25 February 2016
EMA/CHMP/196953/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Alprolix

International non-proprietary name: eftrenonacog alfa

Procedure No. EMEA/H/C/004142/0000

Note

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

Table of contents

List of abbreviations

ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
aPTT	activated partial thromboplastin time
BMI	body mass index
BU	Bethesda unit
CI	confidence interval
CL	clearance
Cmax	maximum observed activity
CNS	central nervous system
CV	coefficient of variation
DNAUC	dose-normalized area under the plasma activity time curve
DP	drug product
DS	drug substance
ED	exposure day
EPD	electronic patient diary
FcRn	neonatal Fc receptor
Fc-sc	Fc single chain
FIXFc-sc	factor IX Fc single chain
HCV	hepatitis C virus
HEK-293	human embryonic kidney 293 cell line
HIV	human immunodeficiency virus
IgG	immunoglobulin
IgG1	immunoglobulin G1
IIV	interindividual variability
IR	incremental recovery
IU	International Unit
IV	intravenous
MRT	mean residence time
NONMEM	nonlinear mixed effect modelling
PD	pharmacodynamic, pharmacodynamics

pdFIX	plasma-derived factor IX
PTP	previously treated patient
PUP	previously untreated patient
Q2	intercompartment clearance between compartments 1 and 2
Q3	intercompartment clearance between compartments 1 and 3
rFIX	recombinant factor IX
rFIXFc	recombinant factor IX Fc fusion protein
rFVIIIFc	recombinant factor VIII Fc fusion protein
SAE	serious adverse event
t1/2	half-life
TEAE	treatment-emergent adverse event
V1	central volume of distribution
V2	volume of peripheral compartment 2
V3	volume of peripheral compartment 3
Vss	volume of distribution at steady state
WFH	World Federation of Haemophilia

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biogen Idec Ltd submitted on 4 June 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Alprolix, 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 18 December 2014.

Alprolix was designated as an orphan medicinal product EU/3/07/453 on 08 June 2007. Alprolix was designated as an orphan medicinal product in the following indication: Treatment of haemophilia B (congenital factor IX deficiency).

The applicant applied for the following indication:

ALPROLIX is a recombinant coagulation factor for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Alprolix 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 eftrenonacog 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 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0303/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0303/2014 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 eftrenonacog 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 11 June 2008, 22 October 2009, 5 November 2009 and 22 July 2010. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

Alprolix has been given a Marketing Authorisation in United States on 28 March 2014, Australia on 17 April 2014, Canada on 20 March 2014, Japan on 4 July 2014 and New Zealand on 3 September 2015.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Andrea Laslop   Co-Rapporteur: Concepcion Prieto Yerro

- The application was received by the EMA on 4 June 2015.

- The procedure started on 25 June 2015.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 September 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 September 2015.

- The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on 25 September 2015

- During the meeting on 22 October 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 26 November 2015.

- The Rapporteurs circulated the Joint CHMP/PRAC Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 6 January 2016.

- During the CHMP meeting on 28 January 2016, 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 2 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 Alprolix.

- The New Active Substance Report was adopted at the CHMP on 25 February 2016

2. Scientific discussion

2.1. Introduction

Haemophilia B (coagulation factor IX [FIX] deficiency) is a rare inherited X-linked recessive bleeding disorder, caused by a missing or defective FIX protein. As haemophilia B is an X-chromosome linked recessive disorder it is more common in men (92%) than in women- 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). It manifests clinically as bleeding into joints, muscles or internal organs, either spontaneously or as the result of accidental or surgical trauma.

Signs and symptoms of haemophilia 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. Haemophilia may be categorised based on endogenous factor activity levels as severe (<1% activity), moderate (1% to 5% activity), and mild (>5% to 40% activity). 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.

The primary aim of care for patients with haemophilia B is to prevent bleeding, this 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). Replacement therapy with exogenous FIX provides a temporary correction of the coagulation factor deficiency by increasing FIX levels and thereby reducing bleeding. 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.

Current replacement therapy includes plasma-derived (pdFIX) as well as recombinant FIX (rFIX) products. These products are indicated for both the prophylactic and acute treatment of bleeding episodes, including bleeding in the perioperative setting. Although these products are generally safe and effective, they are limited by relatively short half-lives, which require frequent infusions to prevent and control bleeding episodes.

Alprolix was developed to have a longer half-life while maintaining the activity profile of FIX as a treatment for haemophilia B.

ALPROLIX (eftrenonacog alfa) is a long-acting, fully recombinant coagulation factor IX Fc fusion protein (rFIXFc) consisting of human coagulation factor IX (FIX) covalently linked to the Fc domain of human immunoglobulin G1 (IgG1).

The fusion of Fc to human FIX is based on an approach for increasing the elimination half-life of therapeutic proteins [Jazayeri and Carroll 2012; Wu and Sun 2014]. While the FIX moiety of rFIXFc retains FIX coagulation activity, the Fc component of rFIXFc binds to neonatal Fc receptor (FcRn), which is expressed on many adult cell types. The Fc domain is responsible for the long circulating elimination half-life of IgG1 through interaction with the FcRn [Roopenian and Akilesh 2007]. The same naturally occurring pathway similarly delays lysosomal degradation of immunoglobulins by recycling the protein back into circulation, and is responsible for their long plasma half-life (Figure 1).

The proposed indication is: Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). ALPROLIX can be used for all age groups.

Calculation of the required dose of recombinant factor IX Fc for "on demand treatment" is based on the empirical finding that 1 International Unit (IU) factor IX per kg body weight raises the plasma factor IX activity by 1 % of normal activity (IU/dL). The required dose is determined using the following formula: Required units = body weight (kg) x desired factor IX rise (%) (IU/dL) x {reciprocal of observed recovery (IU/kg per IU/dL)}

For long term prophylaxis against bleeding, the recommended starting regimens are either:

- 50 IU/kg once weekly, adjust dose based on individual response or

- 100 IU/kg once every 10 days, adjust interval based on individual response.

The highest recommended dose for prophylaxis is 100 IU/kg, which can be used to guide dosing in bleeding episodes and surgery:

Dosing for treatment of bleeding episodes and surgery is guided according to the degree of haemorrhage and corresponding factor IX level required. (See SmPC section 4.2.)

The rFIXFc clinical development program was designed in accordance with regulatory advice and the EMA guideline on the clinical investigation of recombinant and human plasma-derived FIX products [EMA (EMA/CHMP/BPWP/144552/2009). Additionally, the EMA guideline on core Summary of Product Characteristics (SmPC) for human plasma-derived and recombinant coagulation FIX products is applicable to rFIXFc and provides recommendations for information to be included in the SmPC for products indicated for use in haemophilia B (CHMP/BPWP/1625/1999 rev 2).

Protocol assistance from the Committee for Medicinal Products for Human Use (CHMP) was sought on the clinical development program, including advice on the topic of significant benefit for orphan medicinal products.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder and solvent for injection. Each vial contains 250IU, 500IU, 1000IU, 2000IU or 3000IU of eftrenonacog alfa (recombinant Factor IX fusion protein (rFIXFc)) as active substance.

As described in section 6.1 of the SmPC, other ingredients are:

Powder: Sucrose, L-Histidine, Mannitol, Polysorbate 20, Sodium hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment);

Solvent: Sodium chloride solution.

As described in section 6.5 of the SmPC , the product is available in a Type 1 glass vial with a chlorobutyl rubber stopper (powder) and in a Type 1 glass pre-filled syringe with a bromobutyl rubber plunger stopper (5 mL solvent). Additional equipment is provided for the administration of the product: a plunger rod, a sterile vial adapter for reconstitution, a sterile infusion set, alcohol swab(s), plaster(s) and gauze pad(s).

2.2.2. Active Substance

General information

ALPROLIX is a long-acting recombinant Factor IX - Fc fusion protein (rFIXFc). rFIXFc is comprised of the full length coagulation Factor IX (FIX) and an Fc domain of a human antibody (IgG1 isotype) with no intervening linker sequence. The rFIXFc molecule is heterodimeric with an rFIXFc single chain (rFIXFc-sc) and an Fc single chain (Fc-sc) bound together through two disulfide bonds in the hinge region of Fc. The FIX portion of the molecule contributes to the blood coagulation activity, and the IgG1 Fc portion binds to the neonatal Fc receptor, FcRn.

The molecular weight of rFIXFc is approximately 98 kDa.

Recombinant FIXFc requires two protein subunits, FIXFc-sc (641 amino acids) and Fc-sc (226 amino acids), to assemble within a transfected cell line to form the final protein product, rFIXFc.

Recombinant FIXFc is a complex molecule, composed of a number of functional domains, which undergo extensive post-translational modifications, e.g. gamma-carboxylation of the propeptide domain, N-glycosylation, O-glycosylation, and β-hydroxylation of the FIX part of the molecule. Furthermore, N-glycosylation is also expected on the Fc portion of the molecule.

Manufacture, characterisation and process controls

The rFIXFc active substance (AS) is manufactured at Biogen Inc, Research Triangle Park, North Carolina, United States using media that is free of animal-derived components and is stored at -70 ± 10°C.

The eftrenonacog alfa manufacturing process is well described. The main steps are fermentation, recovery and purification. In-process controls are listed and the applicant confirms that no reprocessing is foreseen. The active substance manufacturing process is considered acceptable.

- Cell line:

Each batch of rFIXFc active substance is produced from a working cell bank (WCB) derived from a human embryonic kidney [HEK] cell line.

- Process:

After thawing of a WCB vial, the culture is expanded using a series of shake flask stages followed by expansion through progressively larger bioreactors, used to inoculate the production culture. The culture suspension is harvested for purification

- Purification:

  The purification process consists of several viral clearance steps before dispensing into storage containers (see container-closure section).

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted.

Raw materials used in the manufacturing process are received, tested, and stored according to pre-determined item specifications and are sourced from Biogen approved suppliers. No material of human or animal origin is used in the manufacture of rFIXFc (further details in section "Adventitious agents"). Water for injections (WFI) used throughout the rFIXFc active substance manufacturing process complies with Ph.Eur. requirements.

Expression system: information about the expression system was provided.

<u>Cell line</u>: rFIXFc is produced in human embryonic kidney (HEK) cells that have been stably transfected with expression plasmids. Related products, from which the desired rFIXFc is purified, are secreted into the cell culture media.

A two-tiered cell bank system consisting of a Master Cell Bank (MCB) and Working Cell Bank (WCB) has been created for rFIXFc active substance manufacturing. A second WCB has been generated (under the same conditions, using the same medium formulation) and is qualified for use as the current WCB. Additional working cell banks will be prepared from the MCB. The protocol has been provided.

Adventitious agents testing were performed on the cell banks according to the requirements of ICH Q5A (R1). The analysis confirmed that the cell banks are of human origin and free of bacteria, fungi, mycoplasma, and adventitious viruses. No adventitious agents were detected using *in vitro* assays and *in vivo* assays for viruses.

Phenotypic characterisation and stability of the WCB was investigated.

Information was also provided on the storage, handling and stability of the cell banks (MCB, WCB) as well as on cell bank testing and genotypic stability.

Control of critical steps and intermediates

A comprehensive overview of the process controls and the acceptable ranges for the operation of critical steps in the rFIXFc active substance manufacturing process is presented in the dossier. In addition, process intermediates were evaluated for stability to establish hold (storage) time limits and conditions.

Control of critical steps is based on an initial risk assessment which was conducted to identify critical quality attributes (CQAs) that could potentially impact product efficacy or safety, followed by a further process risk assessment to identify operating parameters that may be further investigated during subsequent process characterisation studies. Following process characterisation, another risk assessment was performed to identify potential modes of failure associated with controlled parameters that may affect process performance or the quality of the product.

The control strategy for the controlled parameters is based on setting of action limits. Exceeding an action limit requires a manufacturing deviation to be issued and the extensive process knowledge gained during process characterization informs the investigation, which requires identification of root cause and appropriate corrective actions to minimize future excursions. A specific process is established to inform whether the affected batch may be released for use or not. In process measurements are also reported for some parameters, which require reporting of results and is not defined as process controls or tests.

In conclusion, the control system in place to monitor critical steps and intermediates is considered adequate to guarantee the consistency of production.

Process validation

Process validation for the rFIXFc active substance process was performed in accordance with the ICH guideline "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients." In addition, the principles outlined in the EMA's "Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission" (EMA/CHMP/BWP/187338/2014)" have been applied.

The rFIXFc active substance manufacturing process has been validated adequately. Process validation is comprised of the following activities:

- Cell culture in bioreactors

- Cell culture harvest

- Purification process

- Clearance validation of process-related impurities including HCP and host cell DNA

Small-scale studies were performed during process development to define the control strategy and identify the parameters for validation.

Process validation as well as some additional relevant results was provided. All results presented in the validation sections indicate that the rFIXFc active substance manufacturing process provides sufficient clearance of potential process-related impurities and that the process performs consistently.

Manufacturing process development

During the course of the product development, rFIXFc active substance was manufactured at three different sites. Throughout development of the clinical and commercial process, the cell line used for the production of rFIXFc has remained unchanged. A comparative investigation (including comparison of release testing results as well as physicochemical and biological characterisation) between different scale processes was performed.

Higher HCP levels were detected in the commercial scale process compared to earlier development processes, however they do not give reason for safety concerns. Indeed, the safety of the product with these higher HCP levels was confirmed in the Phase 3 studies, indicating the commercial process is capable of clearing HCP to safe levels.

Characterisation

Extensive physicochemical and *in vitro* biological characterisation was conducted on the primary reference standard and rFIXFc AS process validation batches, manufactured using the commercial process. Appropriate state-of-the-art and also several orthogonal techniques were applied. The results of the physicochemical and *in vitro* biological characterization presented demonstrate the integrity and consistency of the structural and biochemical characteristics of the rFIXFc active substance.

Factor IX potency: FIX potency measurement is based on the Ph.Eur. one-stage clotting assay. Respective assay validation was performed and the method is suitable for the intended use.

As part of validation, a comparative study was conducted in order to evaluate differences in the results when different activated partial thromboplastin time (aPTT) reagents and coagulation instruments were used. The results reveal an underestimation of FIX potency when kaolin-based reagents were used.

The applicant states that the cleavage leading to different forms observed by reducing SDS-PAGE may occur non-enzymatically or by other enzyme(s) during rFIXFc manufacture. The applicant was asked to describe the investigations carried out to identify the mechanisms involved in this cleavage during the manufacturing process. Uncertainties in active/inactive cleavage forms of rFIXFc determined by SDS PAGE were clarified.

- Impurities (that are present or potentially present in the rFIXFc active substance (AS) manufactured using the proposed commercial manufacturing process have been evaluated: .Product-related impurities

- Process-related impurities including HCP and host cell DNA

- Contaminants: endotoxin and bioburden.

The characterisation results demonstrate that the impurity levels in the rFIXFc active substance are sufficiently low to ensure drug safety, and are consistent among the rFIXFc batches manufactured to date.

Overall, the characterisation is considered appropriate for this type of molecule

Specification

The specifications were developed in line with ICH Guideline Q6B. Ph. Eur. 2522 Human Coagulation Factor IX (rDNA) Concentrated Solution has been taken into consideration when developing the specifications for the active substance, where relevant. The specifications adequately control the physicochemical characteristics, identity, purity and biological activity of the molecule.

Detailed method descriptions for all non-compendial methods as well as for the FIX coagulation activity assay were provided.

The applicant demonstrated that the levels of impurities did not significantly increase during the finished product manufacturing process (further details in paragraph "Product Specification"). Since the stated impurities have been present in product used in clinical trials, their presence in the commercial FP is considered clinically qualified. The applicant was requested to tighten specified limits during the review process to ensure satisfactory product control and consistency.

Although the CHMP considers the specifications adequate to control AS/FP, recommendations are made for submission of further batch data to determine, based on additional manufacturing experience, if certain specifications may be tightened further to assure enhanced product.

Analytical Methods

The analytical methods applied are adequately described and validated in accordance with ICH guidelines. In particular, the Activated Partial Thromboplastin Time (aPTT) method was successfully validated for determining the identity and biological activity of rFIXFc AS and FP for release and stability.

Batch analysis

The data of batch analyses for the batches manufactured at different scales, including commercial scale, are provided in the dossier.

The release specifications were revised over the development of the product; all batches met their release specifications in place at the time of release

Reference Standards

Biogen has established a primary reference standard (PRS) and qualified two working reference standards (WRS) for use in the testing and characterisation of rFIXFc. Selection and qualification of future working reference standards is explained in the dossier and information on stability is given.

A confirmation was given that newly established primary reference standards will be calibrated against the current WHO International Standard for FIX.

Container closure system

The rFIXFc active substance is stored at -70 ± 10 °C in containers that have been qualified for long-term storage, and shipping studies were performed in order to validate their use.

Stability

Stability data for rFIXFc active substance on batches manufactured using the commercial process were provided.

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life of 48 months at -70±10°C for the active substance.

In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

New Active Substance

The Applicant stated that eftrenonacog alfa is a biological substance not previously authorised as a medicinal product in the European Union and requested that eftrenonacog alfa contained in ALPROLIX to be considered a new active substance (NAS) in itself.

Eftrenonacog alfa is a fully recombinant fusion protein comprising of the full length coagulation Factor IX (FIX) covalently linked to the Fc domain of human immunoglobulin G1 (IgG1).

Based on the assessment of the submitted data CHMP concluded that eftrenonacog alfa is a new active substance that has not been authorised European Union previously. From a quality perspective, it can be regarded as a NAS in itself.

2.2.3. Finished Medicinal Product- Powder

Description of the product and pharmaceutical development

The rFIXFc finished product is a lyophilized powder in a vial which is reconstituted with 5ml sodium chloride solution from a pre-filled syringe. The finished product is supplied in strengths of 250, 500, 1000, 2000, and 3000 IU per vial. The excipients chosen for rFIXFc finished product have a history of use in commercial biopharmaceutical formulations, and have been widely used for intravenous administration. All excipients are of compendial grade and tested as described in the current compendial monographs. The finished product is formulated with L-Histidine, mannitol, sucrose and polysorbate 20, sodium hydroxide (for pH adjustment) and hydrochloric acid (for pH adjustment).

The rFIXFc finished product is lyophilized in a USP/Ph. Eur. Type I glass vial. The vials are closed with a chlorobutyl stopper. The stoppered vials are sealed with aluminum seals with a flip off cap of various colours, dependent on vial strength. All strengths use the same container closure system.

Representative Certificates of Analyses for each component have been submitted. Those parts which are in contact with the product comply with the respective Ph. Eur. monographs.

The development of the rFIXFc finished product formulation was completed in several stages during clinical development. Pre-formulation studies were conducted to evaluate different parameters and degradation profiles.

A liquid formulation of rFIXFc was developed for preclinical studies and Phase 1/2a clinical trials. A lyophilized rFIXFc powder for solution for injection was subsequently developed for Phase 3 pivotal clinical trials and commercial use.

Development of the product for the Phase1/2a studies was performed at a development site, however product development for Phase 3 trials and commercial use occurred at a different site. The technology transfer included development and process optimizations in order to achieve a suitable manufacturing process for clinical and commercial finished product supply.

Manufacture of the product and process controls

Manufacturers and sites performing control testing and release on the finished product were provided.

There are no product overages; however, there is an overfill to ensure the correct delivered dose.

---

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

The manufacturing process for the rFIXFc finished product consists of the following steps: buffer preparation, thawing and pooling of rFIXFc active substance, compounding, filling and lyophilization, final packaging and inspection, prior to shipping, labeling and secondary packaging.

The applicant confirms that no reprocessing steps are foreseen for the manufacture of finished product. Shipping studies were used to qualify the method of transport for active substance, finished product, solvent syringes, and finished goods. In all instances, the shipping methods discussed demonstrated adequate robustness to qualify the method of transport. The shipping methods ensure that product temperature is maintained and package integrity is preserved.

The process controls and the acceptable ranges for the operation of critical steps in the rFIXFc finished product manufacturing process are described. These controls have been established to direct the unit operations, monitor performance, and ensure that the process operates in a manner consistent within the process design parameters. The controls, action limits, in-process specifications, and rationale for parameters that are most important for maintaining process and product consistency are discussed. The process controls described in this section are those that have been identified as important to monitor consistent performance of the process. Hold times are listed and are supported by data generated using the validated process.

Process Validation is comprised of the following activities: process consistency, hold times, and aseptic manufacturing conditions.

Process consistency validation of the rFIXFc finished product manufacturing process was demonstrated by the acceptable completion of validation runs according to pre-specified protocols. Several lots of finished product were successfully manufactured at the proposed highest and lowest commercial doses. Lots were manufactured at maximum and minimum lot sizes. Supplemental validation was also executed for the intermediate strengths. These supplemental lots provided additional demonstration of process consistency.

The applicant has sufficiently justified that the detected extractables (generated under worst case conditions) do not pose a toxicological concern or a risk to patient safety.

Product specification

The commercial release and stability specifications for all rFIXFc finished product strengths include tests for:

- identity

- biological activity

- purity and impurities

- quantity

- safety

- physicochemical characteristics

Specifications are common across all strengths of the finished product, with few exceptions. For these attributes, the appropriate adjustments have been made to the limits in the higher strength presentations compared to the lowest strength presentation.

Impurities present or potentially present in rFIXFc finished product are the same as those present or potentially present in rFIXFc active substance. The release and characterisation test results indicate that the levels of impurities are low and consistent across rFIXFc finished product lots and strengths. In

addition the results demonstrate that the levels of impurities did not significantly increase during the finished product manufacturing process.

The acceptance criteria for release testing were established based on a combination of: clinical experience, rFIXFc finished product lot release data, manufacturing capability and consistency, analytical test method capability, developmental studies, regulatory guidelines, and pharmacopoeial monographs. For each quantitative quality attribute, the range of results seen in the rFIXFc finished product batches manufactured for commercial or clinical use was subjected to statistical analysis to confirm that the commercial specifications adequately reflect an acceptable level of consistency and process capability.

Analytical methods

The analytical procedures have been briefly described; all non-compendial analytical methods have been validated for all strengths of rFIXFc finished product testing in accordance with ICH principles.

Batch analysis

Batch analysis data have been presented for finished product manufactured from active substance produced with different scale processes and using the commercial process at the finished product manufacturing site. All batches met the release specification valid at the time of release and confirm consistency.

Stability of the product

Based on the provided data, a 48-month shelf-life is agreed for all rFIXFc lyophilized FP strengths at the long-term storage temperature of 2 to 8°C. Within the 48-month shelf-life period, storage of up to 6 months at room temperature (not to exceed 30°C/86°F) is also agreed, to allow flexibility to the patient prior to dosing. After storage at room temperature, the product may not be returned to the refrigerator.

A bracketed stability study design was applied to the finished product stability lots manufactured from the commercial scale active substance. The bracketing was designed in accordance with ICH Guideline Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products to include process validation lots at the low and high end of the bracket. Additional strengths of finished product were introduced later in development, and the stability study bracket was expanded to accommodate these additional strengths.

Photo-stability studies were also performed, and have demonstrated that the secondary packaging provides acceptable protection from light exposure.

In accordance with EU GMP guidelines[2], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA

2.2.4. Finished Medicinal Product- Solvent

Description of the product and pharmaceutical development

All relevant information has been provided by the applicant about the solvent: an aseptically filled, terminally sterilized sodium chloride solution used for the reconstitution of all strengths of the rFIXFc lyophilized finished product. The solvent is supplied as a 5 mL fill in a single-use prefilled syringe.

An extensive leachable and extractable study was performed for solvent syringes and demonstrates the suitability of the syringe components.

---

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

A container closure integrity test has shown that the seal integrity of the rFIXFc solvent syringe container closure system remains integral during long-term storage.

Manufacture of the product and process controls

The rFIXFc solvent is manufactured, tested, stored, labeled, and packaged in accordance with current Good Manufacturing Practice. The rFIXFc solvent is filled into the syringes and terminally sterilized. Three commercial scale lots of solvent for rFIXFc were manufactured during the validation campaign.

Specific parameters measured during the solvent manufacturing process are considered critical (CIPT, CCP or CIPC) and are controlled to ensure a consistent and reproducible manufacturing process. This results in finished product that meets quality release specifications.

Product specification

Analytical methods

All used analytical procedures are consistent/comply with the respective Ph. Eur. monographs.

Batch analysis

Solvent batch release results are provided. The data indicate consistent manufacture of the solvent, meeting its predefined specifications and quality attributes.

Stability of the product

Based on the stability data for all lots, a 48-month shelf life is proposed for the rFIXFc solvent from the date of manufacture when stored at 2 to 30°C.

Solvent lots from the clinical and process validation campaigns put on stability were manufactured using the same formulation and filled in the same container closure as will be used for commercial manufacture.

Comparability exercise for finished medicinal drug product

N/A

Adventitious agents

The following efforts are taken by the manufacturer in order to ensure safety with regard to adventitious agents: no material of human or animal origin is used in the manufacture of rFIXFc; adventitious agents testing are performed on the cell banks; and the manufacturing process has sufficient capacity for the reduction of viral particles. The effectiveness of these process steps has been sufficiently demonstrated for their capacity to remove viruses.

Viral safety is considered sufficiently assured for rFIXFc as appropriate overall reduction factors for all viruses investigated were presented.

Virus validation reports were provided for all the viral clearance process steps investigated.

GMO

N/A

2.2.5. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.7. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends further points for investigation (see DS specifications).

2.3. Non-clinical aspects

2.3.1. Introduction

The pharmacology program utilized *in vitro* and *in vivo* assays to extensively characterize the coagulation properties of rFIXFc. The Fc domain was added to provide a longer elimination half-life for rFIXFc, but it was also critical to demonstrate that the Fc domain did not interfere with the ability of the FIX domain to properly interact with other members of the coagulation cascade. The recombinant coagulation factor IX Fc fusion protein (rFIXFc, BIIB029) was characterized in non-GLP single-dose pharmacokinetic (PK) studies performed in normal mice, FIX-knockout (haemophilia B [HemB]) mice, FcRn knockout mice, hFcRn transgenic mice, Sprague Dawley rats, HemB dogs, and cynomolgus monkeys.

The toxicology program for the recombinant coagulation factor IX Fc fusion protein (rFIXFc, BIIB029) was designed to support chronic administration for the treatment of haemophilia B. rFIXFc has been evaluated for its toxicological effects in 2 species, Sprague Dawley rats and cynomolgus monkeys, as well as for local tolerance and thrombogenic potential in New Zealand White rabbits. The GLP toxicology studies in rats and monkeys were repeat-dose studies of up to 4 weeks and 27 weeks, respectively. No single-dose, acute toxicology, nor juvenile toxicology studies were conducted with rFIXFc.

2.3.2. Pharmacology

Primary pharmacodynamic studies
In vitro characterization assays, including interactions with phospholipid surfaces, formation of the Tenase complex, and inhibition by ATIII, demonstrated that the post-translational modifications of rFIXFc were comparable to BeneFIX. The greater than 30-fold increase in residual activated FIXa in BeneFIX accounted for increased thrombin generation in the TGA assay. Although the specific activity of rFIXFc is approximately 2-fold lower on a molar basis when compared to BeneFIX, this should have no effect on the dosing of patients.

In vivo Studies were performed to demonstrate that the prolonged elimination half-life of rFIXFc resulted in prolongation of PD effects and efficacy in FIX-deficient animals. Comparisons with BeneFIX were used to establish the relationships among PK, PD, and efficacy.

The nonclinical PD evaluations of rFIXFc as a long-acting FIX were performed by dosing via intravenous (IV) infusion in HemB mice and dogs. IV infusion is the route of administration in the clinical treatment of haemophilia B.

The recombinant protein rFIXFc of this replacement therapy is designed to restore native factor IX by genetic fusion of the native Thr148 allelic form of human plasma-derived factor IX with an IgG1 Fc single

chain fragment, connected with a second Fc single chain through disulfide bonds. Genetic fusion of the FIX subunit with the Fc single chain is generated with no intervening sequence. This design of the construct aims to extend serum persistence of the construct due to pH dependent binding to FcRn, while maintaining FIX subunit activation by the same enzymes which activate FIX. The active ingredient carries quite complex posttranslational modifications.

Table 1: in vivo Primary pharmacodynamic studies

Study No. and Title	Species	Single Dose (unless otherwise noted); route of administration	Key Findings
R-FIX-017 Efficacy of FIXFc Monomer and BeneFIX in FIX-Deficient Mice	HemB mice	5 mg/kg rFIXFc (219 IU/kg); 0.78 mg/kg rFIX (200 IU/kg); IV Single and multiple dose (Day 0, 4 and 8)	Sustained clotting activity as measured by WBCT for rFIXFc compared to rFIX in HemB mice.
R-FIX-027 Comparability of Pharmacokinetics and Pharmacodynamics of FIXFc Phase 1/2a DP and Phase 3 DP after a Single IV Dose in FIX-deficient Mice	HemB mice	200 IU/kg; IV	Similar sustained clotting activity (aPTT) for both rFIXFc liquid DP from ▆▆▆ DS scale and rFIXFc lyophilized DP from ▆▆▆ DS scale (manufacturing process BIIB029-A) in HemB mice.

Study No. and Title	Species	Single Dose (unless otherwise noted); route of administration	Key Findings
N-FIX-010-R1 Efficacy Comparison of rFIXFc ▮▮▮ , Lyophilized Drug Product and ▮▮▮ Lyophilized Drug Product by Whole Blood Rotation Thromboelastometry in FIX-deficient Mice	HemB mice	rFIXFc (Lyophilized DP from ▮▮▮ DS scake and Lyophilized DP from ▮▮▮ DS scale), 50 IU/kg; rFIX, 100 IU/kg; IV	Similar acute clotting activity (ROTEM), but sustained activity compared to BeneFIX for both lyophilized DP from ▮▮▮ DS scale (manufacturing process BIIB029-A) and lyophilized DP from ▮▮▮ DS scale (manufacturing process BIIB029-B) in HemB mice.
R-FIX-014 Characterization of FIXFc for a Hemophilic Dog Study, and the Pharmacodynamics and Pharmacokinetics of FIXFc in Hemophilic Dogs	HemB dogs	2.86 or 2.90 mg/kg (135 or 137 IU/kg); IV	rFIXFc normalized clotting time for 144 hours in HemB dogs.
R-FIX-031-R1 Acute Efficacy of rFIXFc in the Tail Clip Bleeding Model of Hemophilia B Mice	HemB mice	40, 80, 120, 240, 360, 720 IU/kg; IV	rFIXFc and BeneFIX are equally effective when measured in an on-demand model for treatment of acute bleeding.
R-FIX-032-R1 Recombinant FIX Fc Fusion Protein: Prophylactic Efficacy in Hemophilia B Mouse Tail Vein Transection Model	HemB mice	4, 13, 40, 120 IU/kg; IV	rFIXFc dosed at 72 hours pre-injury is equally effective as BeneFIX dosed at 24 hours pre-injury in protecting post- tail vein transection re-bleeding and survival, demonstrating that rFIXFc results in prolonged prophylactic activity versus BeneFIX.

aPTT = activated partial thromboplastin time; DP = drug product; DS = drug substance; HemB = haemophilia B; Hem B mice = FIX-Deficient Mice; IV = intravenous; ROTEM = rotation thromboelastometry; WBCT = whole blood clotting time

The clotting activity of the construct as measured in the one-stage clotting assay showed about 2-fold lower specific activity on a molar basis for rFIXFc in comparison to BeneFIX. Consequently a series of chromogenic assays characterized the enzymatic activity of rFIXFc. Titration of FXIa-activated FIXa-Fc and BeneFIXa with Antithrombin III showed that Antithrombin III inhibited the activity of FIXa-Fc when present at equal or greater molar ratios. The same method determined the concentration at which the Antithrombin III inhibition of active FIX was relieved, and showed that that FXIa-activation of FIXFc and BeneFIX generated around 90% FIXa-Fc and around 97% BeneFIXa. Incubation of FVIIa/TF with FIXFc and BeneFIX converted FIX-Fc and BeneFIX completely to its activated forms. Only when FIXFc or BeneFIX was activated with FXIa, in the presence of FVIIIa and cephalin as a source of phospholipids, the Tenase complex formed with a significantly increased rate of FXa generation. In absence of FVIIIa, or prior activation with FXIa or in absence of phospholipids the rate of FXa generation was significantly decreased.

A 35-40 fold lower level of activated FIX in rFIXFc (in comparison to BeneFIX) was detected by measuring the rate of FXa generation by FVIIIa and FXIa-activated FIXFc or BeneFIX compared to that by FVIIIa and different levels of non-activated forms. BeneFIX seems to contain about 0.2-0.4% FIXa, which is consistent with result of the FIXa ELISA, detecting about 0.1% activated FIX in BeneFIX and <0.006% in FIXFc.

Measuring the rate of FXa generation after addition of FIXa at increasing concentrations to fixed concentrations of phospholipids, FX, calcium ions and FVIIIa reflects the interaction between FIXa and FVIIIa and showed similar Kd values for FIXa-Fc (1.74 ± 0.1 nM) and BeneFIX (1.55 ± 0.1 nM) and both molecules exhibited similar Vmax (FIXa-Fc 4.4 ± 0.1 nM/min, and BeneFIXa 4.0 ± 0.1 nM/min).Further results generated by two variants of this method using cephalin or platelets instead of phospholipids generally confirmed similar affinities and Vmax values for the interaction of FIXa-Fc and BeneFIXa with FVIIIa.

Kinetics of FX activation by FXIa-activated or FVIIa/TF-activated FIX/FVIIIa-based Tenase complex using phospholipids exhibited similar kinetics towards the FX substrate. These results were confirmed by assaying FX activation kinetics by FIXa-Fc and FVIIIa-based Tenase complex on platelets and on activated platelets.

Additionally, the activity of FIXa towards the FIXa substrate was similar for FXIa-activated FIXFc and BeneFIX over a range of FIXa concentrations ranging from 0.025 to 12.5 nM.

Thus in vitro studies confirmed that functionality of the FIX subunit was retained as shown with comparable activation kinetics, similar FXase complex formation and comparable affinity of Xase complex formed by FIXFc towards FX. Different in vitro thrombin generation activity per unit of FIX activity between rFIXFc and BeneFIX was shown to be based on minor amounts of activated FIX in BeneFIX, not present in rFIXFc.

Comparable peak clotting activities are reported 15 minutes after single or multiple administration of equal activity doses of rFIXFc or BeneFIX to HemB mice, whereas prolonged PD effect was detectable only for rFIXFc, which correlated well with PK data (based on rFIXFc specific ELISA) (Report No. R-FIX-017).

Prolonged clotting activity was confirmed by a study in HemB dogs, as measured by whole blood clotting time and aPTT (Report No. R-FIX-014). Acute efficacy studies in HemB mice finally indicated in vivo efficacy by simulating bleeding phenotypes ranging from normal to severe haemophilia with the tail clip bleeding model. Prophylactic efficacy study in HemB mice applying rFIXFc 72 hours prior tail vein transection (TVT), while infusing BeneFIX 24 hours prior TVT showed similar percentages of survival, supporting evidence for a longer duration of protection for rFIXFc.

Binding of rFIXFc to FcRn from rats, monkeys and humans measured by surface plasmon resonance was comparable to binding of hIgG to FcRn of different species, indicating higher affinity toward rat FcRn (Report No. R-FIX-042) and supporting the selection of rats and monkeys for RDTSs.

Secondary pharmacodynamic studies

No studies on secondary pharmacodynamics were submitted (see discussion on non-clinical pharmacology).

Safety pharmacology programme

Safety pharmacology studies were not submitted with rFIXFc, but relevant safety pharmacology parameters which included the cardiovascular system, central nervous system, or respiratory system were measured and included as part of the repeat-dose toxicology studies in rats or cynomolgus monkeys (See repeat toxicity studies).

Pharmacodynamic drug interactions

Non-clinical studies on interactions of rFIXFc with other drugs have not been submitted (see discussion on non-clinical pharmacology).

2.3.3. Pharmacokinetics

The recombinant coagulation factor IX Fc fusion protein (rFIXFc, BIIB029) was characterized in non-GLP single-dose pharmacokinetic (PK) studies performed in normal mice, FIX-knockout (haemophilia B [HemB]) mice, FcRn knockout mice, hFcRn transgenic mice, Sprague Dawley rats, HemB dogs, and cynomolgus monkeys.

Different analytical methods were developed to support the nonclinical PK studies of rFIXFc, including assays to measure plasma levels of rFIXFc antigen (ELISA) and activity (one-stage aPTT assay). In rats and mice, direct comparisons were made with the PK of rFIX (BeneFIX®), while in dogs and monkeys only rFIXFc was tested and compared with previously published results with BeneFIX and plasma-derived FIX (Mononine®)

In addition, PK parameters were determined in repeat-dose GLP toxicology studies, in which some animals developed anti-drug antibodies. Nonclinical PK comparability studies were also conducted to complement the assessment of analytical comparability to support rFIXFc manufacturing changes made during the course of development.

FcRn knockout mice [Roopenian 2003] were used to demonstrate that the FcRn receptor is needed to achieve the longer elimination half-life observed for rFIXFc compared to rFIX, since the elimination half-life advantage of rFIXFc was lost in the absence of FcRn, while it was restored in human FcRn transgenic mice.

Table 2: PK and toxicology studies

Overview			Test Article: rFIXFc	
Type of Study	**Test System**	**Method of Administration**	**Testing Facility**	**Study Number**
Absorption				
Single-dose PK	Normal mice; HemB mice; Sprague Dawley rats	IV	Biogen Idec	R-FIX-015
Single-dose PK	Normal mice; HemB mice; Sprague Dawley rats	IV	Biogen Idec	R-FIX-023
Single-dose PK	HemB mice	IV	Biogen Idec	N-FIX-011
Single-dose PK	FcRn knockout mice; hFcRn Transgenic mice	IV	Biogen Idec	R-FIX-025
Single-dose PK	HemB mice	IV	Biogen Idec	R-FIX-027
Single-dose PK	HemB mice	IV	Biogen Idec	N-FIX-009-R1
Single-dose PK	HemB dogs	IV	Francis Owen Blood Research Labs, University of North Carolina, Chapel Hill	R-FIX-014
Single-dose PK	Cynomolgus monkeys	IV	Battelle, Columbus, OH	N-FIX-006
Single-dose PK	Cynomolgus monkeys	IV	Battelle, Columbus, OH	N-FIX-008-R2
Repeat-dose toxicology/PK (GLP)	Sprague Dawley rats	IV	Battelle, Columbus, OH	N102010
Repeat-dose toxicology/PK (GLP)	Cynomolgus monkeys	IV	Battelle, Columbus, OH	N102011
Repeat-dose toxicology/PK (GLP)	Cynomolgus monkeys	IV	Battelle, Columbus, OH	N102015
Transplacental transfer of rFIXFc	Pregnant female HemB mice, fetuses and pups	IV	Biogen Idec	R-FIX-048

GLP = Good Laboratory Practice; HemB = haemophilia B; IV = intravenous

In all species, rFIXFc showed more than a 3-fold longer elimination half-life than rFIX. Together, these studies support the potential of rFIXFc to provide a prolonged protective haemostatic effect, resulting in the need for less frequent dosing of rFIXFc as compared to FIX, while maintaining the protection needed for prophylaxis in humans with FIX deficiency. In a placental Transfer of rFIXFc in Pregnant Female Factor IX Deficient (HemB) Mice (R-FIX-048) the extent of rFIXFc transfer from pregnant females to her pups ranged from 1.7% to 3.7% with an average transfer of 2.6% ± 0.60%. at 24 or 48 hours post-infusion.

2.3.4. Toxicology

Single dose toxicity

No single-dose toxicity studies were conducted with rFIXFc.

Repeat dose toxicity

The toxicology program for the recombinant coagulation factor IX Fc fusion protein (rFIXFc, BIIB029) was designed to support chronic administration for the treatment of haemophilia B.

Description and key findings from non-GLP and GLP studies are presented in the tables 8 and 9 below:

Table 3: non-GLP pilot toxicology studies conducted with rFIXFc

Study Number and Title	Species	Dose and Frequency	Key Findings
Non-GLP Pilot Toxicology Studies			
N-FIX-003 Pilot Repeat Dose Study of FIXFc in Rats and Immunization with FIXFc for Control Antibodies	Sprague Dawley Rats	25 and 100 IU/kg Twice weekly IV for 5 or 7 weeks	• Repeat doses were well-tolerated • Antibodies to rFIXFc (3 of 6 treated rats at 25 IU/kg and 9 of 11 treated rats at 100 IU/kg)
N-FIX-002A Pilot Repeat Dose Study of FIXFc in Cynomolgus Monkeys	Cynomolgus Monkeys	25, 100 and 500 IU/kg Once weekly IV for 8 weeks	• One early death (Day 21) at 25 IU/kg; cause unknown • Antibodies to rFIXFc (4 of 11 treated animals); no neutralization of endogenous FIX

Table 4: GLP repeat-dose toxicology studies conducted with rFIXFc

Study Number and Title	Species	Dose and Frequency	Key Findings
GLP Repeat-Dose Toxicology Studies			
N102010 4-Week IV Dose Toxicity and PK Study of FIXFc in Rats Followed by a 4-Week Recovery Period	Sprague Dawley Rats	0, 50, 200 and 1000 IU/kg Every 4 days for 4 weeks (8 IV doses)	• Repeat doses were well-tolerated • Antibodies to rFIXFc (≈50% at 50 and 200 IU/kg and ≈75% at 1000 IU/kg) • NOAEL was 1000 IU/kg
N102011 5-Week IV Dose Toxicity and PK Study of FIXFc in Cynomolgus Monkeys Followed by a 4-week Recovery Period	Cynomolgus Monkeys	0, 50, 200 and 1000 IU/kg Once weekly IV for 5 weeks	• Repeat doses were well-tolerated • Dose-related increases in Antibodies to rFIXFc • Transient increases in PT, primarily at 1000 IU/kg (artifact of in vitro assay conditions) • NOAEL was 1000 IU/kg
Supplemental Report R-FIX-026 for study N102011			• Transient increases in PT were an artifact due to high plasma concentrations of rFIXFc which interfered with in vitro assay conditions used to measure PT.
N102015 27-Week IV Dose Toxicity and PK Study of FIXFc in Cynomolgus Monkeys Followed by a 4-Week Recovery Period	Cynomolgus Monkeys	0, 50, 200 and 1000 IU/kg Once weekly IV for 27 weeks	• Repeat doses were well-tolerated • Hypersensitivity (2 of 12 high dose animals) • Antibodies to rFIXFc (18 of 28 treated animals); no neutralization of endogenous FIX • NOAEL was 1000 IU/kg

rFIXFc has been evaluated for its toxicological effects in 2 species, Sprague Dawley rats and cynomolgus monkeys, as well as for local tolerance and thrombogenic potential in New Zealand White rabbits. The GLP toxicology studies in rats and monkeys were repeat-dose studies of up to 4 weeks and 27 weeks, respectively.

Male and female animals were used in the GLP toxicology studies in rats and monkeys. The highest dose used in the toxicology studies, 1000 IU/kg, was 10 times higher than the highest routine dose of 100 IU/kg and 6.7 times higher than the highest dose of 150 IU/kg allowed for surgery or major bleeding episodes in the clinical studies.

Liquid formulations of the drug substance were used in the GLP repeat-dose toxicology studies in rats and monkeys. The lots of rFIXFc used in these studies are representative of the material used in the clinical studies and intended for commercial use (specific activity was approximately 60 IU/mg for these toxicology lots).

Following completion of the GLP repeat-dose toxicology studies, a lyophilized formulation of rFIXFc was developed which was compared to the liquid formulation in studies of local tolerance and thrombogenic potential in rabbits.

Genotoxicity

Genotoxicity studies have not been submitted (see discussion on non-clinical pharmacology).

Carcinogenicity

Carcinogenicity studies have not been submitted (see discussion on non-clinical pharmacology.

Reproduction Toxicity

Reproductive and developmental studies have not been submitted (see discussion on non-clinical pharmacology).

Toxicokinetic data

N/A

Local Tolerance

Local tolerance was monitored in the 3 repeat-dose toxicology studies by gross and microscopic evaluations of the IV injection sites. In addition, a single-dose local tolerance study (ASL00018) was conducted in rabbits using IV and paravenous (PV) dosing. Two formulations (liquid and lyophilized) of rFIXFc were evaluated in this local tolerance study using 20 male New Zealand White rabbits. In comparison to microscopic findings in control animals or control injection sites, there were no exacerbated local reactions due to administration of rFIXFc.

There were microscopic findings (mixed cell dermal inflammation and dermal edema) at some sites where lyophilized rFIXFc was administered; however, sites where vehicle or negative controls or frozen liquid rFIXFc (IV and PV) were administered were also affected at a similar incidence and severity. The microscopic findings were not attributed to IV or PV lyophilized rFIXFc administration.

Lyophilized rFIXFc drug product administered at 566 IU/mL as a single IV injection or a single PV injection to New Zealand White rabbits was well tolerated and produced similar results compared to a single IV or PV injection of frozen liquid rFIXFc drug product or vehicle or negative controls.

There were no adverse changes attributed to lyophilized rFIXFc administration.

Other toxicity studies

Relatively crude, plasma-derived FIX products have demonstrated thrombogenic activity in clinical use [Coppola 2012; Scharrer 1995]. Therefore, the thrombogenic potential of rFIXFc was evaluated in the Wessler stasis model using New Zealand White rabbits in 2 separate studies. In addition to saline and vehicle controls, BeneFIX, and a positive control (Profinine® SD, a plasma derived non-activated FIX concentrate that also contains prothrombin, factor X and low levels of factor VII) were used. rFIXFc seems to have a low thrombogenic risk as results from the Wessler stasis model indicate. Mean thrombi scores of rabbits treated with rFIXFc (liquid and lyophilized formulations) from both Wessler studies were similar to mean thrombi scores from rabbits treated with saline or vehicle.

2.3.5. Ecotoxicity/environmental risk assessment

The active substance is a protein, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, rFIXFc is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

In support of the nonclinical developmental program for the recombinant coagulation factor IX Fc fusion protein (rFIXFc, BIIB029) the preclinical developmental program was designed to support chronic administration for the treatment of haemophilia B. The design of the product aims to extend serum

persistence due to pH dependent binding to FcRn, while maintaining FIX subunit activation by the same enzymes which activate FIX. The active ingredient carries quite complex posttranslational modifications.

rFIXFc behaves similarly to BeneFIX in a number of *in vitro* characterization assays. The comparisons between rFIXFc and BeneFIX were performed in FXa generation assays that utilized preformed Tenase complex.

The *in vivo* studies demonstrated an improved PD profile that correlated with the enhanced PK properties (eg, increased half-life) observed for rFIXFc relative to BeneFIX. Dosing rFIXFc on an equal activity basis to BeneFIX produces comparable acute activity but prolonged ability to correct the clotting defect in the HemB mouse and HemB dog models.

In an acute efficacy model in HemB mice, rFIXFc is comparable to BeneFIX, while in a prophylactic bleeding model, rFIXFc results in 3-fold longer lasting protection compared to BeneFIX. Thus, rFIXFc is comparable to BeneFIX when dosed on potency to treat acute bleeding episodes, but results in sustained, long-acting prophylactic procoagulant activity and survival relative to BeneFIX at later time points. The survival protection provided by rFIXFc and BeneFIX for HemB mice post-TVT activities also suggests that the plasma FIX activity determined by the one-stage clotting assay (FIX-specific aPTT) could be used to predict efficacy.

Studies in HemB mice demonstrated similar sustained clotting activity (aPTT) for rFIXFc liquid DP from small clinical scale DS and lyophilized DP from large clinical scale DS. Similar acute clotting activity (ROTEM), but sustained activity in HemB mice compared to BeneFIX, was also shown for lyophilized DP from the large clinical and commercial DS scales. These PD studies demonstrated comparability, thus supporting the use of rFIXFc from the different manufacturing processes in GLP toxicology studies and clinical studies.

The absence of secondary PD and PD drug interaction studies as well as the integration of safety pharmacology measurements into the RDTSs is acceptable in view of the nature of the compound.

The primary PD studies demonstrated the long-acting clotting activity of rFIXFc in 2 animal models of haemophilia B compared to a currently licensed rFIX product (ie, BeneFIX). This prolonged clotting activity correlated with a prolonged survival benefit in haemophilia B bleeding model. Therefore, the results of the in vitro and in vivo PD studies support the clinical development of rFIXFc. Since no secondary pharmacodynamic effects are expected, the omission of studies on secondary pharmacodynamics is acceptable.

In all nonclinical PK studies, rFIXFc was administered either by IV bolus injection or infusion in order to model the route of administration in the clinic. The analytical methods that were developed to support the nonclinical PK studies of rFIXFc include assays to measure plasma antigen concentrations of rFIXFc (ELISA) and assays to measure FIX activity (one-stage aPTT assay).

FcRn knockout mice [Roopenian 2003] were used to demonstrate that the FcRn receptor is needed to achieve the longer elimination half-life observed for rFIXFc compared to rFIX, since the elimination half-life advantage of rFIXFc was lost in the absence of FcRn, while it was restored in human FcRn transgenic mice.

The provided PK studies demonstrate that rFIXFc has an extended half-life and support the potential of rFIXFc to provide a prolonged protective haemostatic effect with less frequent dosing of rFIXFc compared to FIX.

Non-GLP pilot studies were conducted in both rats (N-FIX-003) and monkeys (N-FIX-002A) to determine the tolerability of repeat dosing of rFIXFc and to assess the development of antibodies to rFIXFc.

Both rats and monkeys were selected as relevant toxicology species using several criteria: mechanism of action of rFIXFc (replacement clotting factor), slower plasma clearance of rFIXFc (binding to FcRn) compared to an rFIX comparator, BeneFIX, and historical database. Rabbits have historically been used for local tolerance and thrombogenicity studies.

In both of these species, IV dosing was well-tolerated for up to 7 weeks (rats; twice weekly dosing) or 8 weeks (monkeys; once weekly dosing). Antibodies against rFIXFc were detected in rats and monkeys in the three repeat-dose toxicity studies. In both species, the antibody response was dose-related (noted as an increase in incidence and endpoint titer). The detected antibodies were "clearing" antibodies, which resulted in more rapid elimination of administered rFIXFc later in the study, compared to the PK profile following the first dose on SD1. Following development of these antibodies, mean AUC remained dose-dependent in both rats and monkeys, although the absolute values were lower compared to SD1 values.

The development of antibodies to rFIXFc is an expected finding in rats and monkeys since the test article is a foreign protein to both species (rFIXFc consists of a single molecule of human FIX fused to the Fc domain of human IgG1 without any intervening sequence). Despite the development of antibodies to rFIXFc, the toxicology of rFIXFc was adequately assessed in these repeat dose studies. The dosing was frequent enough to maintain exposure throughout the dosing periods.

The early death of 1 monkey at the lowest dose of 25 IU/kg was considered not to be related to the administration of rFIXFc. Although the cause of death was not determined for this animal, repeat dosing was well-tolerated in the same study at doses of 100 and 500 IU/kg. Furthermore, repeat dosing for 27 weeks was well-tolerated at doses of 50, 200 and 1000 IU/kg in a GLP study in monkeys (N102015).

Due to the lack of significant adverse toxicological findings in the 5-week study in monkeys, even with the development of antibodies, a 27-week study was conducted. In the 27-week study, there was no indication that the anti-rFIXFc antibodies cross-reacted with endogenous FIX. There was no evidence of organ toxicity due to antibody/antigen complex formation, as there were no histopathological changes in rats or monkeys treated with rFIXFc.

The results of these 2 pilot studies provided sufficient information for selection of dose and frequency of administration of rFIXFc in repeat-dose GLP toxicology studies in rats and monkeys. Based on plasma elimination half-lives of approximately 1 day in rats and approximately 2 to 3 days in monkeys, dosing frequencies were chosen to be every 4 days in rats and weekly in monkeys. These dosing frequencies ensured that animals in all GLP repeat-dose studies were exposed to rFIXFc on a continuous basis, with concentrations fluctuating between Cmin and Cmax.

Consistent with ICH S6 Guideline (1997) and Addendum (ICH S6(R1), 2012), genotoxicity tests have not been conducted with rFIXFc since there is no known mechanism by which rFIXFc can interact with DNA [Gocke 1999. Carcinogenicity studies have not been conducted with rFIXFc as based on a weight-of-evidence approach and consistent with the ICH S6 Guideline (1997) and Addendum (ICH S6(R1)). The lack of such data is addressed in the SmPC section 5.3.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, rFIXFc is not expected to pose a risk to the environment.

Animal reproduction studies have not been conducted with ALPROLIX. Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during pregnancy and breast-feeding is not available. Therefore, factor IX should be used during pregnancy and breast-feeding only if clearly indicated. In a placental Transfer of rFIXFc in Pregnant Female Factor IX Deficient (HemB) Mice (R-FIX-048) the extent of rFIXFc transfer from pregnant females to her pups ranged from 1.7% to 3.7% with an average transfer of 2.6% ± 0.60%. at 24 or 48 hours post-infusion. This information has been

reflected in the SmPC section 5.3. The lack of information on fertility, embryo-foetal development, pregnancy and breastfeeding is reflected in the SmPC section 4.6.

In a thrombogenicity study, rFIXFc seems to have a low thrombogenic risk as results from the Wessler stasis model indicate. Mean thrombi scores of rabbits treated with rFIXFc (liquid and lyophilized formulations) from both Wessler studies were similar to mean thrombi scores from rabbits treated with saline or vehicle (see SmPC section 5.3.).

Non-clinical data reveal no special hazard for humans in line with other products based on thrombogenicity test in rabbits (Wessler stasis model) and repeated dose toxicity studies (which included assessment of local toxicity, male reproductive organs and electrocardiographic parameters) in rats and monkeys. Studies to investigate genotoxicity, carcinogenicity, toxicity to reproduction or embryo-foetal development have not been conducted. In a placental transfer study, ALPROLIX has been shown to cross the placenta in small amounts in mice.

2.3.7. Conclusion on the non-clinical aspects

The primary PD studies demonstrated the long-acting clotting activity of rFIXFc and PK studies demonstrate that rFIXFc has an extended half-life. Non-clinical data reveal no special hazard in line with what would be expected from the type of product. The non-clinical aspects of Alprolix have been studied adequately and all relevant information has been 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**

• Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
SYN-FIXFC-07-001	7 sites in the United States (6) and Hong Kong (1)	Phase I/II; Open-label, multicentre, safety, dose-escalation	1, 5, 12.5, 25, 50 and 100 IU/kg	Safety, PK	1 IU/kg: 1/1 5 IU/kg: 1/1 12.5 IU/kg: 2/1 50 IU/kg: 5/5 100 IU/kg: 5/5	30 days after administration of rFIXFc	All male; 18-76	PTPs ≥18 years of age with severe haemophilia B	Safety in all treated patients evaluated by physical examination, vital signs, electrocardiogram (ECG), laboratory changes over time, adverse events (AEs), and antibody development.
998HB102	50 sites in Australia, Belgium, Brazil, Canada, China, France, Germany, Hong Kong, India, Italy,	Phase III; Open-label, multicenter, nonrandomized, uncontrolled; Active comparator (BeneFIX) for sequential PK	Starting dose: **Arm 1** (prophylaxis): 50 IU/kg every 7 days (Interval kept steady) **Arm 2** (prophylaxis):	Efficacy and safety (comparative PK)	**N=123** **Arm 1**: 63/59 **Arm 2**: 29/27 **Arm 3**: 27/26 **Arm 4**:	**Arm 1**: Up to 52 (±1) weeks **Arm 2**: At least 26 weeks (up to ~50 EDs) **Arm 3**: Up to 52 (±1)	All male; 30 (12-71); **Arm 1**: 28 **Arm 2**: 33 **Arm 3**:	PTPs ≥ 12 years old with severe Haemophilia B	Number of bleeding episodes (spontaneous and traumatic) with rFIXFc per subject annualized over the study period (comparison between Arms 1 and 2 versus Arm

	Japan, New Zealand, Russia, South Africa, Sweden, UK, USA	subgroup	100 IU/kg every 10 days (Dose kept steady) **Arm 3** (on demand): 20 - 100 IU/kg **Arm 4** (surgical): 40 - 100 IU/kg		Arm 4 only n=4/3 Arm 4, then Arm 1 n=2 Joined from another arm n=6	weeks **Arm 4**: During preoperative period, surgery, and rehabilitation period	36 **Arm 4**: 34.5		3)
9HB02PED	16 sites/ Australia, Ireland, the Netherlands, South Africa, UK, USA	Phase III; Open-label, multicenter, nonrandomized; Uncontrolled	Individualized prophylaxis (starting regimen of 50 to 60 IU/kg every 7 days); and As needed for perioperative management;	Efficacy and safety	30/27	~50 weeks (at least 50 EDs)	4.5/95.5; 46.2	PTPs <12 years old with severe haemophilia B	Occurrence of inhibitor development
9HB01EXT interim CSR	47 sites/ Australia, Belgium, Brazil,	Phase III; Open-label, multicenter, long-term,	Weekly prophylaxis with 20 to 100 IU/kg,	Safety and efficacy	~120 planned; 116 enrolled	At least 100 EDs (including parent study)	~120 planned; 116 enrolled	Adult and pediatric PTPs with Haemophilia	Occurrence of inhibitor development

| | Canada, China, France, Germany, Hong Kong, India, Ireland, Italy, Japan, the Netherlands, Poland, South Africa, Sweden, UK, USA | extension study; Uncontrolled | or individualized interval prophylaxis with 100 IU/kg every 8 to 16 days or 2 times per month; or Episodic (on demand) regimen; and As needed for perioperative management | | as of 17 October 2014; 20 completed | | as of 17 October 2014; 20 completed | B who have completed Study 998HB102 or Study 9HB02PED | |

2.4.2. Pharmacokinetics

PK results are available from 3 completed studies:

Study SYN-FIXFc-07-001 was a Phase 1/2a, open-label, multicenter, dose-escalation study designed to evaluate the safety and PK of rFIXFc given as single IV doses of 1 to 100 IU/kg to 14 previously treated patients (PTPs) ≥ 18 years of age with severe Haemophilia B (≤ 2 IU/dL or ≤ 2% endogenous FIX).

Fifteen subjects were enrolled at 7 sites, and 14 subjects received an IV injection of rFIXFc. One subject each received 1, 5, 12.5, and 25 IU/kg; 5 subjects each received 50 and 100 IU/kg. Subjects receiving 1 or 5 IU/kg did not undergo sampling for full PK profiles. Subjects receiving rFIXFc at dose levels of 12.5, 25, 50, and 100 IU/kg underwent PK sampling at pre-dose; immediately after the dose; and 0.25, 1, 3, 6, 9, 24, 48, 72, 96, 120, 168, and 240 hours (10 days) after the dose. After the 100 IU/kg dose, samples were also taken at 12 and 14 days. PK data for the subject receiving 12.5 IU/kg were not evaluable because his plasma FIX levels were detectable only up to 96 hours post-dose, resulting in a truncated terminal phase that was less than 3 times the estimated terminal $t_{\frac{1}{2}}$. Of the 11 subjects dosed at 25 to 100 IU/kg, 6 had baseline activities of ≤ 1 IU/dL, and the remaining 5 had baseline activities of 2 IU/dL. The estimated PK parameters included Cmax, AUCinf, CL, Vss, MRT, $t_{\frac{1}{2}}\alpha$, $t_{\frac{1}{2}}\beta$, and IR. In addition, Time to 1% and Time to 3% were derived as surrogate measures for duration of therapeutic FIX activity. PK parameter summaries are provided for the 12.5, 25, 50, and 100 IU/kg dose groups.

Study 998HB102 was a multiple-dose, open-label, Phase 3 study to evaluate the safety, tolerability, PK, and efficacy of rFIXFc administered as an IV injection in 123 adult or adolescent PTPs ≥ 12 years of age with severe haemophilia B.

The study had 4 treatment arms, comprising 2 prophylaxis arms (Arm 1: weekly prophylaxis, and Arm 2: individualized interval prophylaxis), an episodic (on-demand) treatment arm (Arm 3), and a perioperative management (surgery) arm (Arm 4). All subjects had PK assessments.

In Arm 1, a subset of 23 subjects (the Sequential PK subgroup) received sequential single IV doses of 50 IU/kg BeneFIX and rFIXFc at the beginning of the study (Baseline) for direct comparison of their respective PK.

BeneFIX was selected as the comparator in the Sequential PK subgroup because it was the only recombinant FIX clotting factor commercially available for haemophilia B at the time of the study. The selection of the 50 IU/kg IV dose of rFIXFc in the Sequential PK subgroup was based on regulatory guidance and the clinical PK evaluation with rFIXFc at this dose in the Phase 1/2a study.

One hundred twenty-three subjects, ≥ 12 years of age, were enrolled across 50 sites globally.

The Sequential PK subgroup received sequential single IV doses of 50 IU/kg BeneFIX and rFIXFc at the beginning of the study (Baseline) for direct comparison of their PK. After a 5-day washout from their previous treatment, the subjects were dosed with 50 IU/kg of BeneFIX and underwent PK sampling scheduled at pre-dose; 10 minutes and 1, 3, 6, 24, 48, 72, and 96 hours post-dose. After the completion of BeneFIX PK assessment and a minimum 120 hour (5 day) washout, the subjects received 50 IU/kg of rFIXFc, and PK samples were collected according to the schedule in Table 3. Sampling timepoints were optimized to cover the main parts of the activity time profile based on the expected longer terminal t½ for rFIXFc. Full PK profiles for BeneFIX and rFIXFc were assessed for 22 evaluable subjects at Baseline. The full PK profile of rFIXFc was further assessed in 21 evaluable subjects with the same dose and sampling scheme at Week 26 (1 subject in the Sequential PK subgroup did not complete the Week 26 visit). The PK assessment of rFIXFc at Baseline and Week 26 was performed using the 1000 IU vial strength.

To evaluate and assess the PK parameter estimates of rFIXFc and BeneFIX at baseline in the Sequential PK subgroup as well as rFIXFc at Week 26 (±1 week) and PK parameter estimates of rFIXFc in other arms, FIX activity (BeneFIX or rFIXFc) over time profiles were analyzed by compartmental and non-compartmental analysis (Activity PK).

Study 9HB02PED was a multiple-dose, open-label, Phase 3, multicentre evaluation of the safety, PK, and efficacy of rFIXFc for routine prophylaxis and control of bleeding in PTPs <12 years of age with severe Haemophilia B.

Thirty subjects were enrolled into the study (15 subjects <6 years of age and 15 subjects 6 to <12 years of age) and underwent an evaluation of the PK profile of prestudy FIX (50 IU/kg) and rFIXFc (50 IU/kg) sequentially. A washout period of 72 to 96 hours with no FIX treatment was required prior to administration of prestudy FIX and prior to the administration of rFIXFc.

Blood sampling schedules were as follows:

o   Samples for PK assessment of prestudy FIX were obtained pre-dose and at 30 (±5) minutes and 3 (±0.5), 10 (±2), 24 (±3), and 48 (±4) hours following prestudy FIX dosing.

o   Samples for PK assessment of rFIXFc were obtained pre-dose and at 30 (±5) minutes and 3 (±0.5), 10 (±2), 24 (±3), 72 (±7), 120 (±12), and 168 (±16) hours following rFIXFc dosing.

After completing the PK assessments, subjects began an individualized prophylaxis regimen with rFIXFc with a starting dose regimen of 50 to 60 IU/kg every 7 days.

Non-compartmental PK analysis was implemented in all subjects with sufficient data (prestudy FIX and/or rFIXFc) to estimate at least 1 PK parameter. For incomplete or nonevaluable PK profiles, only a subset of the PK parameters were presented, as appropriate. NCA was conducted for FIX activity data from the one-stage aPTT clotting assay using Phoenix™ WinNonlin® (Version 6.2.1.51).

In addition to the conventional PK analysis, a population PK model was initially developed for rFIXFc based on the clinical PK data from the Phase 1/2a study and the Phase 3 study in adults and adolescents using nonlinear mixed effects modeling. The population PK model was later updated with inclusion of the clinical PK data from children <12 years of age from Study 9HB02PED.

Analytical methods

The selected bioanalytical methods are in accordance with applicable guidelines and were appropriately validated and therefore endorsed.

A Comparative Field Study conducted to evaluate the performance of rFIXFc aPTT activity assay in clinical hemostasis laboratories found some reagent dependent variability. Accordingly the applicant proposes to include wording in the rFIXFc SmPC to alert physicians to the fact that use of kaolin-based reagents can lead to an underestimation of rFIXFc. Reference is made to SmPC, section 4.2 Treatment monitoring.

Results

A summary of **PK parameters** by dose and by age category is presented in the following two tables.

Table 11: Phase 1/2a Study (SYN-FIXFc-07-001): FIX Activity PK Parameters (Arithmetic Mean ± SD)

Dose (IU/kg)	n	C_{max} IU/dL	AUC_{inf} h·IU/dL	CL mL/h/kg	V_{ss} mL/kg	MRT h	$t_{½α}$ h	$t_{½β}$ h	IR IU/dL per IU/kg	Time to 1% days	Time to 3% days
25	1	20.4	766	3.56	271	76.2	0.612	53.5	0.771	7.34	3.81
50	5	47.5 ± 12.9	1700 ± 548	3.44 ± 0.833	262 ± 54.2	77.0 ± 6.80	3.31 ± 3.13	57.6 ± 8.27	0.870 ± 0.214	10.1 ± 1.58	6.28 ± 1.11
100	5	98.5 ± 7.84	4020 ± 986	2.84 ± 0.657	183 ± 27.9	65.9 ± 10.3	10.3 ± 5.64	56.5 ± 14.1	1.02 ± 0.113	12.3 ± 2.49	8.53 ± 1.58
Mean	11	NA	NA	3.18 ± 0.745	227 ± 57.1	71.9 ± 9.66	NA	56.7 ± 10.4	0.930 ± 0.179	NA	NA

AUC_{inf} = area under the plasma activity time curve from time zero to infinity; CL = clearance; C_{max} = maximum concentration or activity; FIX = factor IX; IR = incremental recovery (calculated as baseline-subtracted C_{max} observed/dose); IU = international unit; MRT = mean residence time; n = number of subjects evaluated; NA = not applicable (parameters are not dose-independent); PK = pharmacokinetic; SD = standard deviation; $t_{½α}$ = alpha half-life; $t_{½β}$ = beta half-life; Time to 1% = model-predicted time after dose when FIX activity has declined to 1 IU/dL above baseline; Time to 3% = model-predicted time after dose when FIX activity has declined to 3 IU/dL above baseline; V_{ss} = volume of distribution at steady state.
Source: Study SYN-FIXFc-07-001 Clinical Study Report Addendum, Table 11-2.

Table 12: Summary of PK Parameters of rFIXFc by Age Category: Geometric Mean (95% CI) — Noncompartmental Methods — One-Stage aPTT Clotting Assay

PK parameter	Pediatric study (9HB02PED)		Phase 3 study (998HB102)	
	<6 years (n=11)	6 to <12 years (n=13)	12 to 17 years (n=11)	>=18 years (n=109)
DNAUC (IU*h/dL per IU/kg)	22.71 (20.32, 25.38)	28.53 (24.47, 33.27)	29.50 (25.13, 34.63)	32.44 (30.95, 34.00)
t1/2 (h)	66.49 (55.86, 79.14)	70.34 (60.95, 81.17)	82.22 (72.30, 93.50)	76.36 (73.04, 79.83)
CL (mL/h/kg)	4.365 (3.901, 4.885)	3.505 (3.006, 4.087)	3.390 (2.888, 3.979)	3.083 (2.941, 3.231)
MRT (h)	83.65 (71.76, 97.51)	82.46 (72.65, 93.60)	93.46 (81.77, 106.81)	88.30 (84.72, 92.03)
Vss (mL/kg)	365.1 (316.2, 421.6)	289.0 (236.7, 352.9)	316.8 (267.4, 375.5)	272.2 (258.3, 286.8)
IR (IU/dL per IU/kg)	0.590 (0.515, 0.675)	0.717 (0.612, 0.841)	0.847 (0.677, 1.060)	0.964 (0.907, 1.025)

Note 1: For the purpose of this table, all treatment arms in the Phase 3 study have been grouped together.
2: CI = confidence interval; CL = clearance; DNAUC = dose-normalized area under the curve; IR = incremental recovery; MRT = mean residence time; t1/2 = terminal half-life; Vss = volume of distribution at steady state.

SOURCE: FACTOR9HB/SCS_SCE/INTERIM1/T-PK-BYSTUDY-NONCOMP.SAS   DATE: 08APR2015

In study 998HB102 the PK profiles of Benefix and Alprolix were compared in study Arm 1. The results are presented below.

Table 13: Comparison of BeneFIX and rFIXFc PK Parameters – Non-Compartmental Methods – One-Stage Clotting Assay, Study 998HB102

PK parameter	n (a)	Geometric mean for rFIXFc baseline PK (95% CI)	Geometric mean for BeneFIX PK (95% CI)	Geometric mean of intra-subject ratio (95% CI) (p-value [b])
Cmax (IU/dL)	22	46.10 (38.56, 55.11)	47.16 (40.71, 54.65)	0.98 (0.85, 1.13) 0.742
AUC/dose (IU*h/dL per IU/kg)	22	31.58 (28.46, 35.05)	15.96 (14.26, 17.88)	1.98 (1.85, 2.11) <0.001
t1/2 (h)	22	77.60 (70.05, 85.95)	32.13 (28.26, 36.52)	2.42 (2.17, 2.69) <0.001
CL (mL/h/kg)	22	3.166 (2.853, 3.514)	6.264 (5.594, 7.014)	0.51 (0.47, 0.54) <0.001
MRT (h)	22	95.82 (86.44, 106.21)	40.15 (35.34, 45.62)	2.39 (2.18, 2.61) <0.001
Vss (mL/kg)	22	303.4 (275.1, 334.6)	251.5 (217.0, 291.5)	1.21 (1.10, 1.33) <0.001
Incremental Recovery (IU/dL per IU/kg)	22	0.9211 (0.7710, 1.1004)	0.9451 (0.8149, 1.0961)	0.97 (0.84, 1.12) 0.713

Footnotes are listed on the last page.

SOURCE: FACTOR9HB/998HB102/CSR/T-PK-NONCOMP.SAS   DATE: 07DEC2012

NOTE 1: The intra-subject ratio is calculated as Baseline rFIXFc / BeneFIX.
    (a) Includes subjects who have evaluable PK profiles for both BeneFIX and baseline rFIXFc
    (b) p-value from an ANOVA model including factors of treatment (BeneFIX vs rFIXFc) and subject.

SOURCE: FACTOR9HB/998HB102/CSR/T-PK-NONCOMP.SAS   DATE: 07DEC2012

NOTE 1: Time to 1% FIX activity = Estimated time after dose when FIX activity has declined to
        approximately 1 IU/dL above baseline.
    2: Time to 3% FIX activity = Estimated time after dose when FIX activity has declined to
        approximately 3 IU/dL above baseline
    3: The intra-subject ratio is calculated as Baseline rFIXFc / BeneFIX.
    (a) Includes subjects who have evaluable PK profiles for both BeneFIX and baseline rFIXFc
    (b) p-value from an ANOVA model including factors of treatment (BeneFIX vs rFIXFc) and subject.

SOURCE: FACTOR9HB/998HB102/CSR/IN-T-PK-COMP.SAS   DATE: 10DEC2012

Figure 3: Mean Observed FIX Activity Over Time: One-Stage Clotting Essay (Linear Scale) – Sequential PK subgroup
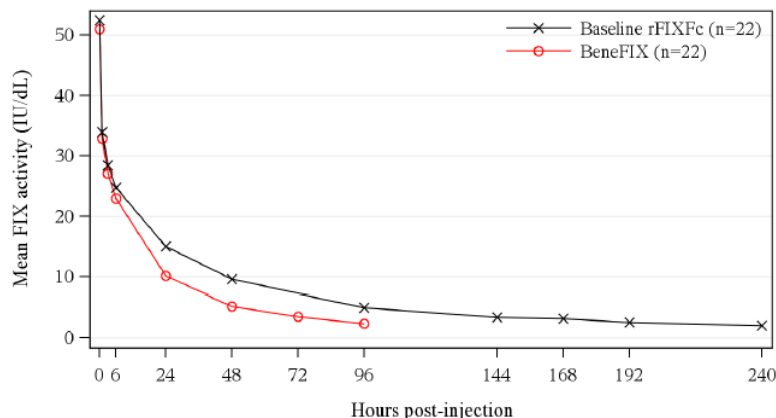
Data presented are observed FIX activity without subtraction of endogenous baseline FIX level and residue FIX level from the previous treatment prior to the PK dose.

SOURCE: FACTOR9HB/998HB102/CSR/F-MEANFIX.SAS   DATE: 07DEC2012

Figure 4: Mean Observed FIX Activity Over Time: One-Stage Clotting Essay (Logarithmic Scale)
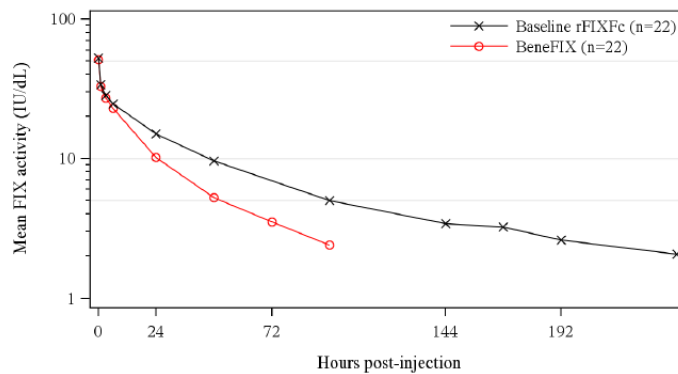
Data presented are observed FIX activity without subtraction of endogenous baseline FIX level and residue FIX level from the previous treatment prior to the PK dose.

SOURCE: FACTOR9HB/998HB102/CSR/F-MEANFIX-LOG.SAS   DATE: 07DEC2012

In the paediatric study, the PK profile of Alprolix was compared to that of the patient´s previous products.

Figure 5: Mean FIX activity over time following pre-study FIX and rFIXFc dosing (MDA): One-stage aPTT clotting assay (linear scale)
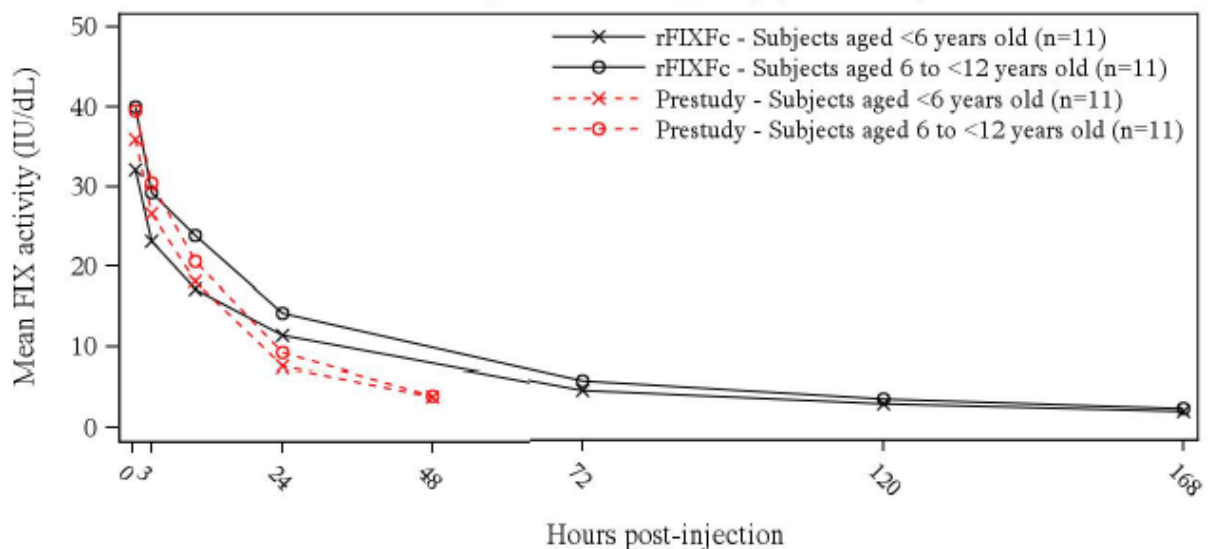
Data presented are observed FIX activity without subtraction of endogenous baseline FIX level and residue FIX level from the previous treatment prior to the PK dose.

SOURCE: FACTOR9HB/9HB02PED/CSR/F-MEAN-FIX.SAS   DATE: 04FEB2015

Figure 6: Mean FIX activity over time following pre-study FIX and rFIXFc dosing: One-Stage aPTT Clotting Assay (MDA) (Logarithmic Scale; 9HB02PED)
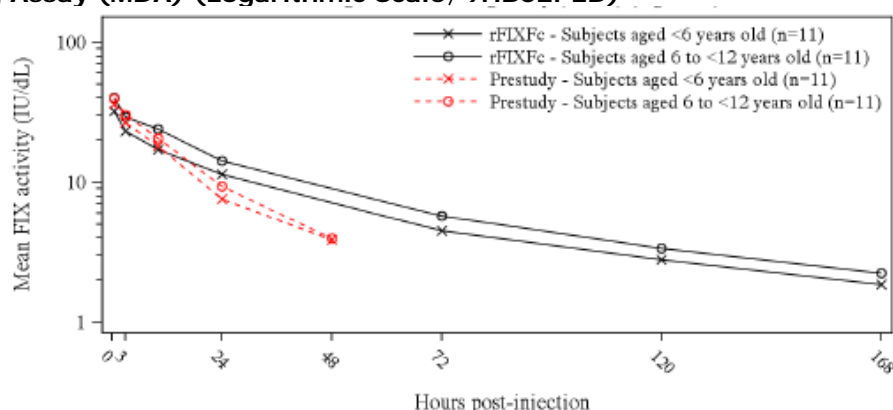
Data presented are observed FIX activity without subtraction of endogenous baseline FIX level and residue FIX level from the previous treatment prior to the PK dose.

SOURCE: FACTOR9HB/9HB02PED/CSR/F-MEAN-FIX-LOG.SAS   DATE: 03MAR2015

Repeat PK after 26 weeks: PK profiles from Baseline and after 26 weeks of dosing were compared to assess the predictability of exposure during chronic drug administration in Arm 1 of study 998HB102.

Table 14: Comparison of rFIXFc PK Parameters at Baseline and Repeat PK Visit After 26 Weeks - Non-Compartmental Methods – One-Stage Clotting Assay, Study 998HB102

PK parameter	n (a)	Geometric Mean for rFIXFc baseline PK (95% CI)	Geometric Mean for rFIXFc repeat PK (95% CI)	Geometric Mean of intra-subject ratio (95% CI)
Cmax (IU/dL)	21	46.42 (38.49, 55.97)	45.10 (40.26, 50.53)	1.03 (0.87, 1.21)
AUC/dose (IU*h/dL per IU/kg)	21	31.71 (28.43, 35.37)	34.16 (30.41, 38.36)	0.93 (0.85, 1.02)
t1/2 (h)	21	77.68 (69.76, 86.50)	78.95 (72.38, 86.11)	0.98 (0.92, 1.05)
CL (mL/h/kg)	21	3.153 (2.827, 3.518)	2.928 (2.607, 3.288)	1.08 (0.98, 1.18)
MRT (h)	21	96.17 (86.32, 107.15)	101.71 (93.38, 110.79)	0.95 (0.89, 1.00)
Vss (mL/kg)	21	303.3 (273.6, 336.2)	297.8 (260.6, 340.3)	1.02 (0.94, 1.11)
Incremental Recovery (IU/dL per IU/kg)	21	0.9274 (0.7696, 1.1176)	0.9024 (0.8077, 1.0081)	1.03 (0.88, 1.21)

Footnotes are listed on the last page.

SOURCE: FACTOR9HB/998HB102/CSR/T-PKRFIX-NONCOMP.SAS   DATE: 07DEC2012

NOTE 1: The intra-subject ratio is calculated as baseline rFIXFc / repeat rFIXFc.
   (a) Includes subjects who have evaluable PK profiles for both baseline and repeat rFIXFc

SOURCE: FACTOR9HB/998HB102/CSR/T-PKRFIX-NONCOMP.SAS   DATE: 07DEC2012

In Arm 2 of study 998HB102 patients received a dose of 100 IU/kg. PK parameters derived from this dose are presented below.

Table 15: Summary of pharmacokinetic parameters for FIX activity - non-compartmental methods — one stage clotting assay; PK analysis set; ARM 2 - Individualized Interval:

	Actual dose (IU/kg)	Cmax (IU/dL)	AUC/dose (IU*h/dL per IU/kg)	t1/2 (h)	CL (mL/h/kg)	MRT (h)	Vss (mL/kg)	Incremental recovery (IU/dL per IU/kg)
n	27	27	27	27	27	27	27	27
Mean	100.31	110.18	38.48	92.00	2.715	91.09	242.1	1.0987
SD	0.833	23.484	7.564	20.867	0.6513	19.635	58.00	0.23630
%CV	0.8	21.3	19.7	22.7	24.0	21.6	24.0	21.5
Geo. mean	100.31	107.87	37.70	89.23	2.652	88.86	235.7	1.0754
Median	100.90	106.31	38.66	100.97	2.586	94.42	239.2	1.0540
Minimum	98.4	59.2	19.3	42.3	1.96	52.5	156	0.587
Maximum	101.3	169.7	50.9	119.7	5.17	128.3	373	1.700

Results from population PK analyses

CPP-12-019-BIIB029: A Population Pharmacokinetic Analysis of rFIXFc in Patients with Severe Haemophilia B

Two studies that used rFIXFc for the treatment of severe Haemophilia B were included within this analysis. Study SYN-FIXFc-07-001 was a Phase 1/2a open-label, multi-center, safety, dose escalation study designed to evaluate the safety and PK of a single dose of FIXFc. Study 998HB102 was an open-label multi-center phase 3 study to evaluate the safety, tolerability, PK, and efficacy of rFIXFc.

A standard population pharmacokinetic approach was taken that included defining a base structure, inter-individual variability and inter-occasion variability, and covariate modeling. All analyses were conducted using NONMEM VII (version 1.0) by a first-order conditional estimation with an interaction term (FOCEI) and a combined additive and proportional residual error structure. Interindividual variability and inter-occasion variability were then tested on the PK parameters as exponential functions. Covariate modeling was performed in a stepwise forward addition and backward elimination manner. Tested covariates included body weight, age, race, blood type, HCT, IgG1concentration, albumin concentration, HCV status, HIV status, FIX genotype, drug product and study. Selection of significant covariate terms was based upon a χ2 -test comparison of a goodness-of-fit index (the OFV), as well as perceived clinical significance. Model checking included run output, goodness-of-fit plots, ETA and CWRES density plots, and individual PK profiles with population and individual predictions.

The final model was further qualified with bootstrapping, visual predictive check, and external validation with the trough/peak dataset.

Results: A three-compartment model described the data well. For a typical 73 kg subject, population predicted clearance (CL) is 2.39 dL/h, volume of central compartment (V1) is 71.4 dL, and volume of distribution at steady state is 198 dL.

Inter-occasion variability (IOV) for CL and V1 were estimated to be 15.1% and 17.4%, respectively, which are smaller than the corresponding inter-individual variability (IIV) (17.7% and 21.7%, respectively).

Body weight (BW) was found to be a covariate influencing CL and V1. The impact of BW on CL and V1 was limited: BW exponent of the power model on CL and V1 are 0.436 and 0.396, respectively. The inclusion of BW in the model reduced IIV for both CL and V1 by only 3.4% and 2.5%, respectively.

Bootstrapping, visual predictive check, and external validation using trough/peak dataset supported the adequacy of the model. Parameter estimates using the modeling dataset were comparable to those obtained using the full dataset.

Simulations based on the model with and without IOV resulted in similar PK profiles at the population level.

BW based and fixed dosing predicted similar PK profiles. The simulations of weekly dosing of 50 IU/kg or 4000 IU of rFIXFc predicted that more than 95% of the population has trough/peak within target range i.e. trough ≥ 1% and peak < 150%, whereas more than 85% of the population was within the range of 1% to 150% on 100 IU/kg (8000 IU) every 10 days, and more than 50% of the population within the range of 1% to 150% on 100 IU/kg or 8000 IU every 14 days.

Simulation of dosing regimens for prophylaxis:

Table 16: Simulation of PK Profile Following Single Dose of rFIXFc

Dose (IU/kg)	End of Infusion	12 hours	24 hours (Day 1)	36 hours	48 hours (Day 2)	72 hours (Day 3)	Day 5	Day 7	Day 10	Day 14
Median [5th, 95th]										
50	50.8 [30.4, 84.5]	21.1 [13.5, 33.6]	14.8 [9.78, 22.7]	10.9 [6.79, 17.1]	8.51 [5.14, 13.2]	5.57 [3.05, 9.27]	3.07 [1.44, 5.62]	1.93 [0.795, 3.71]	1.1 [0.277, 2.33]	0.559 [0, 1.38]
100	102 [60.8, 169]	42.3 [26.8, 67.3]	29.5 [19.6, 45.5]	21.8 [13.7, 34.1]	17 [10.5, 26.6]	11.1 [6.22, 18.5]	6.14 [3.05, 11.0]	3.88 [1.82, 7.28]	2.19 [0.775, 4.56]	1.08 [0.125, 2.58]

CPP-15-012-BIIB029: Population PK for RFIXFC

Data were available from 3 clinical trials of rFIXFc in previously treated haemophilia B patients. The first study (SYN-FIXFc-07-001) was a Phase 1/2a open label, multi-center, safety, dose escalation study in adult patients (≥18 years). The second study (998HB102) was a Phase 3 open-label multi-center study to evaluate the safety, tolerability, PK and efficacy of rFIXFc in adult and adolescent patients (≥12 years). The third study (9HB02PED) was an open-label multicenter study evaluating the safety, PK, and efficacy of rFIXFc in pediatric patients (<6 years and 6 to <12 years).

Nonlinear mixed effects modeling (NONMEM) was used to develop a population PK model to describe the PK profile in pediatric and adult haemophilia B subjects. Prior knowledge indicated that a three-compartment model described individual PK profiles for rFIXFc in adult and pediatric (>12 years) subjects with severe haemophilia B, based upon data from the Phase 1/2a Study SYN-FIXFc-07-001 and the Phase 3 Study 99HB102. Thus, the three-compartment model was evaluated as the base structural model.

Results: A three-compartment disposition model with an additive and proportional residual error model adequately described the pharmacokinetic profile for FIX activity. The effect of weight, applied using a power model (allometric type), was found significant on all the PK model parameters. Additionally, a study effect for the Phase 1/2a study was found on clearance.

CPP-13-014-BIIB029: Population PK Analysis of 3000IU and 1000IU Vial Strength Comparability

The objectives of this analysis were to evaluate the availability of the pharmacokinetics (PK) data associated with 3000IU vial strength and assess the feasibility to compare 3000IU and 1000IU vial strength through population pharmacokinetic modeling; and to evaluate vial strength (3000IU vs 1000IU) as a covariate in population PK modeling.

This study was based on the previous population pharmacokinetic analysis (CPP-12-019- BIIB029). The data were from two studies that used rFIXFc for the treatment of severe haemophilia B. Study

SYN-FIXFc-07-001 was a Phase 1/2a open-label, multi-center, safety, dose escalation study designed to evaluate the safety and PK of a single dose of rFIXFc. Study 998HB102 was an openlabel multi-center phase 3 study to evaluate the safety, tolerability, PK, and efficacy of rFIXFc.

FIX activity measurements associated with doses from solely either 3000IU or 1000IU vial strength in the phase 1/2a and phase 3 study were included in this analysis. Taking all the analyses into account, there seems to be no effect of vial strength (3000IU versus 1000IU) on the PK of rFIXFc.

2.4.3. Pharmacodynamics

No dedicated PD studies were submitted.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics data of rFIXFc are available from three completed clinical studies. Study SYN-FIXFc-07-001 was a phase I/II dose escalation study investigating PK of rFIXFc at doses of 1 (n=1), 5 (n=1), 12.5 (n=1), 25 (n=1), 50 (n=5) and 100 (n=5) IU/kg.

Study 998HB102 was a phase III clinical trial with 4 study arms (Arm 1: weekly prophylaxis, sequential PK subgroup; Arm 2: individualized interval prophylaxis; Arm 3: on-demand treatment; Arm 4: surgery arm) and a total of 123 patients ≥ 12 years of age were included with all patients undergoing PK evaluation of rFIXFc. A subset of the patients also underwent a PK evaluation of Benefix for comparison against rFIXFc. Furthermore, a subset of patients had a repeat PK evaluation after 26 weeks as requested by the guideline.

Study 9HB02PED was the paediatric trial and PK parameters of rFIXFc at a dose of 50 IU/kg were investigated in a total of 24 children (11 patients were <6 years of age and 13 patients were 6-<12 years of age) fulfilling the guideline requirement regarding number of patients with available PK results. All patients underwent PK evaluation of their previous FIX and subsequently PK evaluation of rFIXFc.

Moreover, three population PK reports were submitted.

PK evaluation comprised estimation of the following parameters: Cmax, t1/2, CL, Vss, MRT, IR and AUC and time to 1% and 3% above baseline. The presented standard PK parameters comprise those relevant on a patient level for a clinical trial setting and are also in line with the FIX guideline.

In study SYN-FIXFc-07-001 initially a non-compartmental PK analysis has been planned and this had been changed to a 2-compartmental analysis, with unknown justification. The former would have been preferred, but as the value of this trial is limited, no further issue is made. In study 998HB102 PK data were analyzed by compartmental and non-compartmental analysis. For description of PK data the apparent PK is of more interest in this assessment and therefore there is preference for the estimates from the NCA. This analysis requires fewer assumptions and treats the data as they are, rather than assuming a certain model. In the paediatric trial PK parameters were analyzed by NCA which is supported.

PK results from the phase I study SYN-FIXFc-07-001 suggest that elimination half-life of rFIXFc was prolonged compared to other licensed FIX products and was more or less comparable between dose levels. Furthermore, a dose-proportional increase of Cmax and AUCinf was observed while CL, Vss and MRT appeared to be dose-independent.

In the phase III trial 998HB102 the comparison against Benefix showed a prolonged t1/2 for rFIXFc and increased AUC, MRT and estimated time to trough levels of 1% and 3% while the CL was decreased.

The repeat PK evaluation in a subset of patients after 26 weeks demonstrate comparability to the PK after first dosing, and thus does not give rise to concern.

Patients in Arm 2 (n=27) underwent a PK evaluation of 100 IU/kg. Sampling time points in this study arm exceed guideline requirements, which is expected for a new product with a prolonged half-life. However, the recommended sampling time point of 1 hour after administration is missing. Theoretically, this could be of concern with regards to assessment of incremental recovery which is determined as the peak factor level recorded in the first hour after infusion as well as determination of Cmax which could be missed with this sampling schedule (the first sampling time points in this study were 10 minutes and 3 hours after administration). Particularly, patients in Arm 2 received a dose of 100 IU/kg which is considerably high compared to usual dosing of FIX products. However, in study SYN-FIXFc-07-001 as well as in Arm 1 sequential PK subgroup of Study 998HB102 (50 IU/kg), the sampling time point of one hour after administration was included. Data show that FIX activity at this time point was lower than at 10 minutes post-dose, suggesting that Cmax as well as IR are covered by sampling 10 minutes after administration. Therefore, Cmax and IR are not considered to be missed in Arm 2 of Study 998HB102 although the one-hour-post-dose sampling time point was skipped.

In the paediatric trial PK results show that rFIXFc has a prolonged terminal half-life and reduced CL compared to pre-study FIX products. Generally, half-life was decreased in children <6 years of age compared to the older age cohort whereas CL was increased in younger children. This was also seen for other licensed FIX products.

The guideline requirement to employ at least 3 different lots is fulfilled; an analysis according to lot showed no differences with regards to PK behavior. However, assessment of this analysis is limited by the small number of patients per lot.

In total, three population PK analyses were submitted. CPP-12-019-BIIB029 is based on PK data from studies SYN-FIXFc-o7-001 and 998HB102. The methodological approach chosen for modelling and simulation appears reasonable.

The applicant concludes that simulations predict "that 50 IU/kg (or 4000 IU) once weekly, or 100 IU/kg (or 8000 IU) every 10-14 days would maintain FIX activity within 1-150% in the majority of the population". This is not fully agreed as at a dose of 100 IU/kg the predicted trough levels are above one for only 50% of the patients (1.08 [0.125; 2.58]). No further issue is made since efficacy data are available and considered more relevant for assessing dosing recommendations of this product than data from population PK modelling.

CPP-15-012-BIIB029 is based on PK data from three clinical trials (SYN-FIXFc-07-001, 998HB102, 9HB02PED) including paediatric data. The methodological approach was to use the same model as identified when using only the data from SYN-FIXFc-07-001 and 99HB102 (see CPP-12-019-BIIB029 above) as the basis. Results show that body weight has an influence on each of the PK parameters. Additionally, a description of the influence of underweight and overweight on the PK data in accordance with the FIX guideline was submitted. IR and DNAUC seem to be increased with increased body weight. This is considered to be covered by the general statement in the SmPC that dose based on bodyweight may require adjustment in underweight or overweight patients and no concerns arise from the presented data.

In CPP-13-014-BIIB029 modelling is based on the model identified in CPP-12-019 (see above) and a covariate for vial strength (1000 IU and 3000 IU) was included. This population PK modelling suggests that there is no influence of the two different vial strengths on the PK of rFIXFc. Furthermore, available safety data do not indicate that higher concentrated vial strengths have a negative influence on the local tolerability.

Furthermore, the FIX guideline requests that the pharmacokinetics of the lowest and highest concentration should be investigated unless otherwise justified. For PK evaluation of rFIXFc only the 1000 IU and 3000 IU vial strengths were used. According to the applicant dosing with lower vial strengths at 50 IU/kg would require multiple vials and larger injection volumes and therefore would result in longer injection times than appropriate for PK assessments. Thus, although not the lowest commercial vial strength, the 1000 IU vial represents the lowest practically evaluable vial strength for PK investigation. This justification is in principal considered acceptable. Moreover, higher concentrations are considered more likely to have an influence on PK and/or safety. From the 3000 IU vial PK data as well as safety data are available indicating no difference compared to lower vial strengths. There was only one patient undergoing PK evaluation after a dose consisting of only 250 IU vials. The applicant provided PK data of this patient compared to that of the remaining patients in the same age cohort. However, due to the small number (i.e. 1 patient) no conclusions can be drawn.

The measurement of FIX activity is a pharmacodynamic marker that reflects the pharmacological activity of the rFIXFc molecule. FIX levels were measured in studies SYN-FIXFc-07-001, 998HB102, 9HB02PED and 9HB01EXT. The PD effects of FIX are closely associated with its' PK parameters, therefore it is not necessary to conduct separate PD studies.

2.4.5. Conclusions on clinical pharmacology

Overall, submitted PK data show that rFIXFc has an improved PK profile compared to other licensed FIX products supporting prolonged treatment intervals.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

N/A

2.5.2. Main study

Pivotal Trial 998HB102

This was an open-label multicenter phase 3 study with 4 treatment arms to evaluate the safety, tolerability, PK, and efficacy of rFIXFc in subjects ≥12 years of age with severe haemophilia B (defined as ≤2 IU/dL [≤2%] endogenous FIX).

Figure 7: Study design (Pivotal Trial 998HB102)
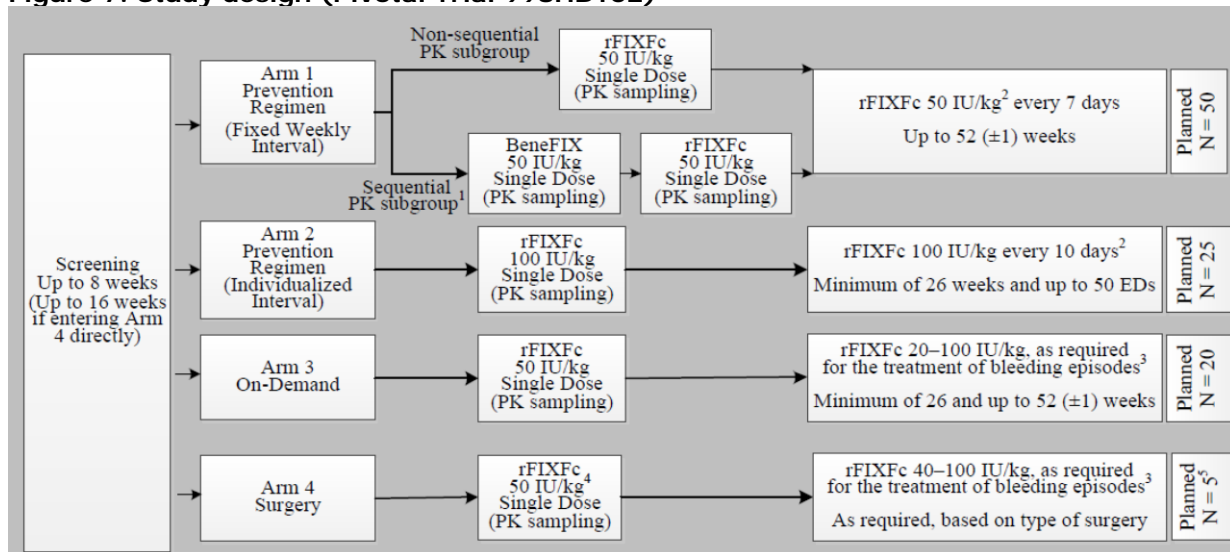
Methods

Study Participants

<u>Inclusion Criteria</u>

Candidates were required to have met the following criteria at screening to be eligible for the study:

1. Able to understand the purpose and risks of the study and to provide signed and dated informed consent and authorization to use protected health information in accordance with national and local subject privacy regulations. If the subject was younger than 18 years of age, then a parent or guardian was to have signed the ICF and the subject was to have signed the assent form as consistent with local authorities.

2. Male, 12 years of age or older, and weighing at least 40 kg

3. Severe haemophilia B, defined as ≤ 2 IU/dL (≤ 2%) endogenous FIX activity, as determined from the central laboratory at the time of screening. If the screening result was >2%, then the severity of haemophilia B was to have been confirmed by documented historical evidence from a certified clinical laboratory demonstrating ≤ 2% factor IX coagulant activity, by the medical record, or by a documented genotype known to produce severe haemophilia B.

4. A PTP, defined as having at least 100 prior EDs to any recombinant or plasma-derived FIX product (fresh frozen plasma treatment was not to be considered in the count of the documented EDs)

5. Bleeding events and/or treatment with FIX during the prior 12 weeks, as documented in the subject's medical records

6. Greater than or equal to 8 bleeding episodes in the 52 weeks prior to enrollment in the study, if treating with an on-demand (episodic) regimen

7. A platelet count ≥ 100,000 cells/μL

8. Immunocompetent, as determined by the Investigator's review of the subject's medical history

9. Viral load of <400 copies/mL, if HIV antibody positive

10. An international normalized ratio <1.40, as defined by the testing laboratory's normal range

11. Subjects entering directly into Arm 4 (Surgery) were to have met all other eligibility criteria AND required major elective surgery.

Exclusion Criteria

Candidates were to be excluded from study entry if any of the following exclusion criteria were noted at screening:

1. Prior history of, or currently detectable inhibitor, as defined by the reporting laboratory (family history of inhibitors was not to be used to exclude the subject) with a positive inhibitor value $\geq$ 0.6 BU/mL ($\geq$ 1.0 BU/mL only for laboratories with a historical lower sensitivity cut-off for inhibitor detection of 1.0 BU/mL)

2. Presence of any other coagulation disorder in addition to haemophilia B

3. Prior history of anaphylaxis associated with any FIX or IV immunoglobulin administration

4. Abnormal renal function, defined as serum creatinine >2.0 mg/dL

5. Active hepatic disease defined as an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 5 times the upper limit of normal

6. For Sequential PK subgroup receiving BeneFIX, an allergy to Chinese hamster proteins

7. Any concurrent clinically significant major disease that, in the opinion of the Investigator, made the subject unsuitable for enrollment

8. Inability or unwillingness to refrain from taking additional prophylactic doses of FIX prior to sports activity or increased physical activity

9. Concurrent systemic treatment with immunosuppressant drugs within the last 12 weeks prior to the study entry (exceptions: ribavirin, treatment of HCV and HIV and/or systemic steroids [a total of 2 pulse treatments within 7 days $\leq$ 1 mg/kg] and/or inhaled steroids)

10. Current enrollment (within the past 30 days) in any other clinical study involving investigational drugs

Treatments

Subjects enrolled in Arm 1 (weekly prophylaxis) received rFIXFc as a prophylactic individualized dose (initially 50 IU/kg) with a fixed weekly dosing interval. The dose could be modified, as guided by PK assessments, to target trough FIX activity levels at 1% to 3% above baseline, or higher as clinically indicated. Subjects continued on a fixed-weekly interval for up to 52 ($\pm$1) weeks.

Subjects enrolled in Arm 2 (individualized interval prophylaxis) received a fixed prophylactic dose (100 IU/kg rFIXFc) at a 10-day dosing interval initially, and thereafter, as guided by PK assessments, the interval could be adjusted to target a trough FIX activity level of 1-3% above baseline, or higher as clinically indicated. Following a 14-day PK assessment, all subjects continued on 100 IU/kg of rFIXFc on their individualized dosing interval for at least 26 weeks and up to 50 exposure days (EDs) overall.

For subjects enrolled in Arm 3, an episodic (on-demand) regimen was initiated with a single dose of rFIXFc at 50 IU/kg followed by a 7-day PK sampling. After completing the PK evaluation, subjects treated bleeding episodes at doses ranging from 20 to 100 IU/kg (based on the severity of the bleeding episode) as needed for up to 52 ($\pm$1) weeks.

Arm 4 (perioperative management) enrolled subjects requiring major surgery. Subjects who entered into Arm 4 were required to receive at least 4 rFIXFc doses before surgery. The prophylactic doses of rFIXFc and the interval of dosing for perioperative management were derived from the subject's baseline PK assessment in addition to consideration of the type of planned surgery. Subjects could enroll from any of

the other treatment arms into Arm 4, or enroll as new subjects scheduled for major surgery that required FIX treatment. Subjects in Arm 4 could join another arm after completing surgery.

Dosing Guidelines for rFIXFc Therapy in haemophilia B

Type of Hemorrhage	Factor IX Level Required (%)	Frequency of Doses (hrs)
Minor		
Epistaxis	25-30	48
Hemarthroses, uncomplicated	25-30	48
Superficial muscular	25-30	48
Superficial soft tissue	25-30	48
Moderate		
Epistaxis	35-50	48
Intramuscular with dissection	35-50	48
Soft tissue with dissection	35-50	48
Mucous membranes	35-50	48
Dental extractions	35-50	48
Hematuria	35-50	48
Hemarthroses, with limited motion	45-80	48
Major		
Epistaxis	60-100	24-48
Pharynx	60-100	24-48
Retropharynx	60-100	24-48
Retroperitoneum	60-100	24-48
Surgery	60-100	24-48
Central Nervous System	60-100	24-48

Caregivers should consult with the Investigator but subjects should be administered only 1 follow-up dose within 24 to 48 hours after the initial dose.

Objectives

Primary Objectives

The primary objectives of the study were as follows:

To evaluate the safety and tolerability of rFIXFc

To evaluate the efficacy of rFIXFc in all treatment arms

To evaluate the effectiveness of prophylaxis over on-demand (episodic) therapy by comparing the annualized number of bleeding episodes between subjects receiving rFIXFc on each prevention (prophylaxis) regimen (Arm 1 and Arm 2) and subjects receiving rFIXFc on an episodic regimen (Arm 3)

Secondary Objectives

The secondary objectives of the study were as follows:

To evaluate and assess the PK parameter estimates of rFIXFc and BeneFIX at baseline in the Sequential PK subgroup as well as rFIXFc at Week 26 (±1 week)

To evaluate subjects' response to treatment

To evaluate rFIXFc consumption

Outcomes/endpoints

The <u>primary efficacy endpoints</u> were as follows:

- Number of bleeding episodes (spontaneous and traumatic) with rFIXFc per subject annualized over the study period (comparison between Arms 1 and 2 versus Arm 3)

The <u>secondary efficacy endpoints</u> were as follows:

- Assessments of response to treatment with rFIXFc for bleeding episodes

This assessment was to be made approximately 8 to 12 hours, if practical, from the time the injection was given to treat the bleeding episode, and prior to any additional doses of rFIXFc, if needed, for the same bleeding episode. Response could also have been assessed by the Physician for subjects who were treated in the hospital with rFIXFc for major bleeding episodes. Responses were to be recorded using the following 4-point scale:

   o Excellent: Abrupt pain relief and/or improvement in signs of bleeding within approximately 8 hours after the initial injection

   o Good: Definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an injection, but possibly requiring more than one injection after 24 to 48 hours for complete resolution

   o Moderate: Probable or slight beneficial effect within 8 hours after the initial injection and requiring more than one injection

   o No response: No improvement, or condition worsened, within approximately 8 hours after the initial injection

- Physicians' global assessments of subjects' response to treatment with rFIXFc

- Total annualized rFIXFc consumption per subject

- Dose per injection for subjects in Arm 1

- Dosing interval for subjects in Arm 2

- The number of annualized spontaneous bleeding episodes (joint, soft tissue, and muscle) per subject

- The number of annualized joint bleeding episodes (spontaneous and traumatic) per subject

- Time from last injection of rFIXFc to the bleeding episode

- Number of injections and dose per injection of rFIXFc required to stop a bleeding episode (joint, soft tissue, and muscle)

- Quality-of-Life (QoL) via Haemophilia-Specific QoL index questionnaires for children (Haemo-QoL) or adults (Haem-A-QoL) for Arms 1 and 2

The <u>endpoints for Arm 4 </u>were as follows:

- Investigators'/Surgeons' assessments of subjects' response to surgery with rFIXFc. The Investigator/Surgeon who completed the surgical procedures was to assess the subject's response to surgery with rFIXFc treatment using a 4-point clinical scale. This assessment was to be completed 24 hours following the surgical procedure, and was to include observations made during surgery and the 24-hour postoperative time period.

- o **Excellent**: intraoperative and postoperative blood loss similar to (or less than) a nonhemophilic patient.

    - No extra doses of rFIXFc needed and

    - Blood component transfusions required were similar to a nonhemophilic patient

- o **Good**: intraoperative and/or postoperative bleeding slightly increased over expectations for a nonhemophilic patient, but the difference was not clinically significant.

    - Intraoperative blood loss no more than 250 mL greater than expected for a non-hemophilic patient and

    - No extra doses of rFIXFc needed and

    - Blood component transfusions required were similar to a non-hemophilic patient

- o **Fair**: intraoperative and/or postoperative blood loss was increased over expectation for a nonhemophilic patient and additional treatment was needed.

    - Intraoperative blood loss 250 mL to 500 mL greater than expected for person without Haemophilia or

    - Extra dose of rFIXFc needed or

    - Increased blood component transfusion requirement

- o **Poor/none**: significant intraoperative and/or postoperative bleeding that was substantially increased over expectations for a nonhemophilic patient, required intervention, and was not explained by a surgical/medical issue other than haemophilia

    - Intraoperative blood loss more than 500 mL greater than for a nonhemophilic patient or

    - Unexpected hypotension or unexpected transfer to intensive care unit due to bleeding or

    - Substantially increased blood component transfusion requirement

- Number of injections and dose per injection required to maintain hemostasis during the surgical period

- Estimated blood loss during surgery

- Number of transfusions required for surgery

Sample size

Because of the limited number of subjects in the haemophilia B population, the sample size of this study was mainly based on clinical rather than statistical considerations. Taking into account the CPMP Note for Guidance [CPMP/BPWG/1625/99 2000], efforts were made to collect sufficient data for assessments of the efficacy and safety of rFIXFc.

Approximately 100 subjects at 75 investigational sites were to be enrolled into 1 of the following treatment arms:

Arm 1, Prevention Regimen (Weekly Prophylaxis): approximately 50 subjects

Arm 2, Prevention Regimen (Individualized Interval Prophylaxis): approximately 25 subjects

Arm 3, On-Demand (Episodic) Regimen: approximately 20 subjects

Arm 4, Surgery (Perioperative Management): at least 10 major surgeries in at least 5 subjects

A key safety objective for any study of a new FIX product is the evaluation of inhibitor development. FDA guidance for adequate demonstration of acceptable inhibitor risk in clinical trials of previously treated FIX patients allows 1 out of 50 subjects to experience an inhibitor, with each subject requiring a minimum of 50 EDs to the study treatment. Under the assumption that the occurrence of inhibitors in a clinical study can be adequately modeled using the binomial distribution, a minimum of 50 EDs would allow for a 2-sided, 95% CI for the true inhibitor incidence of (0.05% to 10.65%) using the exact, Clopper-Pearson method if 1 case of inhibitor formation was observed.

Another consideration in the study sample size was the evaluation of the effectiveness of prophylaxis over episodic therapy. Using a Poisson regression model with no overdispersion, the study sample size was projected to have greater than 95% power at the 2-sided 0.05 level of significance. This was considered based on the following:

- The power was calculated for hypothesis tests between Arm 1 and Arm 3.

- It was assumed that the minimum follow-up time for subjects in Arm 1 would be 48 weeks starting from the first prophylaxis dose (10 days after the first rFIXFc dose on study), and the minimum follow-up time for subjects in Arm 3 would be 26 weeks starting from Day 1.

- An 80% retention rate was assumed; therefore, the total follow-up time of each treatment arm was calculated as 1920 subject-weeks (40 subjects) for Arm 1 and 416 subject-weeks (16 subjects) for Arm 3.

- The annualized bleeding rate for subjects in this population using episodic treatment was at least 8 bleeding episodes per subject per year.

To be considered of clinical importance, there had to be at least a 50% reduction in annualized bleeding episodes.

Randomisation

Subjects were not randomized. Subjects were assigned to treatment arms according to the clinical site's standard of care and Investigator decision, following discussion with each subject.

Blinding (masking)

This was an open-label study.

Statistical methods

The statistical methods planned in the protocol were further elaborated in a Statistical Analysis Plan (SAP), prior to database lock.

The All-Enrolled Analysis Set was defined as subjects who were registered as enrolled by IXRS and assigned a unique subject identification number.

The Full Analysis Set (FAS) was defined as subjects who received at least 1 dose of rFIXFc. The analysis of efficacy was performed in this population. Subjects who received a dose of BeneFIX, but did not receive any rFIXFc were not included in this population.

The Safety Analysis Set was defined as subjects who received at least 1 dose of BeneFIX or at least 1 dose of rFIXFc. The analysis of safety was performed in this population.

Statistical Analysis of Haemostatic Efficacy Endpoints

The primary efficacy endpoint was the annualized number of breakthrough bleeding episodes during the efficacy period. Bleeding episodes classified as unknown were also included in the determination of the

annualized bleeding rate. The comparison of annualized bleeding rates between the 2 prevention regimens (Arms 1 and 2) and the episodic regimen (Arm 3) were performed in a hierarchical, step-down fashion as follows:

The analysis proceeded by comparing annualized bleeding rates between Arm 1 (Weekly Prophylaxis) and Arm 3 (Episodic Regimen) using a Poisson regression model with treatment arm as a covariate. If the treatment factor in the Poisson regression model failed to show statistical significance at the 2-sided 5% level based on a contrast between Arms 1 and 3, then testing was to stop and the study would have failed to demonstrate a difference between any prophylaxis regimen and the episodic regimen. If the estimated ratio of annualized bleeding episodes was less than 0.5 for Arm 1:Arm 3, then clinical importance of the weekly prophylaxis regimen would have been demonstrated. If the treatment factor in the model was significant at the 2-sided 5% level, then testing was to proceed to the comparison of Arm 2 (Individualized Interval Prophylaxis) with Arm 3 (Episodic Regimen) in the same fashion. If the treatment contrast in the model for Arm 2 versus Arm 3 was significant at the 2-sided 5% level and the estimated ratio of the annualized bleeding rates was less than 0.5 for Arm 2:Arm 3, then clinical importance of the individualized interval prophylaxis regimen would have been demonstrated. A test for overdispersion was to be conducted to check the fit of the model. If no overdispersion was detected at the 2-sided 5% level of significance, results from the Poisson regression model were to be used. Otherwise, a negative binomial model, which accounts for overdispersion was to be used. Test results were tabulated by treatment arm along with the annualized bleeding rate ratios and the 95% CIs.

Results

Participant flow

Figure 8: Overview of Subject Disposition
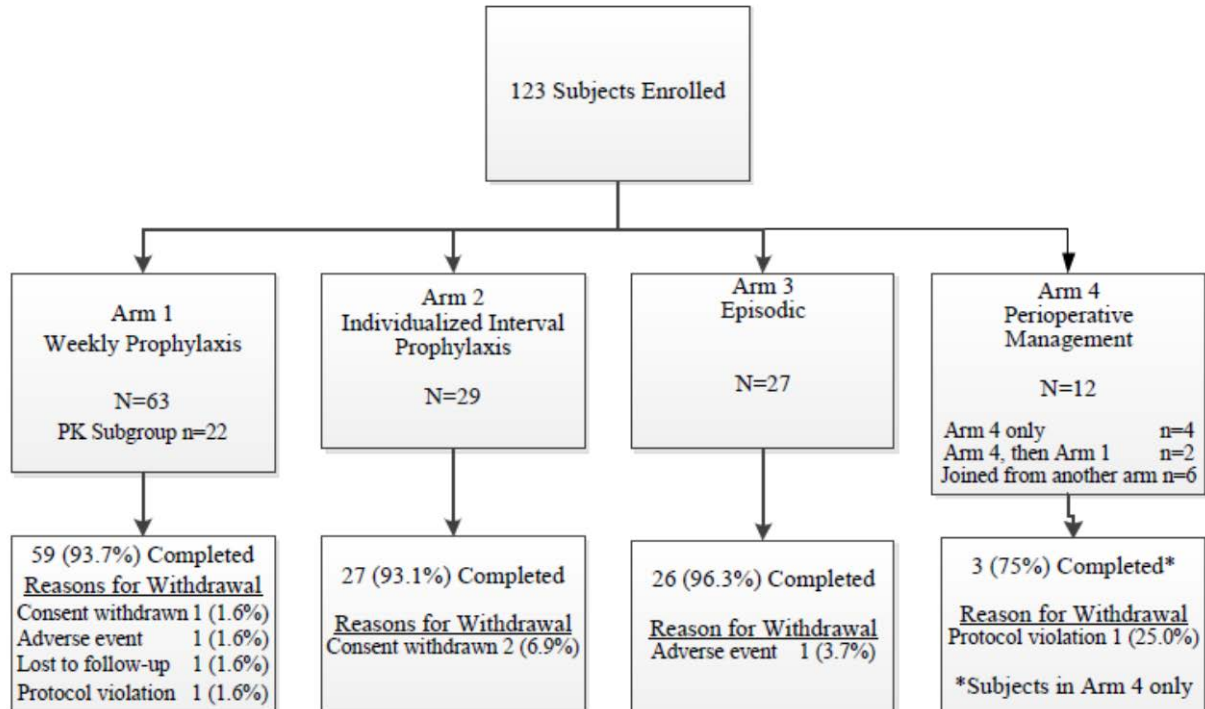
Recruitment

The first subject was treated with rFIXFc on 22 January 2010 and the last subject received the last dose on 19 July 2012. The last subject completed the study on 29 July 2012.

Conduct of the study

Five global protocol amendments and 1 administrative amendment were implemented during the course of this study.

Main amendments were:

Under Protocol Amendment 3: Primary objectives were added to further assess efficacy, starting dose, maximum dose and wash out periods were amended, PK timepoints were redefined, requirements to open Arm 4 to enrolment changed and definition of major surgery was clarified.

Under Protocol Amendment 4: the sample size was increased, definition of bleeding episodes and their management clarified, some of the scales for bleeds and surgery were revised.

Under Protocol Amendment 6: An additional interim analysis and further primary objectives were added. Sample size was also increased.

Protocol Deviations

There were subjects with deviations that were considered major: informed consent issues, investigational product (IP) issues, and subjects who took excluded medication. Informed consent issues included incomplete documentation of process, subject did not sign and date ICF/HIPAA, not completing all questions on the informed consent form, subjects initials not provided on all informed consent/HIPAA pages, site staff did not sign and date informed consent/HIPAA, incorrect informed consent version signed by the subject, procedures completed prior to informed consent process, subject not re-consented with revised informed consent/HIPAA in a timely manner, and approved informed consent/HIPAA manually altered. IP issues were incorrect treatment with study drug, primarily dosing non-compliance.

Six subjects (4.9%) were identified who had major deviations that were considered to have a potential impact on the primary efficacy endpoint. Of these 6 subjects, 2 did not participate in the efficacy period and as such were already excluded.

Baseline data

The *demographic profile* for subjects in the Safety Analysis Set was similar across all treatment arms. All subjects were male. The median age was 30 years (range 12 to 71 years), with 11 subjects (8.9%) 12 to 17 years old, 110 subjects (89.4%) 18 to 64 years old, and 2 subjects (1.6%) at least 65 years old. Of the subjects in the 12 to 17 year subgroup, 2 subjects were 12 years old, 2 were 14 years old, 3 were 15 years old, 1 was 16 years old, and 3 were 17 years old.

Of the 123 subjects enrolled, 73 (59.3%) were white, 29 (23.6%) were Asian, 10 (8.1%) were black, 10 (8.1%) were classified as other, and 1 (0.8%) was American Indian or Alaska Native. The median weight was 73.30 kg (range 45.0 to 186.7 kg) and median body mass index was 24.78 kg/m2 (range 15.2 to 49.6 kg/m2).

In general, the distribution of subjects was well balanced across the 3 main geographic regions of Europe (29.3%), North America (30.9%) and other countries (39.8%). When each region was examined by treatment arm, there were a smaller percentage of subjects in Arm 3 from Europe (7.4%) as compared with Arm 1 (33.3%) and Arm 2 (41.4%). At study entry, HIV status was positive in 9 subjects (7.3%) and HCV status was positive in 70 subjects (56.9%). HCV history was comparable and HIV history varied from 3.4% to 16.7% across treatment arms.

Baseline disease characteristics were representative of a population with severe haemophilia B. All subjects had a baseline FIX level ≤2%, 50.4% of subjects had target joints, and 40.2% of subjects had been treated with a prophylactic regimen as their most recent regimen prior to receiving treatment in this study. The range of FIX genotypes was also representative, with the most common mutations being

missense (55.3%) and nonsense (18.7%). Treatment arms were examined for a balanced distribution of hHaemophilia history. There was a similar distribution in Arms 1 and 2 for prior treatment with prophylaxis (53.2% and 51.7%, respectively). All subjects in Arm 3 were previously treated with an episodic regimen at study entry. When the number of bleeding episodes within the last 12 months was examined by prior regimen, the median number of bleeding episodes reported in the subjects on a prior episodic regimen in Arms 1 and 2 was greater than the median number of bleeding episodes reported in subjects in Arm 3. The median number of bleeding episodes reported in subjects on a prior prophylaxis regimen was similar in Arms 1 and 2.

Of the 123 subjects in the Full Analysis Set, the following 9 subjects did not contribute data for the efficacy period: 2 subjects in Arm 1, 3 subjects in Arm 2, and 4 subjects in Arm 4. The reasons for exclusion were as follows: 2 subjects received only 5K rFIXFc, 2 subjects withdrew after their PK evaluations, 1 subject had a single prophylaxis dose following his PK evaluation and withdrew from the study (no efficacy assessments could be made from a single dose), and 4 of the 6 subjects who entered directly into Arm 4 did not transition to Arm 1, 2, or 3 following their surgical/rehabilitation period.

Numbers analysed

Analysis Populations

The All-Enrolled Analysis Set was defined as subjects who were registered as enrolled by IXRS and assigned a unique subject identification number.

The Full Analysis Set (FAS) was defined as subjects who received at least 1 dose of rFIXFc. The analysis of efficacy was performed in this population. Subjects who received a dose of BeneFIX, but did not receive any rFIXFc were not included in this population.

The Safety Analysis Set was defined as subjects who received at least 1 dose of BeneFIX or at least 1 dose of rFIXFc. The analysis of safety was performed in this population.

The Pharmacokinetic Analysis Set (PKAS) is described in the PK part of this AR.

Efficacy endpoints were analyzed for 114 subjects (61 in Arm 1, 26 in Arm 2, and 27 in Arm 3).

Of the 123 subjects in the Full Analysis Set, the following 9 subjects did not contribute data for the efficacy period: 2 subjects in Arm 1, 3 subjects in Arm 2, and 4 subjects in Arm 4. The reasons for exclusion were as follows: 2 subjects received only 5K rFIXFc, 2 subjects withdrew after their PK evaluations, 1 subject had a single prophylaxis dose following his PK evaluation and withdrew from the study (no efficacy assessments could be made from a single dose), and 4 of the 6 subjects who entered directly into Arm 4 did not transition to Arm 1, 2, or 3 following their surgical/rehabilitation period.

Outcomes and estimation

Routine Prophylaxis

- The **weekly dose** of rFIXFc for subjects on **weekly prophylaxis** (**Arm 1**) decreased from the starting regimen of 50 IU/kg to a median of **45.17** IU/kg (range **25.0** to **74.3** kg IU/kg) when averaged over all eligible doses administered during the efficacy period. The median dose when calculated for the last 6 months on study in subjects on study for at least 9 months (40.70 IU/kg, range 21.3 to 82.7 IU/kg) was similar to the median dose for the last 3 months on study in subjects on study for at least 6 months (40.52 IU/kg, range 16.7 to 87.6 IU/kg), when averaged over all eligible doses administered during the respective time intervals. The median number of prescribed dose changes was 1.

Table 17: Summary of prophylactic dose for subjects in Arm 1 - Full analysis set

```
                                              Arm 1 - Fixed weekly interval
                                                       (N=63)

Total number of prescribed dose changes per subject
    0                                             11 ( 18.0%)
    1                                             25 ( 41.0%)
    2                                             16 ( 26.2%)
    3                                              7 ( 11.5%)
    4                                              1 (  1.6%)
    > 4                                            1 (  1.6%)

    n                                             61
    Mean                                          1.4
    SD                                            1.07
    Median                                        1.0
    Min, Max                                      0, 5


Footnotes are listed on the last page.

SOURCE: FACTOR9HB/998HB102/CSR/T-PROPHDOSE-ARM1.SAS           DATE: 07DEC2012
```

- The dosing interval of rFIXFc for subjects on individualized interval prophylaxis (Arm 2) started at 10 days, with a median interval when averaged over all eligible dosing intervals during the efficacy period of 12.53 days (range 7.8 to 15.9 days). The median dosing interval calculated for the last 6 months on study (in subjects on study for at least 9 months) was 13.81 days (range 7.8 to 19.1 days), and for the last 3 months on study (in subjects on study for at least 6 months) was 14.00 days (range 7.7 to 20.8 days) when averaged over all eligible dosing intervals during the respective time intervals. The median number of prescribed interval adjustments was 2. A total of 12 subjects (46.2%) achieved a dosing interval of 14 days or longer for the last 6 months on study (in subjects on study for at least 9 months) and 14 subjects (53.8%) achieved this for the last 3 months on study (in subjects on study for at least 6 months).

Table 18: Summary of prophylactic dosing interval for subjects in Arm 2 - Full analysis set

```
                                              Arm 2 - Individualized interval
                                                       (N=29)

Total number of prescribed dosing interval changes per subject
    0                                              1 (  3.8%)
    1                                             10 ( 38.5%)
    2                                              6 ( 23.1%)
    3                                              6 ( 23.1%)
    4                                              2 (  7.7%)
    > 4                                            1 (  3.8%)

    n                                             26
    Mean                                          2.0
    SD                                            1.22
    Median                                        2.0
    Min, Max                                      0, 5


Footnotes are listed on the last page.

SOURCE: FACTOR9HB/998HB102/CSR/T-PROPHDOSE-ARM2.SAS           DATE: 07DEC2012
```

- For subjects in Arm 1, the median monthly prophylactic dose was 193.57 IU/kg, and the median annualized consumption was 2447.11 IU/kg. For subjects in Arm 2, the median monthly prophylactic dose was 244.66 IU/kg, and the median annualized consumption was 3156.77 IU/kg. Consumption of rFIXFc appears broadly comparable with other FIX products. However, a calculation of total annualized consumption for treatment arms 1- 3 is missing and should be provided.

- The annualized bleeding rate estimated by the negative binomial model was 3.12 on weekly prophylaxis (Arm 1), 2.40 on individualized interval prophylaxis (Arm 2), and 18.67 on episodic treatment. This corresponded to reductions in estimated annualized bleeding rate of 83% (Arm 1) and 87% (Arm 2) as compared to on demand (episodic) treatment (Arm 3).

Table 19: Comparison of Annualized Bleeding Episodes – Negative Binomial Model

	Arm 1 (N=63)	Arm 2 (N=29)	Arm 3 (N=27)
Number of subjects	61	26	27
Negative binomial model estimated annualized number of bleeding episodes per subject (95% CI) (a)	3.12 (2.46, 3.95)	2.40 (1.67, 3.47)	18.67 (14.01, 24.89)
Negative binomal model bleeding rate ratio (95% CI) (b)	0.17 (0.11, 0.24)	0.13 (0.08, 0.20)	
Negative binomal model p-value (b)	<0.001	<0.001	

- The mean bleeding rates based on observed data (3.07, 2.45, and 18.70 in Arms 1, 2, and 3, respectively) were comparable to the rates estimated from the negative binomial model.

- The mean bleeding rates based on observed data for subjects on a prior episodic regimen were 3.16, 2.07, and 18.70 for subjects in Arms 1, 2, and 3, respectively, and are comparable to the rates estimated from the negative binomial model.

- The mean bleeding rates based on observed data for subjects on a prior prophylactic regimen were 2.99 and 2.83 for subjects in Arms 1 and 2, respectively, and are comparable to the rates estimated from the negative binomial model.

Treatment of Bleeding Episodes

- Across Arms 1, 2, and 3, there were 636 bleeding episodes during the efficacy period. Overall, 97.3% of bleeding episodes were controlled with 2 or fewer injections of rFIXFc, with 90.4% controlled by 1 injection. No bleeding episodes required more than 3 injections.

- A total of 714 rFIXFc injections were administered to treat the 636 bleeding episodes. Of these, 566 rFIXFc injections (82.0%) were rated by subjects as producing an excellent or good response, and 110 rFIXFc injections (15.9%) were rated as moderate. Of the 613 first injections evaluated for response, 513 first injections (83.7%) were rated by subjects as excellent or good, 90 (14.7%) were rated as moderate, and 10 (1.6%) were rated as having had no response. The assessment of the haemostatic response to injections for bleeding episodes should be provided for mild, moderate and severe bleedings from all treatment arms.

- The median dose per injection to treat a bleeding episode in Arms 1, 2, and 3 was 47.1 IU/kg, 44.8 IU/kg, and 46.0 IU/kg, respectively. The median total dose per bleeding episode was 51.5 IU/kg for subjects in Arm 1, 49.6 IU/kg for subjects in Arm 2, and 46.6 IU/kg for subjects in Arm 3.

Table 20: Summary of Number of Injections Required for Resolution of a Bleeding Episode

Method of analysis	Arm 1 (N=63)	Arm 2 (N=29)	Arm 3 (N=27)	Total (N=119)
Per bleeding episode (a)				
1	142 (85.0%)	57 (85.1%)	376 (93.5%)	575 (90.4%)
2	15 (9.0%)	8 (11.9%)	21 (5.2%)	44 (6.9%)
3	10 (6.0%)	2 (3.0%)	5 (1.2%)	17 (2.7%)
4	0	0	0	0
>4	0	0	0	0
1	142 (85.0%)	57 (85.1%)	376 (93.5%)	575 (90.4%)
>1	25 (15.0%)	10 (14.9%)	26 (6.5%)	61 (9.6%)
<=2	157 (94.0%)	65 (97.0%)	397 (98.8%)	619 (97.3%)
>2	10 (6.0%)	2 (3.0%)	5 (1.2%)	17 (2.7%)
n (b)	167	67	402	636
Mean	1.2	1.2	1.1	1.1
SD	0.54	0.46	0.31	0.40
Median	1.0	1.0	1.0	1.0
25th, 75th percentile	1.0, 1.0	1.0, 1.0	1.0, 1.0	1.0, 1.0
Min, Max	1, 3	1, 3	1, 3	1, 3

Footnotes are listed on the last page.

SOURCE: FACTOR9HB/998HB102/CSR/IN-T-NUMINJ.SAS   DATE: 10DEC2012

Perioperative Management

- Investigators'/Surgeons' assessments of hemostasis during surgery were excellent or good in 100% of the 14 major surgeries in 12 subjects.

- A total of 12 of the 14 major surgeries (85.7%) required only 1 injection to maintain hemostasis during the surgery, with a median dose per injection of 90.91 IU/kg (range 49.4 to 142.3 IU/kg).

- Median total rFIXFc consumption was 146.1 IU/kg on the day of surgery, 164.6 IU/kg on Day 1 to Day 3 after surgery, and 277.1 IU/kg on Day 4 to Day 14 after surgery.

Table 21: Surgery Arm: Total rFIXFc Consumption (IU/kg) per Major Surgery

	Arm 4 – Surgery (N=12)
On the day of surgery	
n (a)	14
Mean	148.90
SD	62.966
Median	146.08
Min, Max	51.3, 264.5
Days 1-3 post surgery	
n (a)	14
Mean	150.14
SD	55.903
Median	164.63
Min, Max	51.3, 238.4
Days 4-14 post surgery	
n (a)	13
Mean	312.62
SD	240.576
Median	277.06
Min, Max	0.0, 906.8

Footnotes are listed on the last page.

SOURCE: FACTOR9HB/998HB102/CSR/T-SRG-RFIX.SAS   DATE: 07DEC2012

	Arm 4 – Surgery (N=12)
Days 1-14 post surgery	
n (a)	14
Mean	440.43
SD	280.212
Median	432.33
Min, Max	98.6, 1084.7
Overall surgical/rehabilitation period (b)	
n (a)	14
Mean	1728.31
SD	1818.747
Median	1231.84
Min, Max	174.8, 6691.1

Footnotes are listed on the last page.

SOURCE: FACTOR9HB/998HB102/CSR/T-SRG-RFIX.SAS   DATE: 07DEC2012

- A total of 15 minor surgeries were performed in 13 subjects while they were receiving rFIXFc treatment. The majority of subjects were treated with a single injection on the day of surgery (range 39.7 IU/kg to 103.6 IU/kg) prior to the procedure. Hemostasis was assessed as excellent or good in 11 minor surgeries, fair for 1 minor surgery, and not provided in 3 surgeries.

Ancillary analyses

Post hoc analysis comparing pre-study with on-study bleeding rates

Table 22: Summary of Bleeding Episodes, Monthly Consumption and Injections in the 12 Months Prior to Study and On-study for Subjects in Study 998HB102 Arms 1 and 2 Who Were on a Prophylaxis Regimen Prior to the Study Full Analysis Set

		Arm 1 Weekly Prophylaxis (N=63)	Arm 2 Individualised Interval Prophylaxis (N=29)	Total Prophylaxis (N=92)
Annualized bleeding rate (a)	n	29	10	39
Pre-study	Mean (SD)	4.83 (6.006)	2.50 (2.369)	4.23 (5.383)
	Median	2.00	1.50	2.00
	25th, 75th percentile	1.00, 6.00	1.00, 4.00	1.00, 6.00
	Min, Max	0.0, 21.0	0.0, 7.0	0.0, 21.0
On-study	Mean (SD)	2.60 (2.546)	1.63 (2.771)	2.35 (2.603)
	Median	2.10	0.00	1.13
	25th, 75th percentile	0.00, 4.01	0.00, 2.30	0.00, 4.01
	Min, Max	0.0, 9.5	0.0, 7.6	0.0, 9.5

In the Phase 3 study in adults and adolescents ≥12 years of age (Study 998HB102), of the 39 subjects who received prior prophylaxis, the mean annualized bleeding rates were 4.23 prestudy and 2.35 on-study. In Arm 1, mean annualized bleeding rates were 4.83 prestudy and 2.60 on-study; and in Arm 2, mean annualized bleeding rates were 2.50 prestudy and 1.63 on-study.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23:

Title: An open-label, multicenter evaluation of safety, pharmacokinetics, and efficacy of recombinant, long-acting coagulation factor IX Fc fusion protein (rFIXFc) in the prevention and treatment of bleeding in previously treated subjects with severe haemophilia B		
Study identifier	998HB102	
Design	Open-label multicenter study	
	Duration of main phase:	72 weeks
Hypothesis	To determine the clinical efficacy of rFIXFc in the treatment of bleeding, in routine prophylaxis, and in perioperative management; and to confirm the prolonged half-life observed in the Phase 1/2a	
Treatments groups	Arm1; weekly prophylaxis	50 IU/Kg once every 7 days, 63 patients
	Arm 2; individualized interval prophylaxis	100IU/kg once every 10 days, 29 patients
	Arm 3; episodic regimen	20-100 IU/kg, 27 patients

	Arm 4 perioperative management		40-100IU/kg as needed for surgical prophylaxis, 12 patients	
Endpoints and definitions	Primary endpoint	Safety	Incidence of inhibitors development	
		Efficacy	Number of bleeding episodes per subject annualized over study period, comparison between Arma1, and 2 versus 3	
	Secondary Prophylaxis efficacy		Dose per injection for subjects in Arm 1, dosing interval for subject in Arm 2	
	Secondary Efficacy to stop the bleeding		Number of injections and dose per injection required to stop a bleeding episode	
	Secondary Perioperative management		Surgeon´s assessment of subject's response to surgery Consumption to maintain hemostasis Blood loss during surgery Number of transfusion required	
Database lock	The last subject completed the study on 29 July 2012			

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	FAS; subjects who received at least 1 dose of rFIXFc			
Descriptive statistics and estimate variability	Treatment group	Arm 1	Arm2	Arm 3
	Number of subject	63	29	27
	ABR	2.95 (IQR range 1.01-4.35)	1.38 (IQR range 0.00-3.43)	17.69 (IQR range 10.77-23.24)
	Median (Range) Prophylactic dose	45.17IU/Kg (25.0IU/Kg-74.3IU/Kg)	12.53 days (7.8 days-15.9 days	

	Median dose per injection to stop the bleeding event	47.1 IU/Kg	44.8IU/kg	46.0IU/kg
	Median total dose to stop the bleeding event	51.5IU/kg	49.6IU/kg	46.6IU/kg
	Haemostatic response in 14 major surgery	13 out 14 surgeries excellent , 1 surgery as good		
	Blood loss during 14 major surgery	100ml		
	Transfusion during 14 major surgeries	2		
Effect estimate per comparison	Primary endpoint	Arm 1 versus Arm 2		Arm 2 versus Arm 3
		0.17 (83% of reduction)		0.13 (87% of reduction)
		p<0.05		P<0.5

Trial 9HB02PED

Methods

The Phase 3 study in children <12 years of age (9HB02PED) was an open-label, multicenter study evaluating the safety, PK, and efficacy of rFIXFc in pediatric male PTPs with severe haemophilia B who had at least 50 EDs to FIX products prior to enrollment. The primary objective of the study was to evaluate the safety of rFIXFc in pediatric PTPs with haemophilia B. Secondary objectives of the study were to evaluate the efficacy and PK of rFIXFc and rFIXFc consumption in the prevention and treatment of bleeding episodes.

Figure 9:
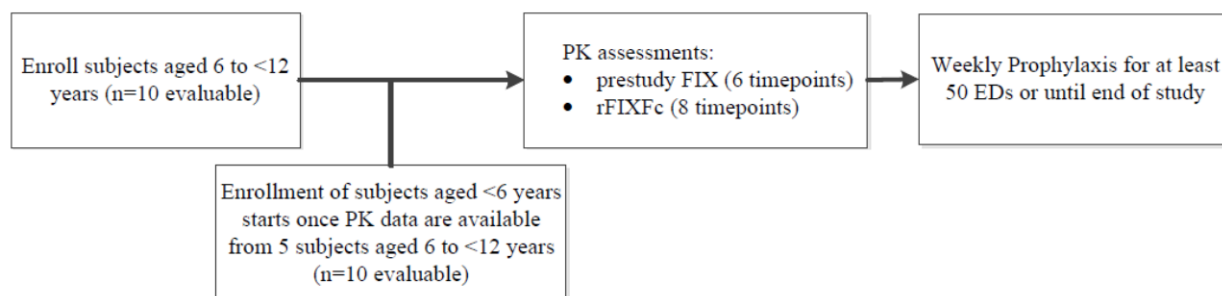
<u>Prophylaxis</u>

After completing the PK assessments, subjects began weekly prophylactic treatment with rFIXFc for approximately 50 weeks, to obtain 50 EDs. One ED was defined as a 24-hour period in which a subject received 1 or more doses of rFIXFc, with the time of the first injection of rFIXFc defined as the start of the ED.

The starting dose regimen for this study was rFIXFc administered weekly at 50 to 60 IU/kg. The dose could be increased to a maximum of 100 IU/kg, and the frequency of administration could be increased to a maximum of twice weekly, based on the subject's enrollment PK data, subsequent FIX trough and peak levels, level of physical activity, and bleeding pattern, in accordance with local standards of care for a prophylactic regimen.

<u>Treatment of Bleeding Episodes</u>

The dose of rFIXFc to treat a bleeding episode was based on the subject's clinical condition, known PK information, type and severity of the bleeding event, and input from the Sponsor, if necessary. Subjects' caregivers were provided with a dosing guideline and instructed to treat at the first sign of a bleeding episode and with a single dose of rFIXFc.

<u>Surgery (Perioperative Management)</u>

Surgery was only allowed in the study after rFIXFc PK assessments had been completed and the subject had at least 3 EDs to rFIXFc without safety concerns. If a subject needed to undergo surgery prior to 3 EDs, he was withdrawn from the study. Bleeding caused directly by surgery was not reported, although undesired or unexpected bleeding during or after surgery was recorded on the eCRF.

Study participants

<u>Inclusion Criteria</u>

To be eligible to participate in this study, candidates must have met the following eligibility criteria at the time of screening.

1. Ability of parent or legal guardian to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations. Subjects could provide assent in addition to the parental/guardian consent, if appropriate.

2. Male, <12 years of age at time of informed consent, and weight $\geq$ 13 kg.

3. Severe haemophilia B defined as $\leq$ 2 IU/dL ($\leq$ 2%) endogenous FIX as documented in medical records from a local clinical laboratory demonstrating $\leq$ 2% FIX:C or a documented genotype known to produce severe haemophilia B.

4. Previously treated subject, defined as having at least 50 documented EDs to any recombinant or plasma-derived FIX product including prothrombin complex concentrate (blood products including fresh frozen plasma treatment were not considered in the count of the documented EDs).

5. If known to be HIV positive, the following laboratory values were required, based on results within last 6 months:

      a. platelet count $\geq$ 100,000 platelets/μL

      b. CD4 count $\geq$ 200 cells/μL

      c. viral load of <400 copies/mL

6. No history of, or currently detectable, inhibitor. This included the following:

 a. at least 2 negative inhibitor tests from the reporting laboratory

 AND/OR

 normal recovery tests within the first 50 EDs to FIX products

 AND

 b. absence of clinical signs of decreased response to FIX administrations

The historical positive inhibitor test was defined as per local laboratory Bethesda value for a positive inhibitor test (i.e., equal to or above lower level of detection). Family history of inhibitors did not exclude the subject.

7. No measurable inhibitor activity at the Screening Visit, measured using the Nijmegen-modified Bethesda assay performed at the central laboratory.

8. Willingness and ability of the subject's parent or legal guardian to complete training in the use of the study electronic patient diary (EPD) and to use the EPD throughout the study.

Exclusion Criteria

Candidates were excluded from study entry if any of the following exclusion criteria existed at the time of screening.

1. Other coagulation disorder(s) in addition to haemophilia B.

2. History of anaphylaxis associated with any FIX or IV immunoglobulin administration.

3. Active renal disease (per the discretion of the Investigator and medical records).

4. Active hepatic disease (per the discretion of the Investigator and medical records).

5. Any concurrent clinically significant major disease that, in the opinion of the Investigator, made the subject unsuitable for enrolment.

6. Current systemic treatment with chemotherapy and/or other immunosuppressant drugs, with the following exceptions: use of steroids for treatment of asthma or management of acute allergic episodes, and routine immunizations.

7. Participation within the past 30 days in any other clinical study involving investigational drugs.

8. Surgery within 30 days prior to the Screening Visit (visit can be rescheduled and subject screened).

Treatments

Prophylaxis

rFIXFc was injected intravenously over several minutes. The starting dose regimen for this study was rFIXFc administered weekly at 50 to 60 IU/kg. The dose could be increased to a maximum of 100 IU/kg, and the frequency of administration could be increased to a maximum of twice weekly, based on the subject's enrollment PK data, subsequent FIX trough and peak levels, level of physical activity, and bleeding pattern, in accordance with local standards of care for a prophylactic regimen.

Dose and interval adjustments were made as follows:

- The dose could be increased or decreased in increments of at least 10 IU/kg.

- The maximum prophylactic dose that was given was 100 IU/kg/injection.

- If weekly dosing at 100 IU/kg was not adequate, the dosing interval could be shortened based on the subject's rFIXFc PK results, FIX trough level, and clinical bleeding profile.

- The maximum dosing frequency was twice weekly.

- The minimum dosing frequency was once weekly.

The maximum dose for routine prophylaxis and treatment of bleeding episodes was 100 IU/kg, although higher doses of up to 150 IU/kg could be used to achieve FIX activity to prevent bleeding (e.g., for surgery).

Additional visits could be scheduled at the Investigator's discretion to repeat measurement of trough levels, if further dose adjustments were needed.

<u>Treatment of Bleeding Episodes</u>

The dose of rFIXFc to treat a bleeding episode was based on the subject's clinical condition, known PK information, type and severity of the bleeding event, and input from the Sponsor, if necessary.

Subjects' caregivers were instructed to treat at the first sign of a bleeding episode and with a single dose of rFIXFc:

Table 24: Dosing Guidelines for rFIXFc Therapy in haemophilia B

Type of Hemorrhage	Factor IX Level Required (%)	Frequency of Doses (hrs)
Minor		
Epistaxis	25-30	48
Hemarthroses, uncomplicated	25-30	48
Superficial muscular	25-30	48
Superficial soft tissue	25-30	48
Moderate		
Epistaxis	35-50	48
Intramuscular with dissection	35-50	48
Soft tissue with dissection	35-50	48
Mucous membranes	35-50	48
Dental extractions	35-50	48
Hematuria	35-50	48
Hemarthroses, with limited motion	45-80	48
Major		
Epistaxis	60-100	24-48
Pharynx	60-100	24-48
Retropharynx	60-100	24-48
Retroperitoneum	60-100	24-48
Surgery	60-100	24-48
Central Nervous System	60-100	24-48

Caregivers should consult with the Investigator but subjects should be administered only 1 follow-up dose within 24 to 48 hours after the initial dose.

<u>Treatment of Subjects Undergoing Surgery (Perioperative Management)</u>

Surgery was only allowed in the study after rFIXFc PK assessments had been completed and the subject had at least 3 EDs to rFIXFc without safety concerns. If a subject needed to undergo surgery prior to 3 EDs, he was withdrawn from the study. Surgeries, elective or emergent, were classified as major and minor as follows:

- Major surgery was defined as any surgical procedure in which a major body cavity was penetrated and exposed, or for which a substantial impairment of physical or physiological function was produced (e.g., laparotomy, thoracotomy, craniotomy, joint replacement, or limb amputation).

- Minor surgery was defined as any surgical procedure that did not typically involve general anesthesia and/or respiratory assistance (e.g., minor dental extractions, incision, and drainage of abscess, or simple excisions).

Objectives

Primary objective:

- To evaluate the safety of recombinant coagulation factor IX Fc fusion protein (rFIXFc) in previously treated pediatric subjects with haemophilia B.

Secondary objectives:

- To evaluate the efficacy of rFIXFc for prevention and treatment of bleeding episodes.

- To evaluate and assess the pharmacokinetics (PK) of rFIXFc.

- To evaluate rFIXFc consumption for prevention and treatment of bleeding episodes.

Outcomes/endpoints

Primary Endpoint

- Occurrence of inhibitor development

Secondary Endpoints

Efficacy Endpoints

- The annualized number of bleeding episodes per subject

- The annualized number of spontaneous joint bleeding episodes per subject

- Assessments of response to treatment with rFIXFc for bleeding episodes, using the 4-point bleeding response scale

- Total annualized rFIXFc consumption per subject for prevention of bleeding episodes

- Total annualized rFIXFc consumption per subject for treatment of bleeding episodes

- Time from last injection of rFIXFc to the bleeding episode

- Number of injections and dose per injection of rFIXFc required to resolve a bleeding episode

Sample size

The determination of the number of subjects was based on clinical rather than statistical considerations. Taking into account the Committee for Proprietary Medicinal Products (CHMP) Note for Guidance [EMA

(EMA/CHMP/BPWP/144552/2009) 2011], approximately 26 subjects (approximately 13 in each age cohort) would be dosed with rFIXFc to achieve a minimum of 10 subjects in each age cohort (<6 years and 6 to <12 years) with at least 50 EDs and adequate prestudy FIX and rFIXFc PK data. This allowed for an approximate 20% dropout rate.

Randomisation

This was a single arm trial.

Blinding (masking)

This was an open-label study.

Statistical methods

Analysis Sets

The Full Analysis Set (FAS) was defined as all subjects who received at least 1 dose of rFIXFc. Analyses of efficacy, patient reported outcomes, and health outcomes were performed in this population.

The Safety Analysis Set was defined as all subjects who received at least 1 dose of their prestudy FIX treatment for the purpose of evaluating PK or at least 1 dose of rFIXFc.

Statistical Analysis of Haemostatic Efficacy Endpoints

Annualized Bleeding Rate

The annualized bleeding rate was summarized using descriptive statistics for each age cohort and overall for the FAS. All types of bleeding episodes (spontaneous, traumatic, and type unknown) were included in determining the annualized number.

The per-subject annualized bleeding rate was calculated for each subject using the following

formula:

$$\text{Annualized bleeding rate} = \frac{\text{Number of bleeding episodes during the efficacy period}}{\text{Total number of days during the efficacy period}} \times 365.25$$

Prestudy and On-study Comparison for Routine Prophylaxis

The comparison of ABR between prestudy and on-study will be assessed using a repeated negative binomial model for the FAS. The log of the efficacy period in years will be fitted as an offset variable. An unstructured covariance matrix is used to model the correlation among repeated measures. The data will be presented by age cohort and overall. The model will have the total number of bleeding episodes during the efficacy period as the dependent variable and group, period (prestudy, on-study) and group-by-period interaction as fixed effects. The group variable has 4 levels for the analysis by age cohort: <6 years old on prophylaxis prestudy regimen, <6 years old on episodic prestudy regimen, 6 to <12 years old on prophylaxis prestudy regimen, and 6 to <12 years old on episodic prestudy regimen. For the overall analysis, the group variable has 2 levels: prophylaxis and episodic prestudy regimens.

Assessments of Response to rFIXFc Injections for Bleeding

Each subject's caregiver provided an assessment of response to each administration of rFIXFc for each bleeding episode using the 4-point scale of excellent, good, moderate, and none.

Response categories of excellent and good were presented combined as well as individually. The number and percentage of injections in each response category were tabulated based on all injections. Two summaries are provided; in the first summary percentages were based on the total number of injections

administered for bleeding episodes for which a response was provided, and in the second summary percentages were based on the total number of bleeding episodes whether or not a response was provided.

Results

Participant flow

Figure 10: Overview of Subject Disposition (N=30 Subjects Enrolled)
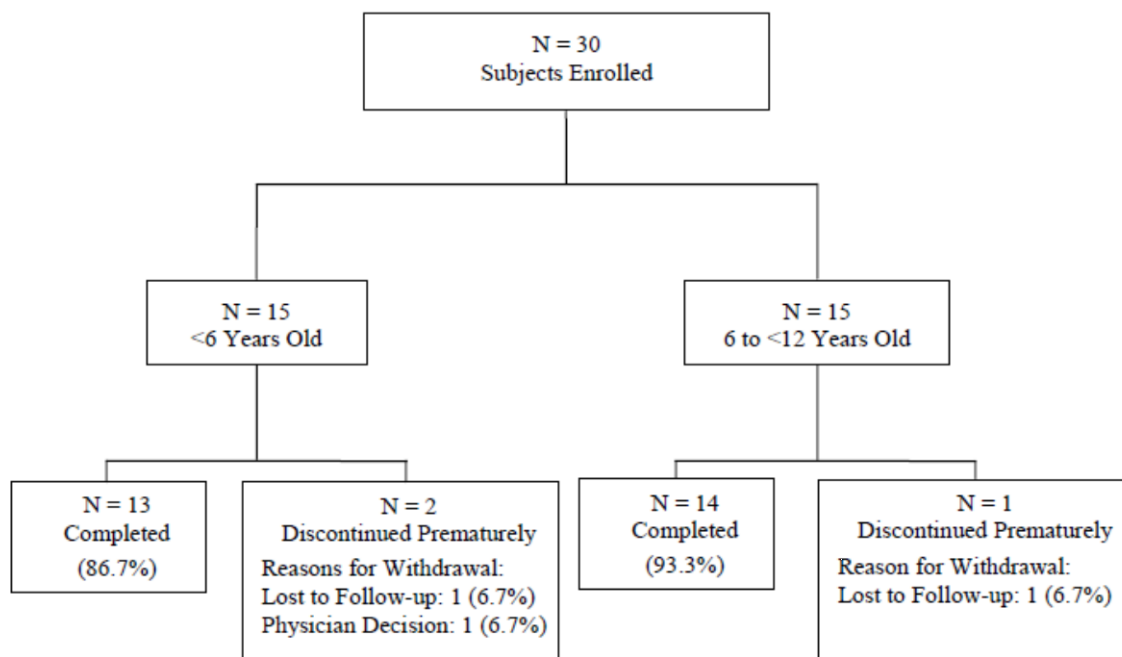
Recruitment

The first subject enrolled and received his first baseline prestudy dose of FIX on 11 May 2012. The first PK dose of the study drug, rFIXFc, was administered on 08 June 2012. In total, 30 subjects enrolled into study (15 subjects in the <6 years of age cohort and 15 subjects in the 6 to <12 years of age cohort). All 30 subjects received study drug rFIXFc. Subjects were assigned to the appropriate age cohort (<6 years of age or 6 to <12 years of age) at the time of enrollment and were analyzed in that same age cohort throughout the duration of the study. The last subject received his last dose of rFIXFc on 24 November 2014. The last subject completed the study on 24 November 2014.

Conduct of the study

Changes in the Conduct of the Study

Two global protocol amendments were implemented during the course of this study.

Protocol Amendment 1:

The primary reason for this amendment was to minimise the number of pre-study FIX PK assessments.

Protocol Amendment 2:

The primary reasons for this amendment were: to add interim PK analyses required regionally, to recategorize patient reported outcomes to exploratory endpoints and increase the sample size.

Protocol Deviations

There were subjects with deviations that were considered major. These deviations included: informed consent issues and deviations categorised as other criteria.

Every deviation associated with the completion of the ICF or the process of consent was considered major, regardless of the nature of the deviation. The majority of informed consent issues were administrative in nature, such as subjects not being re-consented with an updated ICF at the next scheduled study visit or subjects not signing assent forms prior to Screening.

There were major deviations characterized as "other" which included: improper delegation of activities, training delays, delayed submission of amendments and improper reporting of SAEs. No subjects were identified as having protocol deviations with a potential impact on the annualized bleeding rate.

Baseline data

At study entry, all 30 subjects had previously been treated prophylactically. Of these, 6 subjects (20.0%) reported a dosing frequency of 1 injection per week, 21 (70.0%) reported 2 injections per week, and 1 (3.3%) reported 3 injections per week. The remaining 2 subjects reported dosing frequencies of every 3 days (1 subject) and every 4 days (1 subject). All of the subjects dosed once weekly were in the <6 years of age cohort. The majority of subjects (16 [53.3%]) were on a prophylactic regimen of FIX for longer than 12 months prior to study entry, with a further 9 subjects (30.0%) on prophylaxis for between 6 and 12 months.

Demographic factors and baseline characteristics: All subjects were male. The median overall age was 5.0 years (range, 1 to 11 years): in the <6 years of age cohort, the median age was 2.0 years (range, 1 to 4 years), and in the 6 to <12 years of age cohort, the median age was 8.0 years (range, 6 to 11 years). The median weight was 15.60 kg (range, 13.5 to 25.4 kg) for subjects <6 years of age and 32.05 kg (range, 20.7 to 54.5 kg) for subjects 6 to <12 years of age. The predominant races represented in the study were white (73.3%) and Asian (16.7%). The main geographic areas represented were North America (46.7%) and Europe (36.7%); 16.7% of the study population was from other geographic areas, which included Australia and South Africa.

All enrolled subjects had severe haemophilia. A total of 25 subjects (83.3%) had a historical FIX activity of <1% and 5 subjects (16.7%) had historical FIX levels of 1% to 2%. Genotype data were determined for all 30 subjects. The distribution of genotypes was representative of a population with severe haemophilia B, i.e. the majority of subjects had missense mutations (13 subjects, 43.3%) or nonsense mutations (11 subjects, 36.7%). A family history of inhibitors was reported in 1 subject (in the <6 years of age cohort).

As would be expected for this pediatric population, there were no enrolled subjects who were known to be positive for HIV or HCV. All subjects were treated prophylactically prior to study entry. In the 12 months prior to the study, the median estimated total number of bleeding episodes across the overall study population was 2.5 (range: 0 to 72), with the majority of subjects (80.0%) experiencing 5 or fewer bleeding episodes. The median estimated number of bleeding episodes in the previous 12 months was 3.0 (range: 0 to 17) in the <6 years of age cohort and 2.0 (range: 0 to 72) in the 6 to <12 years of age cohort.

Summary of main efficacy results

Prophylaxis

The median average dosing interval during the Efficacy Period was 6.99 days (range: 5.9 to 10.8 days), with no difference in median average dosing interval between cohorts. The median average dosing interval calculated for the last 3 months on study (in subjects on study for at least 6 months) was 6.98 days for the FAS (range: 5.0 to 76.8), the <6 years of age cohort (range: 6.8 to 76.8), and the 6 to <12 years of age cohort (range: 5.0 to 10.1). The majority of subjects (29 subjects; 96.7%) made no changes to their prescribed dosing interval over the course of the study. The median number of prescribed interval adjustments was 0.0 (range: 0 to 1).

Table 25: Summary of last prescribed dose and dosing frequency, age cohort <6 years old (N=15)

Age cohort: <6 years old (N=15)

Dose (IU/kg)	Dosing frequency	
	Once weekly	Every 5 days
40	1 (6.7%)	0
50	4 (26.7%)	0
57	1 (6.7%)	0
60	5 (33.3%)	0
61	1 (6.7%)	0
64	1 (6.7%)	0
65	1 (6.7%)	0
70	1 (6.7%)	0
n	15	0
Mean	57.13	
SD	7.689	
Median	60.00	
Min, Max	40.0, 70.0	

NOTE: Percentages are based on the number of subjects treated with rFIXFc in each age cohort or overall.

SOURCE: FACTOR9HB/9HB02PED/CSR/T-LASTDOSE-FREQ.SAS   DATE: 03MAR2015

Table 26: Summary of last prescribed dose and dosing frequency, age cohort <12 years old (N=15)

Age cohort: 6 to <12 years old (N=15)

Dose (IU/kg)	Dosing frequency	
	Once weekly	Every 5 days
50	6 (40.0%)	0
60	6 (40.0%)	0
66	1 (6.7%)	0
69	1 (6.7%)	0
100	0	1 (6.7%)
n	14	1
Mean	56.79	100.00
SD	6.635	
Median	60.00	100.00
Min, Max	50.0, 69.0	100.0, 100.0

NOTE: Percentages are based on the number of subjects treated with rFIXFc in each age cohort or overall.

SOURCE: FACTOR9HB/9HB02PED/CSR/T-LASTDOSE-FREQ.SAS   DATE: 03MAR2015

The median average weekly dose of rFIXFc for subjects <6 years of age was 59.40 IU/kg (range: 31.0 to 68.6 IU/kg) across the study and 60.41 IU/kg (range: 5.4 to 72.1 IU/kg) over the last 3 months of the study for those who were in the study for at least 6 months. For subjects in the 6 to <12 years of age cohort, the median average weekly dose was 57.78 IU/kg (range: 46.5 to 110.1 IU/kg) across the study and 61.55 IU/kg (range: 37.1 to 142.7 IU/kg) over the last 3 months of the study for those who were in the study at least 6 months (Table 47).

Over half of subjects (63.3%) made no changes to their prescribed starting dose over the course of the study, and 30.0% made 1 dose change during the study. The median number of prescribed dose changes per subject was 0.0 (range: 0 to 2).

The mean annualized bleeding rate was 1.72 in the <6 years of age cohort, 2.80 in the 6 to <12 years of age cohort, and 2.26 in the total of both age cohorts.

Table 27: Summary of Annualized Bleeding Rates

	Age cohort		
	<6 years old (N=15)	6 to <12 years old (N=15)	Total (N=30)
Annualized bleeding rate (Episodes/Year)			
0	6 (40.0%)	4 (26.7%)	10 (33.3%)
>0-5	7 (46.7%)	9 (60.0%)	16 (53.3%)
>5-10	2 (13.3%)	2 (13.3%)	4 (13.3%)
>10-20	0	0	0
>20	0	0	0
Annualized bleeding rate per subject			
n	15	15	30
Mean	1.72	2.80	2.26
SD	1.933	3.172	2.639
Median	1.09	2.13	1.97
25th, 75th percentile	0.00, 2.90	0.00, 4.17	0.00, 3.13
Min, Max	0.0, 5.6	0.0, 10.0	0.0, 10.0

Footnotes are listed on the last page.

SOURCE: FACTOR9HB/9HB02PED/CSR/T-ABR.SAS   DATE: 03MAR2015

Overall, 10 subjects (33.3%) had no bleeding episodes reported during the Efficacy Period: 6 subjects (40.0%) in the <6 years of age cohort and 4 subjects (26.7%) in the 6 to <12 years of age cohort. No subjects had an annualized bleeding rate of more than 10 episodes per year.

Treatment of Bleeding Episodes

There were 60 bleeding episodes during the efficacy period. Overall, 91.7% of bleeding episodes were controlled with either 1 or 2 injections of rFIXFc, with 75.0% resolved with a single injection. No bleeding episodes required more than 3 injections.

A total of 80 injections were administered to treat the 60 bleeding episodes. Of the 67 rFIXFc injections evaluated for response, 60 (89.6%) were rated by subjects as producing an excellent or good response, 6 (9.0%) were rated as moderate, and 1 (1.5%) was rated as none. Of the 53 first injections evaluated for response, 47 first injections (88.7%) were rated by subjects as excellent or good, 5 (9.4%) were rated as moderate, and 1 (1.9 %) was rated as none. Of the 5 first injections assessed as moderate, 2 of the 5 bleeding episodes were controlled with a single injection. A total of 15 bleeding episodes in 8 subjects required a second injection. However, the applicant is asked to clarify why an unusually high percentage of injections 13/80 (16.25 %) were not evaluated for response.

Of the 80 injections administered to treat bleeding episodes, analysis per bleeding episode showed that 1 injection of rFIXFc was adequate to resolve 86.4% of bleeding episodes in the <6 years of age cohort, 68.4% in the 6 to <12 years of age cohort, and 75.0% for the total of both age cohorts. The majority were resolved by 2 or fewer injections (95.5%, 89.5% and 91.7% of subjects <6 years of age, subjects 6 to <12 years of age, and the total of both age cohorts, respectively). The applicant is asked to provide the assessment of bleeding events summarized by mild, moderate and severe bleeds.

The median average dose per injection to treat a bleeding episode was 63.51 IU/kg. The median total dose per bleeding episode was 68.22 IU/kg.

Perioperative Management

No major surgeries were performed during the study. Three minor surgeries in 2 subjects were performed while they were receiving rFIXFc treatment (1 in the <6 years of age cohort and 2 in the 6 to <12 years of age cohort). Investigators' assessments of hemostasis during minor surgery were excellent in all 3 minor surgeries.

Table 28a: Summary of main efficacy results

Title: An Open-label Multicenter Evaluation of Safety, pharmacokinetics, and efficacy of recombinant coagulation factor IX fusion protein, BIIB029, in the prevention and treatment of bleeding episodes in pediatric subjects with haemophilia B			
Study identifier	9HB02PED		
Design	Open-label, uncontrolled, multicenter		
	Duration of main phase:		The per-subject duration of study participation for the treatment and follow-up periods was approximately 54 weeks. The time required for screening and PK assessments was approximately 3 months.
Hypothesis	To determine the clinical efficacy of rFIXFc in the treatment of bleeding, in routine prophylaxis, and in perioperative management of pediatric patients, study the PK in the children. This study is part of approved PIP (EMA-000914-PIP01-10-M02		
Treatments groups	6years of age		50IU/kg-60IU/kg every 7 days, 15 patients
	6 to <12 years of age		50IU/kg-60IU/kg every 7 days, 15 patients
Endpoints and definitions	Primary endpoint	Safety	Incidence of inhibitors development
		Efficacy	Number of bleeding episodes per subject annualized over study period,
	Secondary Prophylaxis efficacy	Efficacy	Dose per injection for subjects
	Secondary Efficacy to stop the bleeding	Efficacy	Number of injections and dose per injection required to stop a bleeding episode

	Secondary Perioperative management	Efficacy	Surgeon´s assessment of subject's response to surgery
			Consumption to maintain hemostasis
			Blood loss during surgery
			Number of transfusion required
Database lock	24 November 2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	FAS		

Descriptive statistics and estimate variability	Treatment group	< 6 year	6 to <12 years	Total
	Number of subjects	15	15	30
	Median (IQR)ABR	1.09(0.00, 2.90)	2.13(0.00,4.17)	1.97(0.00, 3.13)
	Median UI/kg (Range IU/kg) Prophylactic weekly dose	59.40 (31.0 to 68.6)	57.78(46.5 to 110.1	61.55(37.1 to 142.7)
	Median dose per injection to stop the bleeding event	63.70(30.1, 133.3)	62.92(16.7, 122.7)	63.51(16.7, 133.3)
	Median total dose to stop the bleeding event	65.37(30.1, 266.7)	89.77(16.7, 362.7)	68.22(16.7, 362.7)

Table 28b: Annualized Bleeding Rates Compared With Bleeding Episodes on the Prestudy Regimen

		Age cohort		
		<6 years old (N=15)	6 to <12 years old (N=15)	Total (N=30)
Annualized bleeding rate (a)	n	15	15	30
Pre-study	Mean (SD)	3.87 (4.549)	7.20 (18.127)	5.53 (13.096)
	Median	3.00	2.00	2.50
	25th, 75th percentile	0.00, 5.00	0.00, 5.00	0.00, 5.00
	Min, Max	0.0, 17.0	0.0, 72.0	0.0, 72.0
On-study	Mean (SD)	1.72 (1.933)	2.80 (3.172)	2.26 (2.639)
	Median	1.09	2.13	1.97
	25th, 75th percentile	0.00, 2.90	0.00, 4.17	0.00, 3.13
	Min, Max	0.0, 5.6	0.0, 10.0	0.0, 10.0

This analysis compared prestudy numbers of bleeding episodes (for subjects who were on a pre-existing prophylaxis regimen in the 12 months prior to the study) with the on-study annualized bleeding rate. The bleeding rate ratio was 0.42 for on-study prophylaxis versus pre-study prophylaxis in the overall study population (corresponding to a 58% reduction in annualized bleeding rate). Bleeding rate ratios in the <6 years of age cohort and the 6 to <12 years of age cohort were 0.46 (a 54% reduction) and 0.39 (a 61% reduction), respectively.

Even though the data are collected retrospectively, the comparison of annualized bleeding rates between prestudy and onstudy product is considered interesting. The incidence of bleeding events is likely underestimated in the prestudy dataset, because documentation is probably less accurate as during a clinical trial.

An improvement in favour of the study product could be shown for the annualized bleeding rate. This is seemingly driven in no small part by a subject who experienced 72 bleeding events prestudy and only 4 onstudy. The applicant has provided a sensitivity analysis excluding this subject from the negative binomial regression model comparing pre- and on-study annualized bleeding rates in order to assess the impact of this patient on the study results. This subject is in the 6 to <12 years old age cohort. The prestudy and on-study estimated annualized bleeding rate (95% CI) is 2.57 (1.49, 4.45) and 2.68 (1.46, 4.91), respectively, as compared to 7.20 (2.10, 24.66) and 2.80 (1.61, 4.85), respectively, in the original analysis. The bleeding rate ratio is 1.04 (0.52, 2.10) compared to 0.39 (0.11, 1.36) in the original analysis. The difference remained not statistically significant (p=0.9081 versus p=0.1397). In the <6 years old cohort, the number of subjects included in the analysis and the results were unchanged.

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

N/A

Table 29: Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials			
Non Controlled trials 998HB102	2/123		

**Supportive study(ies)**

Trial 9HB01EXT

This extension study evaluated the long-term safety and efficacy of rFIXFc in previously treated subjects with haemophilia B and allowed subjects from the Phase 3 studies (Study 998HB102 and Study 9HB02PED), and from other rFIXFc studies to continue treatment with rFIXFc. This interim report for the extension study evaluated the long-term safety of rFIXFc in subjects with haemophilia B from the Phase 3 studies (Study 998HB102 and Study 9HB02PED) as of the 17 October 2014 data cut-off. Of the 116 subjects who participated in the parent studies, 93 (80.2%) were enrolled from Study 998HB102 and 23 (19.8%) were enrolled from Study 9HB02PED.

Subjects ≥12 years of age follow a prophylactic (weekly, individualized interval, or personalized) regimen, or an episodic regimen. Personalized prophylaxis is allowed for additional rFIXFc dosing, such as that given prior to physical activity, supplementing a background of any individualized interval regimen or weekly regimen. The starting dose in the extension study is based on the subject's PK profile and dose from the parent study. All subjects ≥12 years of age are allowed to change treatment regimens (e.g., from prophylaxis regimen to episodic dosing or from episodic dosing to prophylaxis regimen) during the study after assessment by the Investigator.

Subjects <12 years of age receive a prophylactic (weekly, individualized, or personalized) regimen and do not have the option to change to on-demand treatment until they reach the age of 12 years.

If a subject requires surgery during this study, either emergent or elective, he may be treated with the dose and regimen of rFIXFc deemed appropriate for the type of surgery. Assessment of hemostasis is conducted in the same manner as the parent studies. Major and minor surgeries conducted during the extension study (9HB01EXT) through 17 October 2014 were evaluated for hemostatic efficacy.

Figure 11: Overview of Subject Disposition (N=116 Subjects Enrolled in Extension Study)
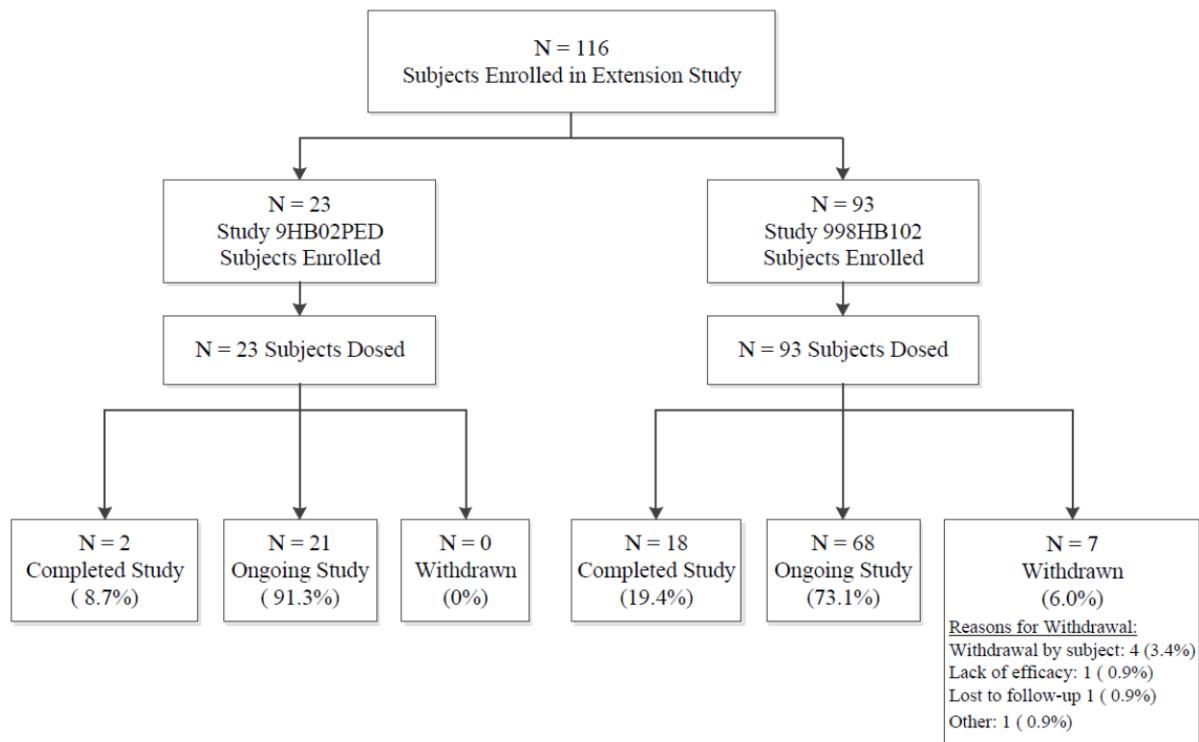
Haemostatic Efficacy

Overall, in subjects enrolled from Study 998HB102, over 96% of bleeding episodes were controlled with 2 or fewer injections of rFIXFc, with over 80% controlled by 1 injection, regardless of the treatment regimen. For weekly, individualized, personalized, and episodic treatment, the median doses per injection to treat a bleeding episode were 51.73, 39.14, 54.57, and 38.66 IU/kg, respectively, and the median total doses to treat a bleeding episode were 52.85, 47.91, 54.87, and 39.42 IU/kg, respectively.

Overall, in subjects who enrolled from Study 9HB02PED and received weekly or individualized prophylaxis in both age cohorts, at least 90% of bleeding episodes were controlled with 2 or fewer injections of rFIXFc. The 1 subject on personalized prophylaxis had 3 bleeding episodes, 2 of which were controlled by 2 injections. For weekly prophylaxis in the <6 years of age cohort, the median average dose per injection to treat a bleeding episode was 58.82 IU/kg, and the median total dose to treat a bleeding episode was 58.82 IU/kg. (No subjects in the <6 years of age cohort received individualized or personalized prophylaxis.) For weekly, individualized, and personalized prophylaxis in the 6 to <12 years of age cohort, the median average doses per injection to treat a bleeding episode were 48.08 IU/kg, 69.44 IU/kg, and 97.11 IU/kg, respectively; and the median total doses to treat a bleeding episode were 56.82 IU/kg, 69.44 IU/kg, and 207.97 IU/kg, respectively.

rFIXFc injections were rated as producing excellent or good responses in 70.5%, 83.3%, 73.8%, and 96.3% of first injections evaluated for response in subjects enrolled from Study 998HB102 receiving weekly prophylaxis, individualized interval prophylaxis, personalized prophylaxis, and episodic treatment, respectively.

In subjects in the <6 years of age cohort who enrolled from Study 9HB02PED, 100.0% of first injections evaluated for response were rated as excellent or good for the subjects receiving weekly prophylaxis.

In subjects in the 6 to <12 years of age cohort who enrolled from Study 9HB02PED, 81.3%, 50%, and 50% of first injections were rated as excellent or good for subjects receiving weekly prophylaxis (in 26 of

32 injections), individualized prophylaxis (in 6 of 12 injections), and personalized prophylaxis (1 of 2 injections).

Routine Prophylaxis

<u>Subjects from Study 998HB102</u>

The mean annualized bleeding rate was 3.73 for subjects on weekly prophylaxis; 3.90 for subjects on individualized prophylaxis; 3.97 for subjects on personalized prophylaxis; and 13.35 for subjects on episodic treatment.

Six subjects had an annualized bleeding rate of more than 20 episodes per year. Of these 6 subjects, 3 were on episodic treatment. The remaining 3 subjects were on prophylaxis and each had multiple target joints.

<u>Subjects from Study 9HB02PED</u>

For subjects on weekly prophylaxis, the mean annualized bleeding rate was 2.47 in the <6 years of age cohort (n=9) and 3.65 in the 6 to <12 years of age cohort (n=10). For subjects from the 6 to <12 years of age cohort who were on individualized prophylaxis (n=5), the mean annualized bleeding rate was 5.97. The annualized bleeding rate was 3.13 for the 1 subject on personalized prophylaxis in the 6 to <12 years of age cohort.

Perioperative Management

Among the total of 15 major surgeries (which included a laminectomy, total knee arthroplasty, craniotomy, etc) performed, evaluation of hemostasis was rated as excellent (13 surgeries) or good (1 surgery) for the <u>14 major surgeries that were assessed for response</u>. Total rFIXFc dose for the 14 days following major surgery had ranged from 118.6 IU/kg to 1947 IU/kg. Evaluation of hemostasis was rated as excellent (9 surgeries) or good (1 surgery) for the 10 minor surgeries that were assessed for response.

<u>Results in this interim study</u> report are broadly comparable to those observed in the parent studies, demonstrating long-term efficacy of treatment with Alprolix. Mean bleeding rates in the enrolled paediatric population is reported to be higher than in the parent study, however, this could possibly be caused by low subject numbers included in the treatment modality and age subgroups. Nevertheless, the applicant is asked to discuss these results in light of the available data. A definitve assessment will only be possible once the final CSR has been provided.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The design of the two submitted pivotal clinical trials investigating the efficacy (998HB102 and 9HB02PED) for Alprolix follows and exceeds the requirements of the currently valid guideline for recombinant FIX products (EMA/CHMP/BPWP/144552/2009 rev 1) regarding the number and age distribution of subjects included as well as the number of exposure days observed. In addition, an interim report of the extension trial 9HB01EXT provides data concerning the sustained efficacy after long term administration of rFIXFc.

In the clinical trials the efficacy of Alprolix was explored for the prevention as well as for the treatment of bleeding events.

Trial 998HB102 investigated the efficacy of Alprolix for prophylactic as well as on-demand treatment in 123 PTPs ≥12 years of age (Arm 1: fixed prophylactic treatment interval i.e. once weekly with adapted dose; Arm 2: fixed prophylactic dose i.e. 100 IU with adapted interval; Arm 3: On demand treatment of

BEs). The applicant has justified the chosen dose with the results from the phase 1/2a study SYN-FIXFc-07-001 and with the simulations in the population PK analysis. Adjustment of doses were allowed to target a trough of 1%-3% during the prophylactic treatment. In addition when patients had at least 3 spontaneous bleeding episodes over a consecutive month period adjustment dose were allowed to target a trough of 3% to 5% above baseline. In arm, 1 dose adjustment was allowed; changes in dose were to be in increments no less than 10 IU/kg and the minimum and maximum dose allowed were 20 IU/Kg and 100 IU/kg, respectively. In arm 2, the interval was adjusted to target trough levels for the subject. It is considered that the dose adjustment was adequately conducted and the threshold levels clinically justified. In general although the design is endorsed, further justification has been provided regarding the allocation of the patients in each arm and regarding sample size. More patients were weekly treated (arm 1) in order to increase the number of ED and enhance the safety database

Trial 9HB02PED investigated the efficacy of Alprolix for the prophylaxis and treatment of bleeds in 30 PTPs <12 years age. Furthermore, in both pivotal as well as in the extension trial the efficacy of Alprolix during surgery was explored (for trial 998HB102 in the dedicated treatment Arm 4).

The investigated patient population was multi-national and included previously treated children (0-<12 years of age), adolescents (11 adolescents between 12 and 17 years of age) and adults suffering from severe to moderately severe haemophilia B defined as FIX levels ≤2%. Given that the patients were treated previously, the protocol of the studies established that patients had to have at least 100 ED to other factor IX in the adult population and 50 ED in the paediatric population. This is not in accordance with the current GL where it is established that a minimum of 150 ED previous to the administration of the new investigational product is needed in PTPs ≥12. However this is not expected to have an important impact on the safety or efficacy of the product.

In trial 998HB102 in adults and adolescents the primary efficacy endpoint was defined as the number of bleeding episodes (spontaneous and traumatic) with rFIXFc per subject annualized over the study period (comparison between Arms 1 and 2 (= prophylactic treatment) versus Arm 3 (on demand treatment)). Relevant secondary efficacy endpoints encompassed the following: Assessments of response to treatment with rFIXFc for bleeding episodes (4 point scale); Physicians' global assessments of subjects' response to treatment with rFIXFc; Total annualized rFIXFc consumption per subject; Dose per injection for subjects in Arm 1; Dosing interval for subjects in Arm 2; The number of annualized spontaneous bleeding episodes (joint, soft tissue, and muscle) per subject; The number of annualized joint bleeding episodes (spontaneous and traumatic) per subject; Time from last injection of rFIXFc to the bleeding episode; Number of injections and dose per injection of rFIXFc required to stop a bleeding episode (joint, soft tissue, and muscle).

For the evaluation of the effects in surgery, Investigators'/Surgeons' assessments of subjects' response to surgery with rFIXFc; Number of injections and dose per injection required to maintain hemostasis during the surgical period; Estimated blood loss during surgery and Number of transfusions required for surgery were defined as endpoints.

In the paediatric study 9HB02PED, the annualized number of bleeding episodes per subject; The annualized number of spontaneous joint bleeding episodes per subject; Assessments of response to treatment with rFIXFc for bleeding episodes, using the 4-point bleeding response scale; Total annualized rFIXFc consumption per subject for prevention of bleeding episodes; Total annualized rFIXFc consumption per subject for treatment of bleeding episodes; Time from last injection of rFIXFc to the bleeding episode; Number of injections and dose per injection of rFIXFc required to resolve a bleeding episode represent the evaluated efficacy endpoints.

Efficacy data and additional analyses

In all, 123 male subjects were enrolled into the pivotal trial 998HB102, 63 in arm 1, 29 in arm 2, 27 in arm 3 and 12 were under perioperative management. Most of them (110) were 18-64 years old. Only 2 subjects were 65 years old or older.

40.2% (49/122) of the patients enrolled were on prophylaxis pre-study regimen and 59.8% (73/122) were under on demand pre-study regimen.

In 998HB102 a statistically significant reduction in the annualized bleeding rate was observed for both the weekly prophylaxis regimen (Arm 1) and the individualized interval prophylaxis regimen (Arm 2) relative to the episodic regimen (Arm 3). However, as the benefits of prophylactic treatment are well established in the haemophilia B population, the evaluation of prophylactic treatment with Alprolix reduces the rate of bleeding events in comparison to on demand treatment is not considered relevant for this MAA. In addition, subjects were not randomized into arms 1 to 3 but assigned after discussion with the investigator, thus further weakening the strength of the evidence of this comparison. However, the mean bleeding rates based on observed data (3.07, 2.45, and 17.69 in Arms 1, 2, and 3, respectively) confirm the beneficial effect of prophylaxis with Alprolix observed in this trial. These annualized bleeding rates also compare favourably to published results from trials with other licensed FIX products.

The percentage of patients without bleeding episodes was smaller (23.0%) in arm 1 than in arm 2 (42.3%). The majority of the subjects in the arm 2 who did not have any bleeding episodes were those without any target joints at baseline. This suggests that those patients with a more favourable phenotype may get clinical benefit from a longer dosing interval. However, considering that the therapy in haemophilia B is tailored on individual basis, both regimens can be relevant in the global approach to the diseases. The weekly dose of rFIXFc for subjects on weekly prophylaxis (Arm 1) decreased from the starting regimen of 50 IU/kg to a median of 45.17 IU/kg (range 25.0 to 74.3 kg IU/kg) when averaged over all eligible doses administered during the efficacy period. The dosing interval of rFIXFc for subjects on individualized interval prophylaxis (Arm 2) started at 10 days, with a median interval when averaged over all eligible dosing intervals during the efficacy period of 12.53 days (range 7.8 to 15.9 days).

Regarding the efficacy in the treatment of bleeding events, 97.3% of bleeding episodes were controlled with 2 or fewer injections of Alprolix, with 90.4% controlled by 1 injection. No bleeding episodes required more than 3 injections. 82.0% of injections were rated by subjects as producing an excellent or good response, and 15.9% of injections were rated as moderate. Of the 635 bleeding episodes that could be classified, 23 (3.6%), 589 (92.8%), and 23 (3.6%) bleeding episodes were classified as mild, moderate, and severe, respectively. Across all 3 treatment arms, bleeding episodes of mild, moderate, and severe degrees were controlled with a single injection in 91.3% (21/23), 91.5% (539/589), and 60.9% (14/23) of cases, respectively. The response to the first injection to treat mild, moderate, and severe bleeding episodes was rated as excellent or good in 85.0% (17/20), 85.1% (486/571), and 47.6% (10/21) of cases, respectively.

Thirty subjects were enrolled into trial 9HB02PED; the median overall age was 5.0 years, 15 were enrolled in the <6 years of age cohort and 15 subjects were enrolled in the 6 to < 12 years cohort. This study enrolled children previously treated with 50 EDs to any recombinant or plasma-derived FIX product including prothrombin complex concentrate. This is not a usual prerequisite as only exposure to FIX is valid in order to minimize the risk of inhibitor formation. Additional information was therefore required in terms of ED. The applicant provided the median and IQR of the ED pre-study to FIX including prothombin complex and the ED to FIX (without prothrombin complex) as requested. Only two patients from South Africa received PCC (containing FIX from pooled fresh plasma). The remaining patients received concentrated FIX product (BeneFIX, AlphaNine and Immunonine). All the patients had been exposed at least 50 ED to previous FIX products and therefore the inclusion criteria have been met.

In the paediatric population of trial 9HB02PED the mean annualized bleeding rate was 1.72 in the <6 years of age cohort, 2.80 in the 6 to <12 years of age cohort, and 2.26 in the total of both age cohorts.

The median average dosing interval during the Efficacy Period was 6.99 days (range: 5.9 to 10.8 days), with no difference in median average dosing interval between cohorts. The majority of subjects (96%) needed no changes to their prescribed dosing interval and 63.3% needed 1 dose change during study. The ranges of doses and dosing interval are wide and thus reflecting the heterogeneity of the results.

The median average weekly dose of rFIXFc for subjects <6 years of age was 59.40 IU/kg (range: 31.0 to 68.6 IU/kg) across the study. For subjects in the 6 to <12 years of age cohort, the median average weekly dose was 57.78 IU/kg (range: 46.5 to 110.1 IU/kg) across the study.

Of the 67 rFIXFc injections evaluated for response, 60 (89.6%) were rated by subjects as producing an excellent or good response, 6 (9.0%) were rated as moderate, and 1 (1.5%) was rated as none. The majority of bleeding episodes were resolved by 2 or fewer injections (95.5%, 89.5% and 91.7% of subjects <6 years of age, subjects 6 to <12 years of age, and the total of both age cohorts, respectively). Of the 60 bleeding episodes that could be classified, 12 (20.0%), 40 (66.7%), and 8 (13.3%) bleeding episodes in subjects <12 years of age were classified as mild, moderate, and severe, respectively. Across the 2 age cohorts, bleeding episodes of mild, moderate, and severe degrees were controlled with a single injection in 91.7% (11/12), 70.0% (28/40), and 75.0% (6/8) of cases, respectively. The response to the first injection to treat mild, moderate, and severe bleeding episodes was rated as excellent or good in 100% (11/11), 86.5% (32/37), and 80.0% (4/5) of cases, respectively. The results have been appropriately reflected under SmPC section 5.1.

The guideline requirement to submit data of a minimum of 5 patients undergoing at least 10 surgical procedures (comprising major surgeries) is exceeded. In all three trials the efficacy of Alprolix during surgery was investigated, resulting in 29 major surgeries performed in 19 subjects in the pivotal phase 3 studies (998HB102 and 9HB02PED) and the ongoing extension study (9HB01EXT) as of 17 October 2014. In addition, 43 minor surgeries were undertaken in the same timeframe. The vast majority of evaluable surgeries were assessed as excellent or good by the surgeon or investigator. In the event of major surgeries the claimed posology in the SmPC is in line with non long-acting product, which is endorsed. Based on data of 40 minor surgeries in 24 subjects >12 years it is stated in the SmPC that the dose frequency should be 24 hours and that a prolonged interval is appropriate in certain patients and circumstances.

The annualized bleeding rates in 9HB01EXT were for subjects enrolled from Study 998HB102 who were on weekly prophylaxis (median: 2.28); individualized interval prophylaxis (median: 2.25), and personalized prophylaxis (median: 2.42), for subjects enrolled from Study 9HB02PED who were on the weekly prophylaxis (medians: 0 for subjects <6 years of age and 2.65 for subjects 6 to <12 years of age); individualized prophylaxis (median: 2.37 for subjects 6 to <12 years of age); and personalized prophylaxis (3.13 in 1 subject in the 6 to <12 years of age cohort). In general these data are in line with those of the parent studies. According to the applicant the differences seen in the number of bleeding episodes are due to the differences in time that patients stayed in the parent study (median of 50.01 weeks) and in the extension study (median of 119.48 weeks). Given the median of the ABR is comparable between parent and extension studies (2.61 and 2.21 respectively) it can be assumed that the efficacy is maintained in the long term treatment.

The applicant has provided an analysis showing that ABR is similar or slightly improved with the treatment of rFIXFc compared to that of the previous prestudy prophylaxis regimen. The annualised consumption for the prophylaxis regimen and the annualized number of prophylaxis injections decreased. In the study 998HB102 the percentage of patients with no bleeding episodes in the 12 months previous to study and on study was similar for the arm 1 (24.1% and 27.6% respectively). For the arm 2 there was a slight improvement with 20.0% in pre-study and 60.0% on-study. Those slightly better results were achieved with lower doses (UI/Kg) and a lower number of injections.

In the paediatric study, an improvement in favour of the study product could be shown for the annualized bleeding rate. This was seemingly driven in no small part by a subject who experienced 72 bleeding events pre-study and only 4 on-study. The applicant has provided a sensitivity analysis excluding this subject from the negative binomial regression model comparing pre- and on-study annualized bleeding rates in order to assess the impact of this patient on the study results. This subject is in the 6 to <12 years old age cohort. The pre-study and on-study estimated annualized bleeding rate (95% CI) is 2.57 (1.49, 4.45) and 2.68 (1.46, 4.91), respectively, as compared to 7.20 (2.10, 24.66) and 2.80 (1.61, 4.85), respectively, in the original analysis. The bleeding rate ratio is 1.04 (0.52, 2.10) compared to 0.39 (0.11, 1.36) in the original analysis. The difference remained not statistically significant (p=0.9081 versus p=0.1397). In the <6 years old cohort, the number of subjects included in the analysis and the results were unchanged (bleeding rate ratio 0.46).

The expectation from a long-acting FIX to the therapeutic of the haemophilic patients is the reduction of treatment burden and the improvement of adherence to the treatment. Although this has not been systematically studied in this application, the above results are adequate to support starting regimens for a long term prophylaxis against bleeding, as either 50 IU/kg once weekly, or 100 IU/kg once every 10 days, based on individual response. The highest recommended dose for prophylaxis is 100 IU/kg. (see section 4.2 of the SmPC).

2.5.4. Conclusions on the clinical efficacy

The submitted data are considered sufficient to demonstrate the efficacy of Alprolix for the prevention and treatment of bleeding events in patients with Haemophilia B as well as efficacy during surgery. The longer half-life of rFIXFc allows for a less frequent administration scheme, which eases the treatment burden.

Data for both investigated dosing strategies (fixed interval and fixed dose approach) are reflected in the SmPC and allow individual tailoring of preventative therapy with Alprolix.

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

- Provide the final study report from study 998HB303 (PUPs study): An Open- Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc; BIIB029) in the Prevention and Treatment of Bleeding in Previously Untreated Patients with Severe haemophilia B

2.6. Clinical safety

The evaluation of safety data from 3 completed clinical studies (Studies SYN-FIXFc-07-001, 998HB102 and 9HB02PED) and the study ongoing (9HB01EXT) was done according to relevant guidelines.

Data from the phase 3 studies 998HB102 and 9HB02PED, and from the ongoing extension study 9HB01EXT (interim data cut-off of 17 October 2014) were pooled for an integrated presentation. Data from the Phase 1/2a study (SYN-rFIXFc-07-001) and perioperative management period are discussed separately because of the relatively small number of subjects and study design differences, which is endorsed.

Patient exposure

For studies 998HB102, 9HB02PED, and 9HB01EXT (data cut-off 17 October 2014) patient exposure is presented in the following two tables:

Table 30: Cumulative Summary of Duration of Dosing With rFIXFc for All Subjects Enrolled in Studies 998HB102, 9HB02PED, and 9HB01EXT by Parent Study

	Parent Study		
	Study 9HB02PED (N=30)	Study 998HB102 (N=123)	Total (N=153)
Cumulative number of weeks on rFIXFc (a)			
At least 13 weeks	29 (96.7%)	119 (96.7%)	148 (96.7%)
At least 26 weeks	28 (93.3%)	117 (95.1%)	145 (94.8%)
At least 39 weeks	25 (83.3%)	112 (91.1%)	137 (89.5%)
At least 52 weeks	23 (76.7%)	100 (81.3%)	123 (80.4%)
At least 65 weeks	22 (73.3%)	93 (75.6%)	115 (75.2%)
At least 78 weeks	21 (70.0%)	91 (74.0%)	112 (73.2%)
At least 91 weeks	15 (50.0%)	90 (73.2%)	105 (68.6%)
At least 104 weeks	4 (13.3%)	89 (72.4%)	93 (60.8%)
At least 117 weeks	0	83 (67.5%)	83 (54.2%)
At least 130 weeks	0	81 (65.9%)	81 (52.9%)
At least 143 weeks	0	79 (64.2%)	79 (51.6%)
At least 156 weeks	0	74 (60.2%)	74 (48.4%)
At least 169 weeks	0	59 (48.0%)	59 (38.6%)
At least 182 weeks	0	19 (15.4%)	19 (12.4%)
At least 195 weeks	0	5 (4.1%)	5 (3.3%)
At least 208 weeks	0	2 (1.6%)	2 (1.3%)
At least 221 weeks	0	2 (1.6%)	2 (1.3%)
Total weeks on rFIXFc			
n	30	123	153
Mean	78.79	134.49	123.57
SD	29.071	60.778	60.152
Median	91.36	167.43	155.01
Min, Max	11.9, 110.5	<1, 229.0	<1, 229.0

NOTE 1: Data cutoff for study 9HB01EXT was 17 October 2014.
2: Percentages are based on numbers of subjects dosed with rFIXFc in each parent study or overall.
3: Time on rFIXFc refers to the length of time from the first rFIXFc dose in the parent study (998HB102 or 9HB02PED) through 17 October 2014 (date of data cutoff) for subjects ongoing in study 9HB01EXT, or the date of last rFIXFc dose or the date of the last non-safety follow-up study visit for subjects who withdrew from the study (998HB102, 9HB02PED or 9HB01EXT) and whose last treatment regimen was prophylactic or episodic, respectively. The time between the parent study and study 9HB01EXT was excluded if the gap was greater than 14 days for subjects originating from study 998HB102 or 7 days for subjects originating from study 9HB02PED, respectively.
(a) A subject can appear in more than one category of treatment duration.

Table 31: Cumulative Summary of Injections and Days of Exposure to rFIXFc For All Subjects Enrolled in Studies 998HB102, 9HB02PED, and 9HB01EXT By Age

	Age cohort (years old)				
	<6 (N=15)	6 to <12 (N=15)	12 to <18 (N=11)	>= 18 (N=112)	Total (N=153)
Total exposure days (a)					
<50	5 (33.3%)	1 (6.7%)	0	23 (20.5%)	29 (19.0%)
50-<100	10 (66.7%)	5 (33.3%)	2 (18.2%)	30 (26.8%)	47 (30.7%)
100-<150	0	8 (53.3%)	3 (27.3%)	15 (13.4%)	26 (17.0%)
150-<200	0	1 (6.7%)	6 (54.5%)	33 (29.5%)	40 (26.1%)
200-<250	0	0	0	9 (8.0%)	9 (5.9%)
250-<300	0	0	0	1 (0.9%)	1 (0.7%)
300-<350	0	0	0	0	0
350-<400	0	0	0	1 (0.9%)	1 (0.7%)
n	15	15	11	112	153
Mean	63.7	100.4	142.3	116.6	111.6
SD	30.44	26.54	44.00	74.67	68.37
Median	83.0	101.0	162.0	116.5	100.0
Min, Max	13, 96	33, 164	58, 184	1, 351	1, 351

```
_____
Total number of
injections per subject
   n                     15            15            11            112           153
   Mean                  64.3          101.9         143.2         118.7         113.5
   SD                    30.57         27.39         44.38         76.16         69.69
   Median                85.0          101.0         162.0         116.5         101.0
   Min, Max              13, 96        33, 168       58, 185       1, 360        1, 360
_____

NOTE 1: Data cutoff for study 9HB01EXT was 17 October 2014.
     2: Percentages are based on numbers of subjects dosed with rFIXFc in each age cohort or overall.
(a) An exposure day is a 24-hour period in which one or more rFIXFc injections are given. All injections
    over the study course are counted.
```

The number of patients largely exceeds the requirements of the guideline where it is stated that 40 PTPs should be investigated (20 ≥12 years, 10 between 6-<12 years and 10 <6 years of age). Safety data for patients ≥ 65 years old are limited since only 2 patients of this age group participated in the trials. This is considered as missing information in the RMP.

Since higher than the usual factor IX doses are proposed in the SmPC, patient exposure was also stratified by doseData on exposure for rFIXFc (<50 IU/kg, ≥50 to ≤75 IU/kg, >75 to ≤100 IU/kg, and >100 IU/kg) for each of the relevant age groups in adult and pediatric subjects revealed a sufficient number of subjects exposed in each of these dose groups to assess clinical safety. Additionally, the incidence of AEs and related AEs presented is generally similar for AEs within each dose group. The same applies for the incidence of treatment emergent adverse events (TEAEs) and adverse event assessed as related between the subjects who received doses ≤ 100 IU/kg and subjects who received doses >100 IU/kg,. The type and incidence of AEs observed in both dose groups are consistent with events typically observed in the haemophilia B population. Furthermore, no unique safety concerns and no vascular thrombotic events were identified in either dose group with respect to TEAES or related TEAEs.

Adverse events

Of the 153 subjects in the Integrated Safety Analysis, 133 subjects (86.9%) reported at least 1 TEAE for a total of 869 TEAEs - 106 subjects (86.2%) from Study 998HB102 and 27 subjects (90.0%) from Study 9HB02PED.

The most frequently reported TEAEs by SOC with an incidence of ≥10% were : infections and infestations (56.9%), gastrointestinal disorders and injury, poisoning, and procedural complications (35.3%); musculoskeletal and connective tissue disorders (32.7%); nervous system disorders (22.2%); general disorders and administration site conditions (19.6%); respiratory, thoracic, and mediastinal disorders (17.6%); and skin and subcutaneous tissue disorders (16.3%). In summary,134 patients (87.6%) are mentioned to have at least 1 AE, including AEs during the perioperative management period for a major surgery.

In the Phase 1/2a study (SYN-FIXFc-07-001) a total of 16 AEs were reported by 7 patients. These AEs were distributed evenly across treatment groups. Most AEs were mild. AEs considered to be related to the study drug were dysgeusia, and headache.

No unexpected AEs emerged during the Perioperative Management Period.

Adverse Drug Reactions:

Most subjects had TEAEs that were judged by the Investigator as unrelated to the rFIXFc treatment. After medical review, a total of 19 AEs were considered as related to study treatment and 18 were included as adverse drug reactions (ADRs): palpitations, breath odour, paraesthesia oral, fatigue, infusion site pain, decreased appetite, dizziness, dysgeusia, headache, hematuria, obstructive uropathy, renal colic, hypotension (Table 32).

Table 32: Cumulative Summary of Adverse Drug Reactions for All Subjects Enrolled in Studies 998HB102, 9HB02PED, and 9HB01EXT

MedDRA system organ class	MedDRA preferred term	Total rFIXFc (N=153)
Total number of ADRs		18
Number of subjects with at least one ADR		14 (9.2%)
CARDIAC DISORDERS	PALPITATIONS	1 (0.7%)
GASTROINTESTINAL DISORDERS	BREATH ODOUR	1 (0.7%)
	PARAESTHESIA ORAL	2 (1.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	FATIGUE	1 (0.7%)
	INFUSION SITE PAIN	1 (0.7%)
METABOLISM AND NUTRITION DISORDERS	DECREASED APPETITE	1 (0.7%)
NERVOUS SYSTEM DISORDERS	DIZZINESS	1 (0.7%)
	DYSGEUSIA	1 (0.7%)
	HEADACHE	2 (1.3%)
RENAL AND URINARY DISORDERS	HAEMATURIA	1 (0.7%)
	OBSTRUCTIVE UROPATHY	2 (1.3%)
	RENAL COLIC	1 (0.7%)
VASCULAR DISORDERS	HYPOTENSION	1 (0.7%)

Serious adverse event/deaths/other significant events

Of the 153 subjects treated with rFIXFc, 39 subjects (25.5 %) experienced a total of 68 serious TEAEs. Two of the serious TEAEs (obstructive uropathy and renal colic) were assessed by the Investigator as related to rFVIXFc treatment. Six serious TEAEs were ongoing as of the interim data cutoff. The remaining serious TEAEs were considered resolved.

No death occurred in any of the studies.

Adverse events of Special Interest

A review of AEs of special interest revealed 17 non-serious AEs of possible allergic reactions, thereof 2 (dizziness and oral paresthesia) were assessed as related to treatment. All of these events were mild to moderate in severity, and none of the events led to treatment discontinuation or subject withdrawal from the study. One non-serious AE of thrombotic event occurred, which was assessed as not related.

Serious bleeding events were reported as 13 serious TEAEs in 11 subjects, thereof I TEAE (renal colic) was assessed as related to rFIXFc treatment.

No reports of inhibitor development, serious related allergic reactions or anaphylaxis and no serious vascular thrombotic events were observed.

Laboratory findings

Haematology and chemistry parameters were collected and urinalysis was conducted in the rFIX-Fc clinical development program and assessed for clinical significance.

The haematology panel consisted of complete blood count [white blood cell (WBC) count and differential, hemoglobin (Hb), hematocrit (HCT), and platelet count]. The clinical chemistry panel included electrolytes (sodium, potassium, chloride), glucose, total protein, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), and serum creatinine. Measurements that were collected in Study 998HB102 and/or

Study 9HB02PED but not in Study 9HB01EXT, i.e., red blood cell (RBC) count, phosphate, bicarbonate, direct bilirubin, indirect bilirubin, and gamma glutamyl transferase.

Laboratory parameters, vital signs and physical findings revealed no particular safety concern.

Nevertheless, several subjects showed abnormal post-baseline hemoglobin and hematocrit values both in the adult and the paediatric populations, that were deemed unrelated to rFIXFc. For study 998HB102 and its extension, Hb was below 115g/L in 5.14% of subjects and hematocrit below 37% in 10.2% of patients. Furthermore, 11 subjects each had ≥1 TEAE of hypertension. The majority of the 11 subjects who reported an AE of hypertension had hypertension in their medical history, reported ongoing treatment with antihypertensive drugs as concomitant medications, or had other potential risk factors such as HIV, HCV, diabetes, etc. None of the adverse events of hypertension were assessed as related to rFIXFc. In addition, the prevalence of hypertension may be increased in haemophilia patients compared to the general age-matched male population.

Safety in special populations

In the main, type and frequency of AEs were similar between subjects < 12 years of age and subjects ≥ 12 years of age. Differences in the frequency of certain AEs are expected for the general population of that age group.

No safety concern regarding rFIXFc treatment in subjects with medical history of hepatic diseases, HIV/HCV status or by geographic locations was identified.

The clinical data from the completed studies 998HB102 and the ongoing extension study 9HB01EXT as of the data cut off of 17 October 2014, includes 2 subjects ≥65 years of age (2/153, 1.3%). The 2 subjects each experienced at least one serious adverse event (SAE): One subject experienced 2 SAEs of angina pectoris; the second subject experienced 1 SAE of arthralgia. None of the SAEs were assessed as related to rFIXFc and none resulted in study discontinuation.

In total, the 2 subjects ≥65 years of age at time of enrollment into the parent study (Study 998HB102) experienced 10 non-serious adverse events (AEs) throughout the parent and extension study as of the data cutoff. None of these AEs led to study discontinuation. The AEs reported included the following: musculoskeletal and connective tissue disorders (3 events); injury poisoning and procedural complications (3 events); infections and infestations (2 events); nervous systems disorders (1 event); and vascular disorders (1 event).

Immunological events

In trial 998HB102 coagulation activation parameters (prothrombin fragment 1 + 2, TAT complexes, D-dimer) were investigated and no changes were detected.

No inhibitor against rFIXFc was reported in the combined total population of 153 subjects.

Anti-rFIXFc binding antibodies (ADA)-positive test results were observed both prior to and following initiation of treatment with rFIXFc. The overall incidence of ADA-positive test results was 3.9% (6 subjects; 2.6% [4/153] prior to treatment with rFIXFc and 1.4% [2/148] post treatment with rFIXFc).

Safety related to drug-drug interactions and other interactions

Formal drug-drug interaction studies are generally not applicable for biologic therapies based on mechanisms of degradation and elimination. Therefore, no formal drug-drug interaction studies were conducted. There were no AEs observed in subjects from Study 998HB102, 9HB02PED, or 9HB01EXT that were suggestive of any potential drug-drug interaction with rFIXFc.

Discontinuation due to adverse events

Two subjects (1.3%) of 153, both from Study 998HB102, were reported to have experienced at least 1 TEAE that led to premature discontinuation of rFIXFc treatment and withdrawal. This included an unrelated SAE of road traffic accident and unrelated SAE of device related infection. Both AEs occurred in areas where it was not possible to provide rFIXFc for the subjects.

Post marketing experience

rFIXFc is commercially available in the United States since 05 May 2014. rFIXFc was approved in Canada on 21 March 2014, in Australia on 01 May 2014, and in Japan on 04 July 2014. No new safety signals and no new potential or identified risks related to rFIXFc have been identified during the post marketing experience as of the DLP of 19 September 2014.

2.6.1. Discussion on clinical safety

All 3 completed clinical studies (SYN-FIXFc-07-001, 998HB102 and 9HB02PED) assessed safety of rFIXFc, with particular emphasis on immunogenicity and development of rFIXFc antibodies. To date, there have been no reports of virus transmission, serious related allergic reactions or anaphylaxis, thromboembolism or inhibitor-development related to rFIXFc. An extension study (9HB01EXT), in which subjects coming from the pivotal trials are included is currently ongoing

Requirements of the EMA FIX Guideline for an application for marketing authorisation ask for 40 PTPs to be investigated, of whom 20 should be PTPs ≥12 years of age, who have at least 150 EDs, another 10 PTPs in the age stratum 6 - <12 years and >50 EDs and an additional 10 should be PTPs <6 years of age and >50 EDs. Nevertheless, the company decided to allow inclusion of subjects with ≥ 100 EDs into Study 998HB102 to improve the feasibility of the study (considering the rarity of haemophilia B patients). This altered definition might slightly increase the risk for the development of inhibitors. The principle of the EMA guidance is to follow a risk-based approach in assessing the immunogenicity of a new FIX product, testing in subjects at low risk initially (PTPs ≥ 150 EDs) and proceeding to PUPs only after inhibitor risk has been evaluated in PTPs. The company submitted several papers, which should show that the risk of inhibitor development in haemophilia patients tends to peak within the first 40 EDs, after which the risk plateaus. Despite some of these papers refer to haemophilia A, the risk of inhibitor development in haemophilia B patients is lower than in haemophilia A patients. Thus, inclusion of subjects with ≥ 100 EDs represents an increased risk for the applicant to observe unfavourable outcomes and therefore no issue is raised.

Guideline requirements regarding patient exposure, with a sufficient number of patients out of the relevant age groups exposed over a sufficiently long period of time are fulfilled. The safety database, however, is limited with regard to elderly patients as only 2 patients older than 65 years of age were included in study 998HB102.

Furthermore, since higher than the usual factor IX doses are proposed in the SmPC, patient exposure was also stratified by dose. Data on exposure for rFIXFc (<50 IU/kg, ≥50 to ≤75 IU/kg, >75 to ≤100 IU/kg, and >100 IU/kg) for each of the relevant age groups in adult and pediatric subjects revealed a sufficient number of subjects exposed in each of these dose groups to assess clinical safety. Additionally, the incidence of AEs and related AEs presented is generally similar for AEs within each dose group. The same applies for the incidence of TEAEs and treatment related AEs between the subjects who received doses ≤ 100 IU/kg and subjects who received doses >100 IU/kg. The type and incidence of AEs observed in both dose groups are consistent with events typically observed in the haemophilia B population. Furthermore, no unique safety concerns and no vascular thrombotic events were identified in either dose group with respect to TEAES or related TEAEs.

Remaining listed adverse events from the main studies, which were considered to be related to rFIXFc treatment, are appropriately reflected in section 4.8 of the SmPC. In the main, type and frequency of AEs were similar between subjects < 12 years of age and subjects ≥ 12 years of age. Differences in the frequency of certain AEs are expected for the general population of that age group. Of note, only 2 patients were treated beyond the age of 65 years.

In summary, 134 patients (87.6%) are mentioned to have at least 1 AE, including AEs during the perioperative management period for a major surgery. Two allergic reactions *dizziness* and *paresthesia*, were considered related by the Investigator and are tabularly depicted in section 4.8 of the SmPC, which is endorsed.

The applicant has adequately assessed the adverse events of special interest for haemophila treatment: inhibitor development, allergic reactions and thrombotic events. Adverse events related to bleeding, infections and hepatobiliary events were described but none of them were assessed as related to rFIXFc and none of them raised any particular safety concern.

Laboratory parameters, vital signs and physical findings revealed no safety concern. As the most important safety aspect of a factor IX product, inhibitor development has to be taken into account. Procedures and definitions regarding inhibitor testing, as conducted in the context of the clinical development programme of rFIXFc, meet the standards set out in the current EMA FIX guidance. Furthermore, it was tested for anti-rFIXFc binding antibodies (ADA), which is considered adequate for a novel recombinant factor IX product. ADA positive test results could be detected both prior to and following initiation of treatment with rFIXFc. The overall incidence of ADA-positive test results was 3.9% (6 subjects; 2.6% [4/153] prior to treatment with rFIXFc and 1.4% [2/148] post treatment with rFIXFc). The presence of an ADA-positive test result did not have an observed clinical impact on the safety of subjects in the parent studies (998HB102 and 9HB02PED) or the extension study and these findings are not indicative of a higher than expected inhibitor incidence under treatment with rFIXFc. A study in previously untreated patients (PUPs) is still ongoing.

The theoretical concern, that a subject's risk of infection might be increased because of saturation of the neonatal Fc receptor by rFIXFc, was addressed by the applicant. Neither evaluation of serum IgG levels nor review of the respective infection event terms showed any results out of the expected ranges.

In the Phase 1/2a study (SYN-FIXFc-07-001) AEs were distributed evenly across treatment groups. Most AEs were mild in severity. No deaths occurred. No FIX inhibitors or anti- FIXFc antibodies were detected. Related AEs dysgeusia and headache are included in the SmPC section 4.8.

No unexpected AEs emerged during the Perioperative Management Period.

rFIXFc is commercially available in the United States since 05 May 2014 and approved in Canada, Australia and in Japan at around the same time. No new safety signals and no new potential or identified risks related to rFIXFc have been identified during the post marketing experience as of the DLP of 19 September 2014.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

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. rFIXFc 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:

- Submission of the final study report from study 9HB01EXT: An Open- Label, Multicenter Evaluation of the Long- Term Safety and Efficacy of Recombinant Human Coagulation Factor IX Fusion Protein (rFIXFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects with haemophilia B (safety extension study)
- Submission of the final study report from study 998HB303: An Open- Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc; BIIB029) in the Prevention and Treatment of Bleeding in Previously Untreated Patients with Severe haemophilia B (PUPs study)
- Submission of Data collected from participation in the European Haemophilia Safety Surveillance System (EUHASS) registry to be provided on an ongoing basis with the PSUR
- Submission of data collected from participation in the European Pediatric Network (PedNet) registry to be provided on an ongoing basis with the PSUR

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Inhibitor development to rFIXFc Serious hypersensitivity, serious allergic reaction, and/or anaphylaxis
Important potential risks	Serious vascular thromboembolic events Medication errors
Missing information	Safety profile in patients >65 years old Safety profile in women (including pregnant and breast-feeding women) Safety profile in PUPs Use of rFIXFc for ITI

Pharmacovigilance plan

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
9HB01EXT: An Open- Label, Multicenter Evaluation of the Long- Term Safety and Efficacy of Recombinant Human Coagulation Factor IX Fusion Protein (rFIXFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects with	The primary objective of the study is to evaluate the long-term safety of rFIXFc in subjects with Haemophilia	Long-term safety evaluation Safety profile in patients ≥65 years old	Ongoing	Submission date dependent on study finish dates. Study last patient, last visit by Q4 2017.

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Haemophilia B (safety extension study, Category 3)	B.			
998HB303: An Open- Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc; BIIB029) in the Prevention and Treatment of Bleeding in Previously Untreated Patients with Severe Haemophilia B (PUPs study, Category 3)	The primary objective of the study is to evaluate the safety of rFIXFc in previously untreated subjects with severe Haemophilia B.	Safety profile in PUPs<18 years old	Ongoing	Final: Submission date dependent on study finish dates. Study last patient, last visit by June 2019 as per the agreed PIP (EMEA-C1-000914-PIP01-10-M02).
Data collected from participation in the European Haemophilia Safety Surveillance System (EUHASS) registry to be provided on an ongoing basis (Category 3)	Monitor the safety of treatments for people with haemophilia, including Elocta.	Inhibitor development Serious allergic reactions or anaphylaxis Serious vascular thrombotic events	Planned – will start upon product launch in the EU	Not applicable. Data will be reviewed on an ongoing basis as a part of pharmacovigilance signal detection and reported within the PSURs when available.

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Data collected from participation in the European Pediatric Network (PedNet) registry to be provided on an ongoing basis (Category 3)	To establish large well documented birth cohorts of patients with haemophilia, enabling studies on side effects and outcome of treatment	Inhibitor development	Ongoing	Not applicable. Data will be reviewed on an ongoing basis as a part of pharmacovigilance signal detection and reported within the PSURs when available.

*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)

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Inhibitor development to rFIXFc	**Section 4.4 of SmPC:** *After repeated treatment with human coagulation factor IX products, patients should be monitored for the development of neutralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.* *There have been reports in the literature showing a correlation between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with factor IX.* *Because of the risk of allergic reactions with factor IX products, the initial administrations of factor IX should, according to the treating*	No additional risk minimization measures are proposed.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	physician's judgement, be performed under medical observation where proper medical care for allergic reactions could be provided. **Section 4.8 of SmPC:** *Patients with haemophilia B may develop neutralising antibodies (inhibitors) to factor IX. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.* **Package leaflet (warnings and precautions):** *Talk to your doctor if you think that your bleeding is not being controlled with the dose you receive, as there can be several reasons for this. For example, the formation of antibodies (also known as inhibitors) to factor IX is a known complication that can occur during the treatment of haemophilia B. The antibodies prevent the treatment from working properly. This would be checked by your doctor. Do not increase the total dose of ALPROLIX to control your bleed without talking to your doctor.*	
Serious hypersensitivity, serious allergic reactions, and/or anaphylaxis	**Section 4.4 of SmPC:** *Allergic type hypersensitivity reactions are possible with ALPROLIX. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.* *In case of anaphylactic shock, standard medical treatment for shock should be implemented.* *Inhibitors:*	No additional risk minimization measures are proposed.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	There have been reports in the literature showing a correlation between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with factor IX. *Because of the risk of allergic reactions with factor IX products, the initial administrations of factor IX should, according to the treating physician's judgement, be performed under medical observation where proper medical care for allergic reactions could be provided.* **Section 4.8 of SmPC:** *Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock). In some cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors.* **Package leaflet (warnings and precautions):** *There is a small chance that you may experience an anaphylactic reaction (a severe, sudden allergic reaction) to ALPROLIX. Signs of allergic reactions may include generalised itching, hives, tightness of the chest, difficulty breathing, and low blood pressure. If any of these symptoms occur, stop the injection immediately and contact your doctor.* *Patients with a factor IX inhibitor may be at*	

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	an increased risk of anaphylaxis during future treatment with factor IX. Therefore, if you experience allergic reactions such as those described above, you should be tested for the presence of an inhibitor.	
Vascular thromboembolic events	**Section 4.4 of SmPC:** *Because of the potential risk of thrombotic complications with factor IX products, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing when administering this product to patients with liver disease, to patients post-operatively, to new-born infants, or to patients at risk of thrombotic phenomena or disseminated intravascular coagulation (DIC). The benefit of treatment with ALPROLIX in these situations should be weighed against the risk of these complications.* **Section 4.8 of SmPC:** *There is a potential risk of thromboembolic episodes following the administration of factor IX products, with a higher risk for low purity preparations. The use of low purity factor IX products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The use of high purity factor IX is rarely associated with thromboembolic complications. ALPROLIX is a high purity factor IX product.* **Package leaflet (warnings and precautions)** *Factor IX products may increase the risk of forming abnormal blood clots in your body, especially if you have risk factors for developing blood clots. Symptoms of a possible abnormal blood clot may include: pain and/or tenderness along a vein, unexpected swelling of an arm or leg, or*	No additional risk minimization measures are proposed.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	sudden shortness of breath or difficulty breathing.	
Medication errors	**Section 4.2 of SmPC:** *Treatment monitoring* *During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated injections. Individual patients may vary in their response to factor IX, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor IX activity) is indispensable.* *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. This is of importance particularly when changing the laboratory and/or reagents used in the assay.* *Measurements with a one-stage clotting assay utilising a kaolin-based aPTT reagent will likely result in an underestimation of activity level.* **Package leaflet** *3. How to use ALPROLIX* *Treatment with ALPROLIX will be started by a doctor who is experienced in the care of patients with haemophilia. Always use this medicine exactly as your doctor has told you (see section 7). Check with your doctor, pharmacist or nurse if you are not sure.* *7. Instructions for preparation and*	No additional risk minimization measures are proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	administration *Check the name and strength of the package, to make sure it contains the correct product.*	
Safety profile in patients ≥65 years old	**Section 4.2 of SmPC:** *There is limited experience in patients ≥65 years.*	No additional risk minimization measures are proposed.
Safety profile in women, including pregnant and breast-feeding women	**Section 4.6 of the SmPC:** *Pregnancy and breast-feeding* *Animal reproduction studies have not been conducted with ALPROLIX. A placental transfer study in mice was conducted (see section 5.3). Based on the rare occurrence of haemophilia B in women, experience regarding the use of factor IX during pregnancy and breast-feeding is not available. Therefore, factor IX should be used during pregnancy and breast-feeding only if clearly indicated.* *Fertility* *There are no fertility data available. No fertility studies have been conducted in animals with ALPROLIX.* **Package leaflet (warnings and precautions)** *If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.*	No additional risk minimization measures are proposed.
Safety profile in PUPs	**Section 4.2 of the SmPC:** *The safety and efficacy of ALPROLIX in previously untreated patients have not yet been established. No data are available.*	No additional risk minimization measures are proposed.
Use of rFIXFc for ITI	Routine pharmacovigilance	No additional risk minimization measures are proposed.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

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, Alprolix (eftrenonacog 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 data supporting this application are derived from three completed and one ongoing clinical study. Pharmacokinetic results show that rFIXFc has an improved PK profile compared to other licensed FIX products. In adults the comparison against Benefix showed a 2.42-fold prolonged t1/2 for rFIXFc and increased AUC (1.9 fold), MRT (2.39 fold) and estimated time to trough levels of 1% and 3% while the CL was decreased (0.51 fold). Also in the paediatric trial PK results show that rFIXFc has a prolonged terminal half-life and reduced CL compared to pre-study FIX products. The repeat PK evaluation in a subset of patients after 26 weeks demonstrates comparability to the PK parameters obtained after first dosing.

The weekly dose of rFIXFc for subjects on weekly prophylaxis (Arm 1) decreased from the starting regimen of 50 IU/kg to a median of 45.17 IU/kg (range 25.0 to 74.3 kg IU/kg) when averaged over all eligible doses administered during the efficacy period. The dosing interval of rFIXFc for subjects on individualized interval prophylaxis (Arm 2) started at 10 days, with a median interval when averaged over

all eligible dosing intervals during the efficacy period of 12.53 days (range 7.8 to 15.9 days). Regarding the efficacy of rFIXFc in the treatment of bleeding events, 97.3% of bleeding episodes were controlled with 2 or fewer injections of Alprolix, with 90.4% controlled by 1 injection. No bleeding episodes required more than 3 injections.

The mean bleeding rates based on observed data [3.07, 2.45, and 17.69 in Arms 1 (prophylaxis, fixed 7 day interval), 2 (prophylaxis, fixed dose of 100 IU/kg), and 3 (on demand treatment), respectively] confirm the beneficial effect of prophylaxis with Alprolix observed in the pivotal trial in PTPs ≥ 12. These annualized bleeding rates also compare favourably to published results from trials with other licensed FIX products. The weekly dose of rFIXFc for subjects on weekly prophylaxis (Arm 1) decreased from the starting regimen of 50 IU/kg to a median of 45.17 IU/kg (range 25.0 to 74.3 kg IU/kg) when averaged over all eligible doses administered during the efficacy period. The dosing interval of rFIXFc for subjects on individualized interval prophylaxis (Arm 2) started at 10 days, with a median interval when averaged over all eligible dosing intervals during the efficacy period of 12.53 days (range 7.8 to 15.9 days). Regarding the efficacy of rFIXFc in the treatment of bleeding events, 97.3% of bleeding episodes were controlled with 2 or fewer injections of Alprolix, with 90.4% controlled by 1 injection. No bleeding episodes required more than 3 injections.

In the paediatric population of trial 9HB02PED the mean annualized bleeding rate was 1.72 in the <6 years of age cohort, 2.80 in the 6 to <12 years of age cohort, and 2.26 in the total of both age cohorts. The median average dosing interval during the Efficacy Period was 6.99 days (range: 5.9 to 10.8 days), with no difference in median average dosing interval between cohorts. The majority of bleeding episodes were resolved by 2 or fewer injections (95.5%, 89.5% and 91.7% of subjects <6 years of age, subjects 6 to <12 years of age, and the total of both age cohorts, respectively).

Proof of efficacy of Alprolix during surgery is based on 29 major surgeries performed in 19 subjects in the pivotal phase 3 studies (998HB102 and 9HB02PED) and the ongoing extension study (9HB01EXT). In addition, 43 minor surgeries were undertaken in the same timeframe. The vast majority of evaluable surgeries were assessed as excellent or good by the surgeon or investigator.

Uncertainty in the knowledge about the beneficial effects

Data regarding the use of Alprolix in previously untreated patients are currently missing; an Open- Label, Multicenter Evaluation of the Safety and Efficacy of rFIXFc in the Prevention and Treatment of Bleeding in Previously Untreated Patients with Severe haemophilia B (PUPs study) is expected to provide this information in the post authorisation setting (see RMP).

Risks

Unfavourable effects

The size of the safety database available at the moment is satisfactory and exceeds guideline requirements. The nature and frequency of the reported adverse events do not give rise to concern and do not reveal unexpected safety signals.

Only a small proportion of observed AEs (18/869) in 15 subjects were assessed as related and Adverse Drug Reactions to rFIX-Fc y the investigators: palpitations (1x), breath odour (1x), paraesthesia oral (2x), fatigue (1x), infusion site pain (1x), decreased appetite (1x), dizziness (1x), dysgeusia (1x), headache (2x), hematuria (1x), obstructive uropathy (2x), renal colic (1x), hypotension (1x).

No related SAEs occurred and importantly, no inhibitor development, thromboembolic event or serious allergic reactions were observed.

Uncertainty in the knowledge about the unfavourable effects

Due to the rarity of the disease the safety database is relatively small although exceeds guideline requirements. Nonetheless, it is limited with regard to the elderly since only 2 patients older than 65 years of age participated in studies. This is included as missing information in the RMP. Apart from that, the database will be expanded by data gathered in the ongoing studies (9HB01EXT, 998HB303).

Data on long-term safety will be obtained in the post-marketing phase through ongoing studies (final study report from study 9HB01EXT) and registries. These data will include information in the elderly which is currently missing.

Data in previously untreated patients will be provided with the submission of the final study report from PUPs study 998HB303: An Open- Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc; BIIB029) in the Prevention and Treatment of Bleeding in Previously Untreated Patients with Severe Haemophilia B (PUPs study).

Effects table

Table 33. Effects Table for Alprolix

Effect	Short Description	Unit	rFIX-Fc	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PK	Half-life	h		Benefix (**998HB102**) Previous FIX products (**9HB02PED**)		
Trial SYN-FIX Fc-07-001	Mean t 1/2ß (2-compartmental model)	h	56.7	-	Small number of subjects	PK in the target population
Trial 998HB102	Mean t ½ (non-compartmental methods)	h	77.6	32.13	Different sampling time points rFIXFc - comparator	PK in the target population
Trial 9HB02PED	Mean t ½ (non-compartmental methods)	h	66.49 (<6 y.) 70.34 (6-<12 y.)		Different sampling time points rFIXFc - comparator	PK special population
Prophylaxis						
Bleeding rate	Annualized bleeding rate	n/year (mean)				
Trial 998HB102						
Arm 1	Prophylaxis, fixed 7 day interval	3.07	63	-	Subjects not randomized but assigned to treatment arm after discussion with the investigator	Summary of main efficacy results
Arm 2	Prophylaxis, fixed dose of 100 IU/kg	2.45	29	-		
Arm 3	On demand treatment of BEs	17.69	27	-		

Effect	Short Description	Unit	rFIX-Fc	Control	Uncertainties/ Strength of evidence	References
Trial 9HB02PED						
<6 years	Prophylaxis once weekly, starting dose of 50-60 IU/kg	1.72	15	-		
≥6 - <12		2.80	15	-		
Treatment of bleeding events		%				
Trial 998HB102		97.3%	636 BEs	-		Summary of main efficacy results
Trial 9HB02PED						
% controlled with ≤ 2 infusions		91.7	60 BEs	-		Summary of main efficacy results
Surgery		%				
Trial 998HB102						
Major	% excellent or good	100	14	-		Summary of main efficacy results
Minor		91.66	12	-		
Trial 9HB02PED						
Major	% excellent or good	-	-	-		Summary of main efficacy results
Minor		100	3	-		
9HB01EXT						Supportive Study
Major	% excellent or good	100	14	-		
Minor		100	10	-		
Unfavourable Effects						
Related AEs	From a total of 869 AEs in 133/153 subj.	#	18	(none)		Discussion on safety
	palpitations		1			
	Breath odour		1			
	Paraesthesia oral		2			
	Fatigue		1			
	Infusion site pain		1			
	Decreased appetite		1			

Effect	Short Description	Unit	rFIX-Fc	Control	Uncertainties/ Strength of evidence	References
	Dizziness		1			
	Dysgeusia		1			
	Headache		2			
	Haematuria		1			
	Obstructive uropathy		2			
	Renal colic		1			
	Hypotension		1			
AEs of special interest	FIX Inhibitor	BU/ml	No inhibitor could be observed	(none)	study procedures for inhibitor evaluation meet current standards	All studies
	Thrombotic event	AE incidence	1 case of device occlusion	(none)		

Abbreviations:

Notes:

Benefit-risk balance

Importance of favourable and unfavourable effects
The submitted PK data show a prolonged half-life of rFIXFc compared to other non-prolonged FIX products. Furthermore, prophylactic as well as haemostatic efficacy of rFIXFc was demonstrated in clinical studies. From these data extended treatment intervals for prophylactic dosing are in general supported. The currently available treatments usually require multiples injections, 2-3 per week. The majority of the patients in the clinical trials have been treated with 50IU/Kg once per week. The dose regimen of Alprolix can be further prolonged to administrations every 10 days with 100 IU/kg in individual patients. This can be considered as an advantage to the patient in this therapeutic area as it is expected to reduce the burden of prophylactic treatment and preserve the venous access.

The safety profile of rFIXFc seems to be in line with other FIX products from the data presented so far.

Benefit-risk balance
The benefit – risk balance in the treatment and prophylaxis of bleeding in patients with haemophilia B is considered positive.

Discussion on the benefit-risk balance

Overall, efficacy of rFIXFc for preventing bleeding episodes, treatment of breakthrough bleeds, on-demand treatment and surgical prophylaxis in adults and children is shown. PK results show that rFIXFc 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 (29 major surgeries performed in 19 subjects).

The safety profile of rFIXFc is comparable to other FIX products but due to the small haemophilia B population the safety database is rather small compared to other new medicinal products. Only a small proportion of observed AEs (18/869) in 15 subjects were assessed as related and Adverse Drug Reactions

to rFIX-Fc by the investigators. No related SAEs occurred and importantly, no inhibitor development, thromboembolic event or serious 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.

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 Alprolix in the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). ALPROLIX 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**

No 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 eftrenonacog 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/0303/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.