - headache (2 events),
  - eczema,
  - dizziness,
  - injection site haematoma, and
  - hypersensitivity.

  In 2 of these subjects, the AEs (headache and hypersensitivity) led to discontinuation of study treatment.

A multidisciplinary sponsor team reviewed all treatment-emergent AEs and categorised the PTs presented in the following table, which is also depicted in section 4.8 of the proposed SmPC.

MedDRA Standard System Organ Class	Adverse reactions	Frequency per patient
Nervous system disorders	Headache	Common
	Dizziness	Uncommon
Immune system disorders	Hypersensitivity	Uncommon
Skin and subcutaneous tissue disorders	Rash	Uncommon
	Eczema	Uncommon

Serious adverse event / deaths / other significant events

A total of 8 treatment-emergent SAEs were reported for 6 subjects (5.6%) in the Overall Safety population (which included subjects in studies 2001, 2004, 3001, and 3002). None of the SAEs were considered by the Investigator to be related to administration of rIX-FP.

There were no deaths.

Laboratory findings

Haematology

In Study 2001, 1 subject had a clinically significant decrease (as rated by the Investigator) in erythrocyte mean corpuscular volume (MCV) which was not accompanied by any AEs.

In Study 3002, treatment-emergent abnormal haematology values were observed in a total of 17 subjects, and were assessed as clinically significant in 4 subjects as follows: 1 subject with high leukocytes, low haematocrit, low haemoglobin, low MCV, and low erythrocytes; 1 subject with low MCV; 1 subject with low erythrocytes, low haematocrit, and low haemoglobin; and 1 subject with low erythrocytes. Of these 4 subjects, 3 reported mild AEs of anaemia, none of which was considered by the Investigator to be related to the administration of rIX-FP.

In Study 3001 and Study 3003, abnormal haematology values were observed in subjects undergoing surgery (4 subjects in Study 3001 and 1 subject in Study 3003). For 2 subjects (one in Study 3001 and 3003 each), AEs of anaemia was reported, but not considered related to FIX-FP.

Biochemistry

In Study 3002, treatment-emergent abnormal ALT (5 patients) and AST (4 patients), were observed in 7 subjects. In the other studies abnormal ALT and AST values were mostly accompanied by liver diseases and abnormal values were observed already at screening.

Markers for Coagulation Activation

Markers of activation of coagulation, including prothrombin fragment 1+2, thrombin-antithrombin (TAT) and D-dimer, were measured before and after injection of rIX-FP in studies 2001 and 3001. These markers were not measured in studies 2004, 3002 or 3003.

In Study 2001, 1 subject had a mild and transient increase in 2 of the 3 markers for activation of coagulation (TAT and D-dimer) after administration of rIX-FP that were assessed by the Investigator as clinically significant. However, there was no clinical evidence of thrombosis.

In Study 3001, none of the markers for activation of coagulation were outside the normal range.

Safety in special populations

Analyses of treatment-emergent AEs and local tolerability data were performed for the following subgroups in the Overall Safety population:

- Age: 0 to <12 (n = 27) and ≥12 to ≤65 years (n = 80)
- BMI: <30 kg/m2 (n = 100) and ≥30 kg/m2 (n = 6)
- Race: white (n = 94), black (n = 2), Asian (n = 10), and other (n = 1).

The analyses were not indicative of a specific pattern in these special populations.

There were no patients above 65 years of age.

Adverse events in subjects undergoing surgical procedures

As of the 09 January 2015 data cut-off, a total of 13 subjects have undergone 1 or more surgical procedures while receiving rIX-FP prophylaxis treatment. Of these subjects, 8 experienced AEs during the perioperative period (2 AEs Anaemia, 2 AEs Pyrexia, 2 AEs Procedural pain, 2 AEs Blister and 1 AE Postoperative wound infection, Abdominal distension, Gastrointestinal injury, Urinary tract infection, Dental caries, Otitis externa each). No AEs were considered to be related to administration of rIX-FP.

Immunological events

Inhibitor formation

No inhibitors against FIX were reported in studies 2001, 2004, 3001, or 3002. As of the 09 January 2015 data cut-off, no inhibitors against FIX were reported in Study 3003.

Antibodies to rIX-FP

In Study 2004, 1 subject tested positive for antibodies against BeneFIX, pdFIX, and rIX-FP before the first injection of rIX-FP (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.

No treatment-emergent antibodies to rIX-FP were reported in the Overall Safety population. As of the 09 January 2015 data cut-off, no treatment-emergent antibodies against rIX-FP were reported in Study 3003 either.

In studies 3001, 3002, and 3003, testing for inhibitors to CHO host cell protein was also performed, and as of the data cut-off date no subjects tested positive.

Hypersensitivity reactions

In the Overall Safety population, there was 1 TEAE 'Hypersensitivity', which was considered being related to rIX-FP treatment. Other hypersensitivity reactions related to study treatment were 'Rash' and 'Eczema'. All these AEs were included as ADRs in section 4.8 of the SmPC (please also see section 'Adverse events' above).

Adverse events of special interest

Besides of immunological events, no further AEs of special interest like in particular thromboembolic events or nephrotic syndrome could be identified.

However, as already mentioned above in subsection 'Laboratory findings', 1 subject had an increase in markers for activation of coagulation (F1+2, TAT and D-dimer). For this 54-year-old subject , no

clinical signs of thrombosis were reported. D-dimer indeed is to be regarded a non-specific marker. Together with the increase of F1+2 and TAT, though, at least laboratory results are indicative of an altered coagulation status in this patient. But as correlating clinical findings could not be observed and increase of the laboratory markers was only transient, definite conclusions cannot be drawn. Thromboembolic events (TEE) are addressed as a potential risk of rIX-FP in the RMP, so that at this stage, no further actions are needed.

Safety related to drug-drug interactions and other interactions

The metabolism of rIX-FP results in smaller peptide fragments and amino acids, and it is unlikely that rIX-FP has the potential to be involved in any metabolism-based drug-drug interactions. Because rIX-FP is administered as an IV injection, there is no potential for an interaction with food.

Discontinuation due to adverse events

Two subjects (1.9%), both from Study 3001, discontinued from study because of AEs. 1 subject experienced a hypersensitivity reaction that is further discussed above in subsection 'Immunological events'. 1 subject experienced a headache, which was considered by the Investigator to be related to rIX-FP; from this case, however, no concern arises.

As of the data cut-off date of 09 January 2015, 1 subject was withdrawn from Study 3003 because of a TEAE (elevated GGT) that was ongoing from Study 3001. The event was initially assessed as related to treatment, but in the end more likely considered attributable to an underlying alcoholic liver disease.

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

Safety data are presented for an overall safety population of 107 previously treated subjects with haemophilia B (factor IX ≤ 2%) out of the completed clinical studies 2001, 2004, 3001, and 3002 and the ongoing study (3003). Patient exposure is in compliance with requirements of the current EMA factor IX guidance with respect to rIX-FP exposure days (EDs) and long-term exposure ≥6 months. The size of the available safety database, 107 subjects of whom 27 are PTPs <12 years (Overall Safety Population) and 80 subjects with 24 < 12 years (ongoing Study 3003), exceeds guideline requirements.

All studies assessed safety of rIX-FP, with particular emphasis on immunogenicity and development of rIX-FP antibodies. To date, there have been no reports of virus transmission, thromboembolism or inhibitor-development related to rIX-FP.

The 107 treated subjects in the Overall Safety Population received a total of 190.257.46 IU of rIX-FP in 6480 infusions. The total number of EDs was 6471, mean EDs were 60.5. Of these, 75 patients (70.1%) had EDs ≥ 50 days, 33 patients (30.8%) ≥ 75 days and 16 patients (15%) ≥ 100 days, which is, according to Guideline requirements considered sufficient.

Of these 107 subjects, 94 subjects (87.9%) reported at least 1 TEAE for a total of 579 AEs. Of these AEs, 483, 88, and 8 were mild, moderate, and severe, respectively. Eight subjects (7.5%) reported 15 AEs (headache, dizziness, feeling hot, injection site erythema, injection site haematoma, rash, eczema, constipation and hypersensitivity), that were considered by the Investigator to be related to treatment. The treatment-related hypersensitivity reaction in 1 subject was, based on a review by the

Independent Data Monitoring Committee (IDMC), assessed as an injection reaction rather than a hypersensitivity reaction. One subject chose to withdraw after occurrence of 5 AEs of rash ("exanthem"). Therefore no specific concerns are noted.

In the supportive study 3003 with data cut-off on 09 January 2015, 29 patients (36.3%) reported a total of 74 TEAEs. All were mild or moderate in severity and not treatment-related.

No difference in the occurrence of AEs between 25 IU/kg, 50 IU/kg and 75 IU/kg were observed and in the main, type and frequency of AEs were similar between subjects 0 to < 12 years of age and subjects ≥ 12 to 65 years of age. Differences in the frequency of certain AEs are expected for the general population of that age group.

The incidence of SAEs (8 in the Overall Safety Population and 2 in Supportive Study 3003) is considered low. All SAEs were not related to the administration of rIX-FP and no death occurred in any of the studies. Local tolerability was good throughout all studies.

Changes in clinical laboratory parameters during studies 2001, 2004, 3001 and 3003 were generally minor and not considered to be clinically significant. Concerning study 3002 in paediatric patients, treatment-emergent abnormal ALT (5 patients) and AST (4 patients) values were observed in 7 subjects. In the other studies abnormal ALT and AST values were mostly accompanied by liver diseases and abnormal values were observed already at screening. The seemingly higher frequency of these treatment emergent abnormalities in study 3002 in comparison to the other studies was not considered to be clinically relevant.

No inhibitors against FIX and no treatment-emergent antibodies to rIX-FP were reported in the Overall Safety population and in Study 3003 at time of data cut-off. Furthermore, no inhibitors to CHO host cell protein in studies 3001, 3002 and 3003 were detected.

Breaking the immunotolerance against serumalbumin is a quite unlikely event due to its abundant presence in serum. Nevertheless, in case antibodies directed against the serumalbumin part of rIX-FP are generated, those may be missed due to the abundant presence of HSA in the plasma samples, potentially cross-reacting with the humoral immune response. Nevertheless no specific concerns have been seen so far, this uncertainty remains to be further reviewed in the post authorisation setting (See RMP).

Besides other process related impurities (like HCPs) also the serine protease Furin is co-expressed with rIX-FP in cell line to ensure efficient cleavage of propeptide to mature rIX-FP and around 1.0-4.4 ppm measured at the Drug Substance level. A discussion on the potential development of Furin antibodies in patients and its clinical impact revealed no concerns.

According to the Guideline on Summary of Product Characteristics (September 2009) section 4.8 of the SmPC *should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility.* Therefore, related AEs "eczema" and "constipation" should also be included in the SmPC section 4.8. Moreover, according to MedDRA, the adverse reactions "infusion site reactions" are listed

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics (see section 4.8.)

Participation in EUHASS registry will enable collection of long-term safety data.
The ongoing extension Safety and Efficacy Extension Study 3003 will aim to evaluate the safety of rIX-FP as measured by new cases of inhibitors against factor IX in Subjects with Haemophilia B, including

PUPs – AEs of special interest include: Hypersensitivity/anaphylactic reactions, TEEs, and development of inhibitors to factor IX. (See RMP).

2.6.2. Conclusions on the clinical safety

From the data as presented by the applicant, no substantial safety concern arises. No serious adverse events could be observed and no inhibitory antibody to rFIX-FP could be detected. Hypersensitivity reactions to rIX-FP, by contrast, occurred during clinical development, but neither frequency nor severity was different from what would be expected for a FIX product. rIX-FP prophylactic doses proposed in the SmPC (up to 75 IU/kg) exceed current factor IX core SmPC recommendations. Dose-related safety data has been provided by the applicant in order to enable re-evaluation of the SmPC posology and/or the possible need for further (post-marketing) measures.

In conclusion, the size of the safety database available at the moment exceeds guideline requirements, and the nature and frequency of the reported adverse events do not give rise to concern and do not reveal unexpected safety signals. rIX-FP was well tolerated in all age groups and safety results are consistent between all submitted clinical trials. Therefore the safety database is considered to be sufficient to support a MA.

The CHMP considers the following measures necessary to address issues related to safety:

- Long-term safety data from patients' participation in EUHASS registry will be provided as part of PSUR reporting.
- Regular reports from the ongoing extension Safety and Efficacy Extension Study 3003 evaluating the safety of rIX-FP focusing on the development of inhibitors against factor IX in Subjects with Haemophilia B, including PUPs – will be provided as part of the PSURs (see RMP).

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and/or CHMP.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	- Hypersensitivity / anaphylactic reactions - Development of inhibitors to factor IX
Important potential risks	- Thromboembolic events (TEE) - Development of antibodies against chinese hamster ovary (CHO) host cell proteins - Dosing errors based on variability in the assays used during treatment monitoring of factor IX levels
Missing information	- Experience in patients with severe renal or hepatic impairment - Efficacy and safety in PUPs - Experience in pregnancy and lactation, including labour and delivery - Experience in elderly patients (aged 65 years and above) - Experience in patients for ITI (off-label use)

Pharmacovigilance plan

Study / activity Category (1-4)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim reports**
CSL654_3003 Clinical study A Phase 3b open-label, multicentre, Safety and Efficacy Extension Study of a Recombinant Coagulation factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Haemophilia B, including PUPs. (Category 3)	Main study: Evaluate the safety of rIX-FP as measured by new cases of inhibitors against factor IX. Surgery substudy: Evaluate the efficacy of rIX-FP in the prevention and control of bleeding in subjects with severe hemophilia B during surgical procedures.	AEs of special interest include: Hypersensitivity/anaphylactic reactions, TEEs, and development of inhibitors to factor IX. Evaluation of AEs, biochemistry, haematology, factor IX inhibitors, antibodies to rIX-FP, antibodies to CHO host cell proteins, local tolerability, physical examination, and vital signs.	Ongoing	Interim updates will be provided to competent authorities with each PSUR and a progress study report will be submitted within 2 years after market authorization.
Participation in EUHASS to collect long-term safety data. (Category 3)	To review the available post-marketing data for safety concerns.	Hypersensitivity/anaphylactic reactions, TEEs, development of inhibitors to factor IX, and usage and safety in the elderly (≥ 65 years).	Planned	Interim updates based on EUHASS reports will be included in each PSUR

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Hypersensitivity/ anaphylactic reactions	Sections 4.3 (Contraindications), 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the proposed SmPC.	None
Development of inhibitors to factor IX	Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the proposed SmPC.	None
TEEs	Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the proposed SmPC.	None
Development of antibodies against CHO host cell proteins	Sections 4.3 (Contraindications), 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the proposed SmPC.	None
Dosing errors based on variability in the assays used during treatment monitoring of factor IX levels	Sections 4.2 (Posology and method of administration)of the proposed SmPC.	None
Experience in patients with severe renal or hepatic impairment	None proposed.	None
Effiacy and safety in PUPs	Section 4.2 (Posology and method of administration) of the proposed SmPC.	None
Experience in pregnancy and lactation, including labour and delivery	Section 4.6 (Fertility, pregnancy and lactation) of the proposed SmPC.	None
Experience in elderly patients (aged 65 years and above)	Section 4.4 (Special warnings and precautions for use) of the proposed SmPC.	None
Experience with patients in ITI (off-label use)	Section 4.4 (Special warnings and precautions for use) of the proposed SmPC advises that the safety and efficacy of using rIX-FP has not been established in ITI.	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Idelvion (albutrepenonacog alfa) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.>

3. Benefit-Risk Balance

Benefits

Beneficial effects

Clinical efficacy of rIX-FP has been investigated, in a step-wise approach: PK calculations have been based upon FIX-activity measurements mainly after 50 IU/kg and amended by 25 and 75 IU/kg ctivity data were used for a population PK analysis, simulating FIX activity levels after pre-defined doses (25, 40, 50, 75 IU/kg). Dosage-suggestions for prophylaxis in Study 2004 (15-35 IU/kg once weekly) and on-demand treatment (initial dose not less than 25 IU/kg) were based upon these results. However, doses for treatment of bleeding episodes as well as for prophylaxis had to be increased during the study. For the following studies 3001 and 3002, initial prophylaxis doses were increased to 35-50 IU/kg and for on-demand treatment to at least 35 IU/kg. Different dosing regimens for prophylactic treatment were investigated due to prolonged half-life, including a once weekly, every 10-day and an every 14-day treatment interval.

Most of the bleeding episodes were treated successfully with 1 or 2 infusions in all studies and haemostatic efficacy was rated as excellent or good for the majority of bleeding episodes.

Subjects who received prophylactic treatment started with 35-50 IU/kg once weekly. A subgroup of patients switched to extended treatment intervals (every 10 or 14 days) with a recommended dose of 75 IU/kg and individual adjustments. 21 PTPs remained on the extended 14 day prophylaxis interval for additional treatment duration of 98 to 575 (median 386) days. From those subjects, 8 (38%) experienced at least one bleeding during the 14 day-prophylaxis, while they had no bleeding events during once weekly prophylaxis. Median Annualised Bleeding Rate (ABR) on 7 day prophylaxis with Idelvion for all bleeds was 0.0 (range 0-6) and on 14 day-prophylaxis it was 1.08 (range 0-9.1).Currently available information support extension of treatment intervals for some patients though potentially associated with an increased risk for bleeding compared to a once weekly regimen. Of note, ABR is not comparable between different factor concentrates and between different clinical studies.

Uncertainty in the knowledge about the beneficial effects.

Efficacy information in previously untreated patients is missing and will be provided from Clinical study 3003; A Phase 3b open-label, multicentre, Safety and Efficacy Extension Study of a Recombinant Coagulation factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Haemophilia B, including PUPs (see RMP).

Efficacy of bleeding control peri-operatively has been documented for rIX-FP and product consumption for major surgeries has been satisfactory although, further data are expected from the surgery substudy of clinical trial 3003 (See RMP).

Risks

Unfavourable effects

Of the 107 subjects, 8 subjects (7.5%) reported 15 AEs (headache, dizziness, feeling hot, injection site erythema, injection site haematoma, rash, eczema, constipation and hypersensitivity), that were considered by the Investigator to be related to treatment. The treatment-related hypersensitivity reaction in 1 subject was, based on a review by the IDMC, assessed as an injection reaction rather than a hypersensitivity reaction. In the clinical study programme of rIX-FP, no inhibitory antibody to the product could be observed in a total of 107 subjects and also no other (non-inhibitory) anti-drug antibody newly emerged under treatment. No thromboembolic events occurred and there were no renal complications. Clinical data are thus not indicative of an elevated inhibitor incidence.

There are insufficient data on inhibitor incidence in PUPs.

Important unfavourable effects of any FIX product include immunogenicity (inhibitor development and hypersensitivity reactions), thromboembolic events and, especially in association with high treatment doses, nephrotic syndrome.

Uncertainty in the knowledge about the unfavourable effects

The rIX-FP safety database is limited with regard to elderly patients aged 65 years and over, which is reflected in the SmPC as well as in the RMP. The uncertainties regarding the missing data in elderly patients have sufficiently been addressed through their reflection in SmPC and RMP.

Moreover, uncertainties exist with regard to possible unfavourable effects related to the albumin fusion technology of this new recombinant FIX product. In this context, uncertainties especially remain as to whether a - yet unobserved - additional potential for immunogenicity has to be taken into account.

Further safety data – including data in previously untreated patients- from the ongoing study 3003 and data from the EUHASS registry are expected in the post-authorisation phase (See RMP).

Effects Table

Effect	Short Description	Unit	rIX-FP	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Pharmacokinetics						
Half-life	Standard PK-parameters according to the Clinical Guideline	hours	≈100	≈20	Narrow database Inhomogeneous group (Severity of Haemophilia) Elevated pre-dose values Cmax might not have been met Sampling points: gaps / abbreviated schedule	Sections: PK, Population PK, Pooled Analysis
IR, Clearance, c_{max}		diverse	As expected dependent on extended half-life	As previously known		
Prophylaxis						
ABR	Annualized bleeding rate for once weekly prophylaxis	No/y median (range)	Study 2004: 2.3 (0;14) Study 3001: 0.6 (0;2.57) Study 3002: Age<6y 2.64 (0;10.7) Age 6 to <12y 3.39 (0;9.5)		ABR vary considerably between studies and depend on dosage-regimen; According to the Clinical Guideline, ABR has not been introduced as an efficacy parameter. Lack of definitions for a “bleed”, for “spontaneous” or “traumatic” nature of such bleed and individual evaluation factors are considered to be challenging when comparing numbers. Some patients received add-on pre-activity treatment Comparison of ABR while on on-demand versus on prophylaxis-regimen is of highly restricted value: On-demand therapy mainly represents severity of haemophilia (overall bleeding frequency) and not efficacy of a certain product. On the other hand, total ABR while on prophylaxis, ideally should aim at zero bleeds. Considerable number of bleeds did not require treatment and are therefore not included in the ABR.	Clinical efficacy

Effect	Short Description	Unit	rIX-FP	Control	Uncertainties / Strength of evidence	References
Consump-tion per interval	Amount of administered FIX Dose per infusion	IU/kg/y IU/kg IU/kg median (range)	Study 3001: 2328 (1668;3852) 48 (34;74) Study 3002: Age <6y 2545 1517;3612 50 (15-77) Age 6 to<12y 2222 1611-3178 43 (26;67)	3084 (780; 11736) Age <6y 5200 (2600; 25480) Age 6 to <12y 3120 (1820; 9464)	Narrow data-base, wide ranges, inhomogeneous disease severity,	
Haemostatic efficacy in bleeding episodes						
Investiga-tor's assess-ment	4-point scale	%	Excellent: 79 Good: 15.6		Subjective assessment	
N/o infusions per bleed		Num-ber	1 inf: 93 2 inf: 5.9			
Perioperative haemostatic efficacy						
Investi-gator's assess-ment	4-point scale	%	15 surgeries all rated excellent or good only 1 RBC transfusion in a Total knee replacement		Subjective assessment	
Consump-tion per inter-vention	Amount of administered FIX within 14 days	IU/kg	81-380		Dosage beyond 14 days postoperative not available	
Unfavourable Effects						
AEs of special interest	FIX Inhibitor	BU/ml	no inhibitor could be observed	(none)	study procedures for inhibitor evaluation meet current standards	all studies
	Hypersensitivity	AE incidence	1 non-serious AE Hypersensitivity, Rash and Eczema each		incidence and severity in an overall safety population of n=107 not different from what would be expected	
	TEEs	AE incidence	} no AE observed		} study procedures for evaluation of possible	

Effect	Short Description	Unit	rIX-FP	Control	Uncertainties / Strength of evidence	References
	Nephr. Syndrome	AE incidence			TEEs and renal complications were appropriate	
Safety of FIX doses up to 75 IU/kg	Idelvion SmPC: up to 75 IU/kg for prophylaxis FIX core SmPC: up to 40 IU/kg	AE incidence; Exposure data	AE incidence not increased for maximum doses >75 IU/kg	(none)		

Abbreviations: BU-Bethesda Unit; TEE-Thromboembolic Event

Benefit-risk balance

Importance of favourable and unfavourable effects

Efficacy of rIX-FP has been established in an extensive clinical investigation program. Results of PK-evaluation reflect relevant increase of half-life when compared with standard FIX-products. Such increase has been awaited by the target population, as treatment intervals for prophylaxis with standard products are short (2-3 times per week) and can be increased to at least once weekly with rIX-FP while maintaining a high standard of bleeding control. Efficacy has been demonstrated by low ABR, lower FIX-consumption when compared with previous treatment and high-level of haemostatic efficacy in the on-demand and surgical setting.

Main advantage of this new FIX product is the assumed extended treatment interval for prophylaxis. It is acknowledged that dosing in haemophilia patients is individual and based on the experience of the treating physician.

The safety profile of rIX-FP seems to be in line with other FIX products from the data presented so far. In theory, higher doses would bear the risk of high maximum activity-levels with consecutive risk of thrombosis or thrombo-embolism at least in patients at risk (e.g. obese, elderly, cardiovascular diseases). Although not observed during the clinical study, the improved efficacy of rIX-FP (and obviously low ABR in study 3001 compared to other licensed FIX products) could lead to a higher risk of thromboembolic events. This is addressed in the RMP.

Benefit-risk balance

The overall Benefit /Risk of Idelvion in the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency) is considered to be positive.

Discussion on the benefit-risk balance

Overall, efficacy of rIX- FP for preventing bleeding episodes, treatment of breakthrough bleeds, on-demand treatment and surgical prophylaxis in adults and children is shown. PK results show that rIX-FP has an improved PK profile compared to other licensed FIX products (prolonged t1/2, increased AUC, MRT, decreased CL). Efficacy and safety were demonstrated in the prophylactic setting, in the on-demand treatment of bleeding events and break-through bleeds with different dosing regimens as well as in surgical interventions. PK results and efficacy results have been translated into relevant posology recommendations.

The safety profile of rIX - FP is comparable to other FIX products but due to the small haemophilia B population the safety database is rather small. Only a small proportion of observed AEs (15/579) in 8 subjects were assessed as related and Adverse Drug Reactions to rIX-FP by the investigators. No related SAEs occurred and importantly, no thromboembolic event or severe allergic reactions were observed. Additional information in long-term use and use in PUPs will be provided from ongoing studies and registries in the post-marketing setting.

Possible unknown unfavourable effects related to the albumin fusion technology of rIX-FP and missing data – especially with regard to previously untreated patients - will be covered by the post-marketing clinical programme, as well as additional data in the peri-surgery setting in accordance with the clinical FIX guidance and has already started.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Idelvion in the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). Idelvion can be used for all age groups, is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that albutrepenonacog alfa is qualified as a new active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0269/2014 of 27 October 2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.