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Final assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Alprolix

eftrenonacog alfa

Procedure no: EMEA/H/C/004142/P46/006

Note

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

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1. Introduction

On Feb 18th, 2020 the MAH submitted a completed paediatric study for Alprolix (Eftrenonacog alfa/ BIIB029) in previously untreated paediatric patients (PUP) in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study 998HB303 (PUPs B) "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 Hemophilia B" is are part of a clinical development program.

As per the *"Guideline on clinical investigation of recombinant and human plasma-derived factor IX products"* (EMA/CHMP/BPWP/144552/2009 Rev. 1; currently under revision), a minimum of 20 previously untreated patients (PUPs) need to be evaluated for efficacy and safety during at least 50 exposure days connected with a post-approval commitment to follow-up at least 20-40 PUPs (20 from efficacy/safety trial and 20 new) for a minimum of 100 ED.

2.2. Information on the pharmaceutical formulation used in the study

Recombinant factor IX Fc fusion protein (rFIXFc) is a long-acting, fully recombinant coagulation factor IX Fc fusion protein consisting of human coagulation factor IX (FIX) covalently linked to the Fc domain of human immunoglobulin G1 (IgG1). The rFIXFc molecule is heterodimeric with a FIXFc single chain (FIXFc-sc, 641 amino acids) and an Fc single chain (Fc-sc, 226 amino acids) bound together through 2 disulfide bonds in the hinge region of Fc. rFIXFc requires the FIXFc-sc and Fc-sc protein subunits to assemble within a transfected cell line to form the final protein product. The molecular weight of rFIXFc is approximately 98 kDa.

The fusion of Fc to human FIX utilized a proven approach for increasing the elimination half-life of therapeutic proteins, including several approved drugs [Jazayeri and Carroll 2012; Wu and Sun 2014]. While the FIX moiety of rFIXFc retains FIX coagulation activity, the Fc component of rFIXFc binds with 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. rFIXFc was developed to have a longer half-life while maintaining the activity profile of FIX as a treatment for hemophilia B.

rFIXFc was approved in the EU on 12 May, 2016, for the treatment and prophylaxis of bleeding in subjects with hemophilia B. The product is also approved in e.g. the US, Canada, Japan, Australia, and Switzerland.

The original marketing authorization application for rFIXFc was based on 1 phase 1/2a dose-escalation study (SYN-FIXFc-07-001) and 2 pivotal phase 3 studies (9HB02PED and 998HB102). Additional studies have been performed (see "Annex - Line Listings" at the end of this report).

Two different formulations of rFIXFc drug product (DP) were used in clinical studies. A frozen liquid formulation was used in the Phase 1/2a study (SYN-FIXFc-07-001), and a lyophilized formulation was used in all subsequent clinical studies including the present study 998HB303.

In Study 998HB303 rFIXFc was supplied in a kit that contained several components: a vial of lyophilized drug, a prefilled diluent syringe, a vial adapter, and a winged infusion set. The lyophilized powder was in a clear glass vial containing 250, 500, 1000, or 2000 IU of rFIXFc (nominal strengths). The drug product was reconstituted with a prefilled diluent syringe containing 5 mL of 0.325% sodium chloride. The formulation of the lyophilized drug product contained rFIXFc, L-histidine, sucrose, mannitol, polysorbate 20, and sodium chloride. The formulation was the same for all 4 strengths (250, 500, 1000, or 2000 IU of rFIXFc).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- 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 Hemophilia B"

2.3.2. Clinical study

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 Hemophilia B"

Study Period:
Date of First Treatment: Nov 13th, 2014
Date of Last Visit: Aug 20th, 2019

Description

Study 998HB303 was a phase 3, open-label, single-arm, multicenter study evaluating the safety and efficacy of rFIXFc in male pediatric PUPs with severe hemophilia B, when used according to local standard of care for implementation of a prophylaxis regimen, including an optional preceding episodic (on-demand) treatment regimen. The primary objective of the study was to evaluate the safety of rFIXFc in PUPs with severe hemophilia B. The secondary objectives were to evaluate the efficacy of rFIXFc in the prevention and treatment of bleeding episodes in PUPs, as well as to evaluate rFIXFc consumption for prevention and treatment of bleeding episodes in PUPs.

Methods

Objectives

Primary Objective:

To evaluate the safety of rFIXFc in previously untreated patients (PUPs) with severe hemophilia B.

Secondary Objectives:

To evaluate the efficacy of rFIXFc in the prevention and treatment of bleeding episodes in PUPs.

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

Exploratory Objective:

To evaluate the effect of rFIXFc on patient-reported health outcomes.

Study design

This was an open-label, single-arm, multicenter study evaluating the safety and efficacy of rFIXFc in pediatric PUPs with severe hemophilia B when used according to local standard of care. For the purpose of this study, a PUP was defined as a subject who had not had prior exposure to FIX concentrates, except for up to 3 injections of commercially available rFIXFc before the confirmation of eligibility and less than 28 days prior to the first Screening Visit. Following the confirmation of eligibility, administration of commercially available rFIXFc was no longer allowed and only rFIXFc labelled for study use was to be administered.

Subjects with a documented plasma FIX activity of ≤2% could be enrolled on the basis of local laboratory results and could receive study drug after samples for FIX activity level and inhibitors had been obtained for testing at the central laboratory. However, any such subject was to be withdrawn if the central laboratory screening results indicated FIX activity level >2% or a positive inhibitor. Baseline incremental recovery (IR) assessments were to be performed as soon as practicable once all eligibility criteria had been met and the subject was enrolled. The Baseline IR Visit activities could be completed on the same day as Screening, or they could be completed as a part of a separate visit or at an unscheduled visit.

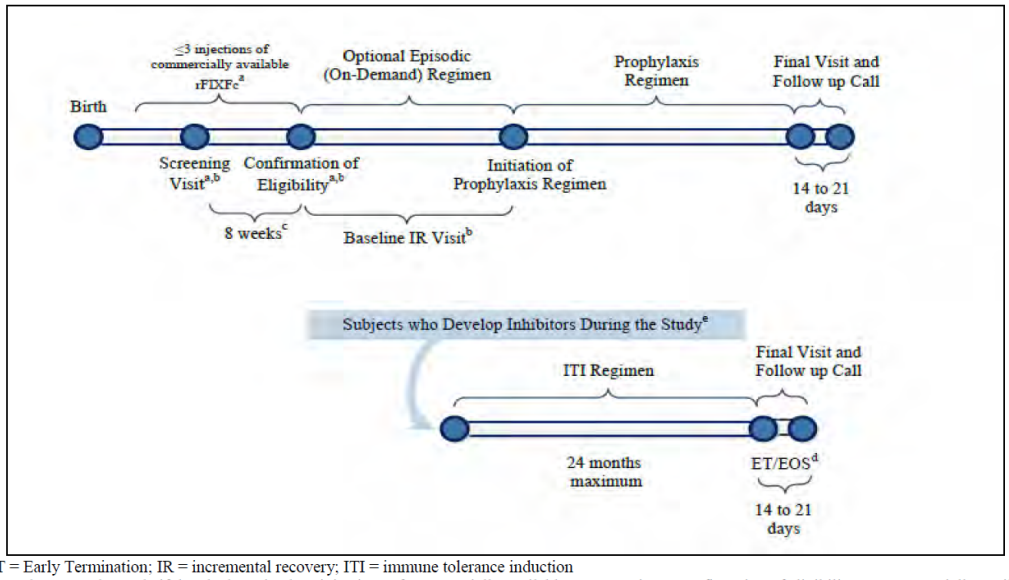
Following the confirmation of eligibility, the Investigator had the option to treat eligible subjects episodically (on-demand) prior to initiating a prophylactic regimen. The duration of episodic treatment was at the Investigator's discretion, in accordance with local standard of care. At least 20 PUPs were planned to complete the study after reaching at least 50 EDs with rFIXFc. 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.

Surgery was allowed during the study.

Immune tolerance induction (ITI) with rFIXFc was allowed during the study for those subjects developing, after exposure to rFIXFc study drug, a positive low titer inhibitor (≥0.60 and <5.00 Bethesda unit [BU]/mL) with bleeding episodes that could not be adequately treated with rFIXFc, or a positive high titer inhibitor (≥5.00 BU/mL).

Because of the risk of allergic reactions with FIX concentrates, the first administration of rFIXFc (commercially available rFIXFc and/or study drug) was performed under medical observation where proper medical care for allergic reactions could be provided. The first injection of rFIXFc study drug after the Screening Visit was administered by the Investigator or a qualified delegate. Thereafter, study drug could be administered by a parent/caregiver, a qualified medical professional under the direction of the Investigator, self-administered by older children, or given at the clinic. Study treatment could also be injected in the hospital, for example, during surgery or during hospitalization due to major bleeding.

Figure 1: Study design



EOS = end of study; ET = Early Termination; IR = incremental recovery; ITI = immune tolerance induction

[a] Subjects were not allowed to enter the study if they had received >3 injections of commercially available rFIXFc prior to confirmation of eligibility, or commercially available rFIXFc more than 28 days prior to the first Screening Visit.

[b] Screening Visit and Baseline IR Visit could be performed as 2 separate visits OR all activities necessary for screening, confirmation of eligibility, and the Baseline IR Visit could be performed at the same visit.

Study population/ Sample size

Because the size of the hemophilia population is limited, the sample size is based on clinical rather than statistical considerations. Taking into account the CHMP Guideline and in an effort to enrol a sufficient number of subjects to assess the efficacy and safety of rFIXFc in this population of primarily very young children, approximately 30 subjects enrolled to achieve at least 20 subjects with no less than 50 EDs by the completion of the study.

Inclusion Criteria:

To be eligible to participate in this study, candidates were required to meet the following eligibility criteria at the time of Screening or at the timepoint specified in the individual eligibility criterion listed:

- Ability of the subject or the subject's legally authorized representative (e.g. their parent or legal guardian) to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information, and/or to provide assent, in accordance with national and local subject privacy regulations.
- Male, age <18 years at the time of informed consent.
- Weight ≥3.5 kg.

- Severe hemophilia B defined as ≤2 IU/dL (≤2%) endogenous FIX documented in the medical record or as tested during the Screening Period. Enrolled subjects whose central laboratory screening results indicated a baseline FIX activity level >2% of normal were withdrawn.

Exclusion Criteria:

Candidates were excluded from study entry if any of the following exclusion criteria existed at Screening or at the timepoint specified in the individual criterion listed.

- History of positive inhibitor testing. A prior history of inhibitors was defined based on a patient's historical positive inhibitor test using the local laboratory Bethesda value for a positive inhibitor test (i.e. equal to or above lower level of detection).
- History of hypersensitivity reactions associated with any rFIXFc administration.
- Exposure to blood components or injection with a FIX concentrate (including plasma derived) other than rFIXFc.
- Injection with commercially available rFIXFc more than 28 days prior to Screening.
- More than 3 injections of commercially available rFIXFc prior to confirmation of eligibility.
- Other coagulation disorder(s) in addition to hemophilia B.
- Any concurrent clinically significant major disease that, in the opinion of the Investigator, would have made the subject unsuitable for enrollment (e.g. HIV infection with cluster of differentiation 4 [CD4] lymphocyte count <200 cells/μL or a viral load >200 particles/μL, or any other known congenital or acquired immunodeficiency).
- Current systemic treatment with chemotherapy and/or other immunosuppressant drugs. Use of steroids for treatment of asthma or management of acute allergic episodes or otherwise life-threatening episodes was allowed. Treatment in these circumstances should not have exceeded a 14-day duration.
- Participation within the past 30 days in any other clinical study involving investigational treatment.
- Current enrollment in any other clinical study involving investigational treatment.
- Inability to comply with study requirements.
- Other unspecified reasons that, in the opinion of the Investigator or Bioverativ, would have made the subject unsuitable for enrollment.

Treatments

Dose selection:

The recommended starting prophylactic dose of rFIXFc in this study, approximately 50 IU/kg weekly, was based on the data from the Phase 1/2a and Phase 3 studies (including pediatric PK data from subjects <12 years of age) and knowledge of increased clearance of factor concentrates in children. This dose was predicted to maintain trough levels >1% in 99% of pediatric subjects. Adjustments to the dose and interval of rFIXFc could have been made in this study based on available PK data, subsequent FIX activity levels, level of physical activity, and bleeding pattern, in accordance with local standards of care for a prophylactic regimen. The dose for treatment of bleeding episodes targeted peak plasma FIX activity of approximately 30% to 100%, in accordance local standards and taking into account lower rFIXFc recoveries observed in young children. If a subject required surgery while participating in this study, the subject could be treated with the dose and regimen of rFIXFc deemed appropriate for the type of surgery.

Dosing procedure:

For the Baseline incremental recovery (IR) measurement, a dose of 50 IU/kg was given in the clinic as an IV injection. The actual potency (= true potency of the vial as measured by a validated potency assay; between approx. 80% and 125% of nominal strength) of rFIXFc was used to calculate the units and volume of rFIXFc infused for the Baseline IR Visit dose.

rFIXFc was delivered via a slow push IV injection over several minutes at a rate of administration determined by the subject's comfort level. Any missed doses were taken as soon as possible or according to the instructions of the Investigator.

Episodic (optional) and prophylactic treatment regimens:

Following confirmation of eligibility and enrolment, the Investigator had the option to treat the subject with an episodic regimen for a period of time before initiating a prophylaxis regimen.

The duration of the **episodic** period was at the Investigator's discretion, in accordance with local standard of care. However, given global standards of care, it was expected that the prophylactic regimen would be initiated prior to or immediately following a third episode of hemarthrosis.

Subjects generally began a **prophylactic** regimen after confirmation of eligibility, prior to or immediately following the occurrence of a third hemarthrosis (joint bleed). The recommended initial prophylactic regimen is 50 IU/kg weekly. Adjustments to the dose and dosing interval could be made based upon available incremental recovery data, subsequent FIX activity levels, level of physical activity, and bleeding pattern, in accordance with local standards of care for a prophylactic regimen.

The subject's parents/caregivers were instructed to **treat at the first sign of a bleeding episode** with a single dose of rFIXFc. The dose of rFIXFc to treat the bleeding episode will be based on the subject's clinical condition, known PK information, type and severity of the bleeding event and input from the Medical Monitor, if necessary.

Duration of Treatment and Follow-Up:

Treatment Period: The study consisted of screening, treatment, and follow-up periods. The duration of individual subject study participation was approximately 6 months to 3 years, including screening and follow-up. Each subject was considered to have completed their treatment period once they reached at least 50 EDs to the study treatment, unless withdrawal from the study occurred, or the end of study (EOS) was declared. The EOS occurred after at least 20 subjects reached at least 50 EDs with rFIXFc. Once this milestone had been achieved, all ongoing study subjects were to return to the study center for the ET/EOS Visit assessments.

Follow-Up Period: Subjects underwent the assessments of the Early Termination (ET)/End of Study (EOS) Visit after at least 50 EDs to rFIXFc had been achieved, if they had withdrawn from the study, or the end of study was declared. A Final Safety Follow-up Visit/Telephone Call was conducted 14 (+7) days after the last dose of rFIXFc to assess the subject's status for AEs, SAEs, and concomitant treatments and procedures. It was at the discretion of the Investigator to conduct the Final Safety Follow-up Visit by telephone or in person.

Outcomes/endpoints

Primary endpoint:

The primary endpoint of the study was the occurrence of inhibitor development.

Secondary endpoints:

The secondary endpoints of the study were:

- The annualized number of bleeding episodes[1)] (spontaneous and traumatic) 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[2)] (Investigator assessment for bleeding episodes treated in the clinic; parent or caregiver assessment for all other bleeding episodes).
- The total number of EDs per subject per year.
- Total annualized rFIXFc consumption per subject for the prevention and treatment of bleeding episodes.
- The number of injections and dose per injection of rFIXFc required to resolve a bleeding episode.
- rFIXFc incremental recovery.

[1)] In this study, a bleeding episode was defined as follows: A bleeding episode started from the first sign of a bleeding episode and ended no more than 72 hours after the last injection to treat the bleeding episode, within which any symptoms of bleeding at the same location, injections less than or equal to 72 hours apart, were considered the same bleeding episode. Any injection to treat the bleeding episode, taken more than 72 hours after the preceding one, was considered the first injection to treat a new bleeding episode in the same location. Any bleeding at a different location was considered a separate bleeding episode, regardless of the time from the last injection.

Bleeding episodes were classified as spontaneous if a parent/caregiver recorded a bleeding event when there was no known contributing factor such as a definite trauma or antecedent "strenuous" activity. The determination of "strenuous" was at the discretion of the Investigator, and the parent/caregiver/subject needed to be instructed by the Investigator.

Bleeding episodes were classified as traumatic if the parent/caregiver recorded a bleeding episode even when there was a known or believed reason for the bleed. For example, when a subject exercised strenuously and then had a bleeding episode in the absence of any obvious injury, the bleeding episode was still recorded as traumatic. Target joint bleeding episodes were considered traumatic if a known action led to bleeding into the joint. The Investigator considered whether events resulting in a traumatic bleeding episode qualified as AEs and should be reported as such.

[2)] Each subject or their parent/caregiver will rate the treatment response to any bleeding episode, using the following 4-point scale (excellent, good, moderate, or none). This assessment is to be made approximately 8 to 12 hours from the time the injection was given to treat the bleeding episode and prior to any additional doses of rFIXFc given for the same bleeding episode.

- Excellent: abrupt pain relief and/or improvement in signs of bleeding within approximately 8 hours after the initial injection
- Good: definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after an injection, but possibly requiring more than 1 injection after 24 to 48 hours for complete resolution

- Moderate: probable or slight beneficial effect within approximately 8 hours after the initial injection and requires more than 1 injection
- None: no improvement, or condition worsens within approximately 8 hours after the initial injection

Investigators recorded assessments of each subject's response to their assigned rFIXFc regimen using the following 4-point scale:

- Excellent: bleeding episodes responded to ≤ the usual number of injections or ≤ the usual dose of rFIXFc, or the rate of breakthrough bleeding during prophylaxis was ≤ that usually observed.
- Effective: most bleeding episodes responded to the same number of injections and dose, but some required more injections or higher doses, or there was a minor increase in the rate of breakthrough bleeding.
- Partially Effective: bleeding episodes most often required more injections and/or higher doses than expected, or adequate breakthrough bleeding prevention during prophylaxis required more frequent injections and/or higher doses.
- Ineffective: routine failure to control hemostasis or hemostatic control required additional agents.

Investigators considered the following, when available, while making the assessment:

- Frequency of rFIXFc injections.
- Response to rFIXFc injection.
- Information reported in the EPD by the subject's parent/caregiver.

Exploratory Endpoints:

The exploratory endpoints included, but were not limited to, health outcomes as captured via a patient reported questionnaire. This questionnaire asked about the impact of hemophilia and treatment on work, school, and caregiver.

Questions were asked at 24-week intervals and the categories questioned were as follows:

- How many times the child's injection was administered by different persons
- Was work missed due to the child's hemophilia
- Was school missed by the child due to his hemophilia
- Was the caregiver's social/leisure time disrupted due to the child's hemophilia
- Was household/domestic routine disrupted due to the child's hemophilia

Assessments of patient-reported health outcomes related to hemophilia included the following:

- Number of hemophilia-related hospitalizations, excluding planned hospitalizations documented at Screening
- Number of hemophilia-related hospitalization days
- Number of hemophilia-related emergency room visits
- Number of hemophilia-related physician visits excluding study visits
- Number of days off school or day care (kindergarten)
- Number of days off work for parent/legal guardian or caregiver (demographic data for caregivers could be collected at the Screening Visit)
- Primary method of administering rFIXFc

Clinical Safety Assessments

- Physical examination
- Medical and surgical history
- Height
- Weight
- Vital signs measurements (blood pressure, pulse rate, respiratory rate, and temperature)
- Concomitant therapy and procedures recording, including concomitant medications taken by the mother of any subject who was receiving breast milk, unless the breast milk was derived from a source other than the mother or the mother did not consent.
- AE and SAE recording

Laboratory Safety Assessments

- Hematology: white blood cell (WBC) count and differential, red blood cell (RBC), hemoglobin, hematocrit, and platelet count
- Blood chemistry: sodium, potassium, chloride, total protein, total bilirubin, gamma glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN), serum creatinine, and glucose
- Urinalysis
- Anti-rFIXFc antibodies (detection, titer, and specificity)
- Neutralizing antibody development (inhibitor) measured by Nijmegen-modified Bethesda assay (see below)

Subjects were tested for inhibitor and anti-rFIXFc antibody formation at each clinic visit. Samples for anti-rFIXFc antibody testing were collected at the same timepoint when any samples were collected for inhibitor testing, including confirmatory and unscheduled inhibitor tests, tests for suspected inhibitor development, and as required before and after surgery. Washout prior to sample collection for inhibitor testing was at least 72 hours.

If inhibitor development was suspected at any time during the study (eg, the expected plasma FIX activity levels were not attained or if bleeding was not controlled with an expected dose), the subject was tested for inhibitors by the central laboratory.

A positive inhibitor test result is defined as an inhibitor test result of ≥0.60 BU/mL that is confirmed by a second test result of ≥0.60 BU/mL from a separate sample, drawn 2 to 4 weeks following the original sample. Both tests were performed by the central laboratory using the Nijmegen-modified Bethesda assay.

A low titer inhibitor is defined as a positive inhibitor test with a result of ≥0.60 and <5.00 BU/mL. A high titer inhibitor is defined as ≥5.00 BU/mL. Subjects with discrepant inhibitor test results (initial low titer result followed by high titer result or initial high titer result followed by low titer result) had repeat inhibitor testing performed by the central laboratory from a separate sample, drawn 2 to 4 weeks following the previous sample. If 2 of 3 test results were <5.00 BU/mL, the inhibitor was considered low titer. If 2 of 3 test results were ≥5.00 BU/mL, the inhibitor was considered high titer.

Table 1: Schedule of events: exposure day milestone visits

Activities	Visits at			
	5 EDs (±2 EDs)	10 EDs (10 to 15 EDs)	20 EDs (20 to 25 EDs)	50 EDs (50 to 55 EDs)
Nijmegen-Modified Bethesda Assay (Inhibitor Assay)[a, b]	X	X	X	X
Anti-rFIXFc Antibody[a]	X	X	X	X
F9 Genotyping[b]	If needed			

ED = exposure day; rFIXFc = recombinant coagulation factor IX Fc fusion protein.

a Washout prior to sample collection for the inhibitor and anti-rFIXFc antibody tests was at least 72 hours. Samples for anti-rFIXFc antibody testing were collected at the same timepoint when any samples were collected for inhibitor testing, including confirmatory and unscheduled inhibitor tests. An unscheduled visit could have been required to obtain samples to confirm a positive inhibitor test result. In addition, if inhibitor development was suspected at any time during the study (eg, the expected plasma factor IX activity levels were not attained or if bleeding was not controlled with an expected dose), samples were collected for inhibitor testing by the central laboratory and for anti-rFIXFc antibody testing.

b If the subject's genotype was not already known at Screening and the sample could not be drawn due to blood volume limitations at the Predose Baseline IR Visit, this assessment could be performed at any other visit. If the subject developed an inhibitor on the study, a sample could be drawn for this testing at any time during the Treatment Period. The parent/legal guardian provided separate consent for genotyping.

Statistical Methods

This is an open-label single arm study so there is no blinding or randomization.

Continuous variables are summarized and presented by number, mean, median, standard deviation, minimum and maximum, and, where appropriate, with the 25th and 75th percentiles. Categorical variables are summarized by the number and percentage in each category.

There is no statistical hypothesis for this study as all but the primary endpoint (inhibitor development) will be analysed descriptively only. Any patient who develops an inhibitor following the initial rFIXFc administration will be included in the numerator. All patients who have received at least 1 dose of rFIXFc will be included in the denominator. An exact 95% confidence interval for the proportion of patients with a positive inhibitor will be calculated using the Clopper-Pearson method for a binomial proportion.

Analysis populations:

The **All-Enrolled Analysis Set (n=33)** was defined as all subjects who were enrolled in the study, whether dosed with rFIXFc or not.

The **Full Analysis Set, FAS (n=33)** was defined as all enrolled subjects who receive at least 1 dose of study rFIXFc. All analyses and summaries of efficacy and exploratory endpoints were based on the FAS, unless otherwise specified.

The **Safety Analysis Set (n=33)** was defined as all subjects who received at least 1 dose of study rFIXFc. All analyses and summaries of safety, demographic, and baseline characteristics were based on the Safety Analysis Set, unless otherwise specified.

The **Surgery Subgroup** was defined as all subjects who underwent major surgery after first dose of study drug.

Subjects who developed a positive inhibitor after exposure to rFIXFc were included in the **Inhibitor Subgroup**.

The **ITI Subgroup** was defined as all patients who consented to and initiated the ITI treatment regimen.

Results

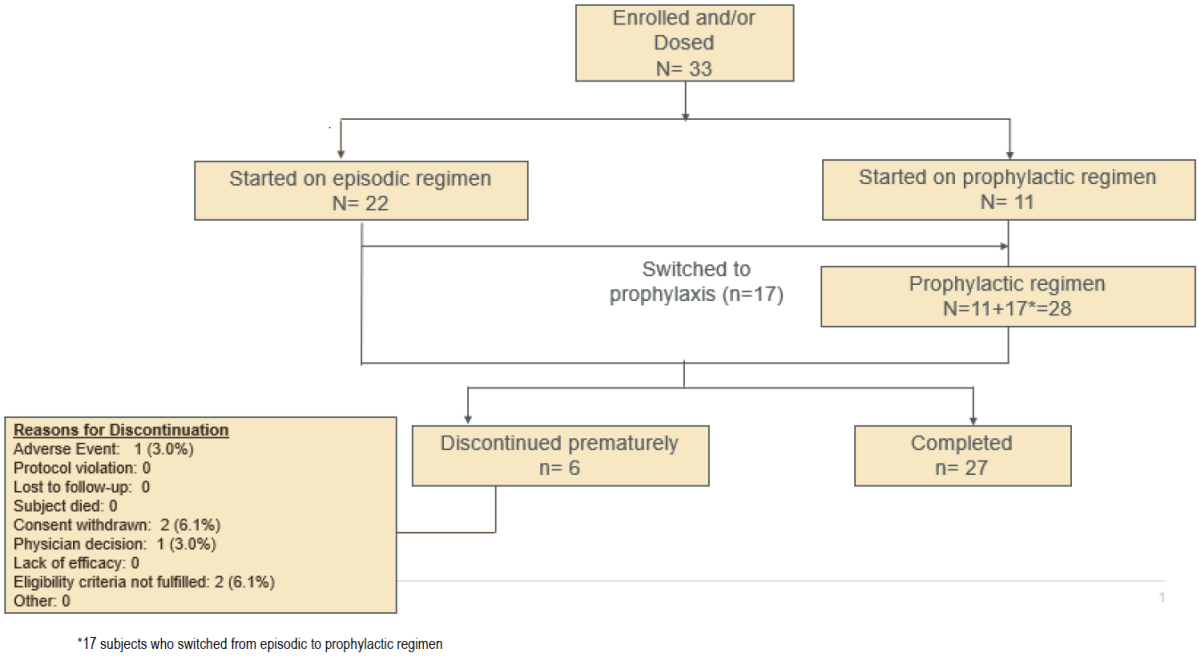
Recruitment/ Number analysed

A total of 38 subjects were screened for eligibility, 5 subjects were screen failure and a total of 33 male subjects were enrolled and received study treatment at 24 investigational sites in 11 countries worldwide.

The highest-enrolling countries were the US (11 subjects), the UK (5 subjects), Ireland, Poland, and France (3 subjects, each). Italy and Sweden enrolled 2 subjects each; Australia, Denmark, Netherlands, and New Zealand enrolled 1 subject each. The sites with the highest enrolment were site 906 in the UK (3 subjects), sites 122 and 301 in the US (2 subjects) each.

The ***All-Enrolled Analysis Set*** had a total of 33 subjects and the ***Safety Analysis Set*** (subjects who had received at least 1 dose of study treatment as of the data cutoff date) had a total of 33 subjects: 22 subjects began study participation on the episodic treatment regimen and 11 subjects began study participation on the prophylactic treatment regimen. Of the 22 subjects who began the study on the episodic treatment regimen, 17 subjects switched from episodic to prophylactic treatment, for a total of 28 subjects who were ever on the prophylactic treatment regimen.

Figure 2: disposition of subjects



Twenty seven of the 33 enrolled subjects (81.8%) had completed study participation, 6 subjects (18.2%) had terminated study participation early.

- 2 subjects enrolled under minimum eligibility criteria but did not meet the full eligibility criteria due to excluded prior medication or disqualifying laboratory result (Baseline FIX activity level ⩾2%).
- 2 subjects terminated early as they withdrew consent.
- 1 subject withdrew from the study due to TESAEs of hypersensitivity and Factor IX inhibition that were considered related to the study treatment.
- 1 subject terminated early due to "physician decision" to close the site.

The last prescribed dosing frequency for each subject was twice weekly (1 subject), every 5 days (1 subject), every 7 days (23 subjects), every 14 days (2 subjects) and on-demand (1 subject).

One subject in the prophylactic group (3.0%) developed inhibitor overall. This subject developed low-titer inhibitor C/M.

Key visits were those in which inhibitor tests were performed. Most subjects completed the Week 12 visit (31, 93.9%), Week 24 visit (29, 87.9%), Week 36 visit (29, 87.9%), Week 48 visit (28, 84.8%), Week 60 visit (24, 72.7%), Week 72 visit (19, 57.6%), and approximately half of all subjects (16, 48.5%) achieved Week 84 visit. Approximately half of the subjects (17, 51.5%) completed the 10-ED inhibitor test visit, 15 subjects (45.5%) completed the 20-ED inhibitor test visit, and 14 subjects (42.4%) completed the 50-ED inhibitor test visit.

Table 2: disposition by treatment regimen

	Treatment regimen			
	Episodic (N=22)	Prophylactic (N=28)	ITI (N=0)	Overall (N=33)
Safety Analysis Set (a)	22 (100.0%)	28 (100.0%)	0	33 (100.0%)
All-Enrolled Analysis Set (b)	22 (100.0%)	28 (100.0%)	0	33 (100.0%)
Full Analysis Set(FAS) (c)	22 (100.0%)	28 (100.0%)	0	33 (100.0%)
Patients with an efficacy period (d)	22 (100.0%)	28 (100.0%)	0	33 (100.0%)
Patients in the Surgery Subgroup (e)	0	0	0	0
Patients in the Inhibitor Subgroup (f)	0	1 (3.6%)	0	1 (3.0%)
Patients with high-titer inhibitors	0	0	0	0
Patients with low-titer inhibitors	0	1 (3.6%)	0	1 (3.0%)
Low-titer C/M	0	1 (3.6%)	0	1 (3.0%)
Low-titer not C/M	0	0	0	0
Patients in the ITI Subgroup (g)	0	0	0	0
Completion status				
Completed (h)	17 (77.3%)	26 (92.9%)	0	27 (81.8%)
Discontinued prematurely	5 (22.7%)	2 (7.1%)	0	6 (18.2%)

	Treatment regimen			
	Episodic (N=22)	Prophylactic (N=28)	ITI (N=0)	Overall (N=33)
Adverse Event	0	1 (3.6%)	0	1 (3.0%)
Protocol Violation	0	0	0	0
Lost to Follow-Up	0	0	0	0
Subject Died	0	0	0	0
Consent Withdrawn	2 (9.1%)	1 (3.6%)	0	2 (6.1%)
Physician Decision	1 (4.5%)	0	0	1 (3.0%)
Lack of Efficacy	0	0	0	0
Eligibility Criteria not fulfilled	2 (9.1%)	0	0	2 (6.1%)
Other	0	0	0	0

NOTE 1: Percentages for Safety Analysis Set and All-Enrolled Analysis Set are based on the total number of patients who were enrolled in the study or who received at least 1 dose of rFIXFc. All other percentages are based on the number of patients in the All-Enrolled Analysis Set.
2: Patients are included in each treatment regimen they participated in and as such may appear in more than one treatment regimen. Each patient is counted only once in the overall column.
3: C/M = clinically meaningful. Not C/M = not clinically meaningful.
(a) All patients who received at least 1 dose of rFIXFc.
(b) All patients who were enrolled in the study, whether dosed with rFIXFc or not.
(c) Enrolled patients who have taken at least 1 dose of rFIXFc.
(d) FAS patients with at least 1 day of treatment for an episodic regimen or at least 2 prophylactic injections for prophylactic regimens.
(e) Patients who have undergone major surgery after first dose of rFIXFc.
(f) Patients who developed a positive inhibitor after exposure to rFIXFc. Patients are included in each group as follows: A high titer inhibitor is a confirmed inhibitor with a titer of ≥5.00 BU/mL. A low titer inhibitor is a confirmed inhibitor with a titer of ≥0.60 and <5.00 BU/mL. A low titer C/M inhibitor is a low-titer inhibitor which met the clinically meaningful criteria per medical adjudication as defined in the SAP. A low titer not C/M inhibitor did not meet the clinically meaningful criteria.
(g) Patients who consent to and initiate the ITI treatment regimen.
(h) Completed means did not discontinue from the study prematurely. Patients who discontinued participation in the study because the study was stopped by the Sponsor are considered to have completed the study.

Baseline data

All subjects who received treatment with rFIXFc had been determined to have severe hemophilia B defined as ≤2 IU/dL (≤2%) endogenous FIX. The summary of medical and surgical history by treatment regimen was typical for this population. All subjects were male, with an overall median age of 0.60 (range 0.08 years to 2 years of age). Most subjects (26, 78.8%) were <1 year of age. Median height was 71.60 cm (range 55 to 91 cm), and median weight was 9 kg (range 4.6 to 17 kg).

Of the 33 subjects who received at least one dose of study treatment, 22 (66.7%) were White, 1 subject (3.0%) each were Asian and Black or African-American. There were 5 subjects (15.2%) who did not have their race reported due to confidentiality regulations. 4 subjects (12.1%) were noted as "other" race. The ethnicity of most subjects was not Hispanic or Latino (26, 78.8%). The ethnicity of 5 subjects (15.2%) was not reported due to local regulations. By geographic region, enrolment was highest in Europe (20, 60.6%), followed by North America (11, 33.3%), and "other" (i.e. Australia, and New Zealand) (2, 6.1%).

Table 3: Demographics and Baseline Characteristics by Treatment Regimen (Safety Analysis Set)

	Treatment regimen			
	Episodic (N=22)	Prophylactic (N=28)	ITI (N=0)	Overall (N=33)
Age (years) (a)				
n	22	28	0	33
Mean	0.53	0.69	0	0.68
SD	0.455	0.446	0	0.491
Median	0.45	0.63	0	0.60
Min, Max	0.08, 2.00	0.08, 2.00	0	0.08, 2.00
Age categories (years)				
n	22	28	0	33
<1	19 (86.4%)	22 (78.6%)	0	26 (78.8%)
1	2 (9.1%)	5 (17.9%)	0	5 (15.2%)
2	1 (4.5%)	1 (3.6%)	0	2 (6.1%)
Height (cm)				
n	19	26	0	29
Mean	67.47	70.90	0	70.89
SD	9.523	9.094	0	9.802
Median	65.00	71.80	0	71.60
Min, Max	55.0, 91.0	55.0, 90.9	0	55.0, 91.0
Weight (kg)				
n	22	28	0	33
Mean	7.99	8.90	0	8.88
SD	2.832	2.791	0	2.980
Median	7.56	9.03	0	9.00
Min, Max	4.6, 16.0	4.6, 17.0	0	4.6, 17.0
Race				
n	22	28	0	33
White	16 (72.7%)	19 (67.9%)	0	22 (66.7%)
Black or African-American	0	1 (3.6%)	0	1 (3.0%)
Asian	0	1 (3.6%)	0	1 (3.0%)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0
Not reported due to confidentiality regulations	3 (13.6%)	4 (14.3%)	0	5 (15.2%)
Other	3 (13.6%)	3 (10.7%)	0	4 (12.1%)
Ethnicity				
n	22	28	0	33
Hispanic or Latino	1 (4.5%)	2 (7.1%)	0	2 (6.1%)
Not Hispanic or Latino	18 (81.8%)	22 (78.6%)	0	26 (78.8%)
Not reported due to confidentiality regulations	3 (13.6%)	4 (14.3%)	0	5 (15.2%)
Geographic Location (b)				
n	22	28	0	33
Europe	13 (59.1%)	17 (60.7%)	0	20 (60.6%)
North America	7 (31.8%)	9 (32.1%)	0	11 (33.3%)
Other	2 (9.1%)	2 (7.1%)	0	2 (6.1%)

Hemophilia History:

Bleeding history in the 3 months prior to study entry was estimated by the Investigator. Overall, 21 subjects (63.6%) had 0 bleeding episodes in the 3 months prior to study entry. The median number of bleeding episodes in the prior 3 months was 0.0, with an overall range of 0 to 5.

The median estimated number of spontaneous bleeding episodes in the prior 3 months was 0.0 with a range of 0 to 3. Similarly, the median estimated number of traumatic bleeding episodes was 0.0 (range 0 to 5).

Table 4: Summary of haemophilia history

Summary of hemophilia history by treatment regimen
Safety Analysis Set

	Treatment regimen			
	Episodic (N=22)	Prophylactic (N=28)	ITI (N=0)	Overall (N=33)
Time since diagnosis of hemophilia (days) (a)				
n	22	28	0	33
Mean	141.0	152.6	0	165.6
Sd	198.90	167.65	0	204.79
Median	84.0	88.5	0	88.0
Min, Max	0, 901	0, 755	0	0, 901
FIX activity at screening (b)				
n	22	28	0	33
<=2%	22 (100.0%)	28 (100.0%)	0	33 (100.0%)
>2%	0	0	0	0
F9 genotype at screening				
n	22	28	0	33
Missense	10 (45.5%)	12 (42.9%)	0	14 (42.4%)
Nonsense	4 (18.2%)	11 (39.3%)	0	11 (33.3%)
Promoter or Regulatory Region Mutation	2 (9.1%)	0	0	2 (6.1%)
Small Deletions (<50 BP)	0	0	0	0
Small Insertions (<50 BP)	0	0	0	0
Large Deletions (≥50 BP)	0	0	0	0
Large Insertions (≥50 BP)	0	0	0	0
Large Structure Change (>50bp)	1 (4.5%)	0	0	1 (3.0%)
Frameshift	1 (4.5%)	1 (3.6%)	0	1 (3.0%)
Splice site change	1 (4.5%)	1 (3.6%)	0	1 (3.0%)
Splicing mutation	0	0	0	0
Other	0	0	0	0
Unknown	3 (13.6%)	3 (10.7%)	0	3 (9.1%)
Family history of inhibitors				
n	22	28	0	33
Yes	2 (9.1%)	4 (14.3%)	0	6 (18.2%)
No	0	0	0	0
Unknown	20 (90.9%)	24 (85.7%)	0	27 (81.8%)
Vaccination within last year				
n	22	28	0	33
Yes	16 (72.7%)	25 (89.3%)	0	27 (81.8%)
No	6 (27.3%)	3 (10.7%)	0	6 (18.2%)
HIV status at screening				
n	22	28	0	33
Yes	0	0	0	0
No	9 (40.9%)	10 (35.7%)	0	12 (36.4%)
Unknown	13 (59.1%)	18 (64.3%)	0	21 (63.6%)
Hepatitis B status at screening				
n	22	28	0	33
Yes	0	0	0	0
No	2 (9.1%)	2 (7.1%)	0	3 (9.1%)
Unknown	20 (90.9%)	26 (92.9%)	0	30 (90.9%)
Hepatitis C status at screening				
n	22	28	0	33
Yes	0	0	0	0
No	2 (9.1%)	1 (3.6%)	0	2 (6.1%)
Unknown	20 (90.9%)	27 (96.4%)	0	31 (93.9%)

Efficacy results

All efficacy endpoints were considered secondary endpoints in this study.

Annualized Bleeding Rate (ABR) by treatment regimen

The median ABR by treatment regimen was 0.21 (range 0.0 to 6.8) and 1.24 (range 0.0 to 5.4) for subjects on the episodic (n=22) and prophylactic (n=28) regimens, respectively. The total number of subject-years followed was 14.02 years for episodic treatment and 38.97 years for prophylactic treatment. The number and percentage of subjects who experienced 0 bleeding episodes was 11 (50.0 %) for the episodic treatment and 8 (28.6 %) for the prophylactic treatment. Five (22.7%) subjects had an ABR of >5-10 on episodic treatment, whereas 2 (7.1%) subjects on prophylactic treatment fell into this category. No subject had an ABR of >10 on either episodic or prophylactic treatment.

Table 5: summary of annualised bleeding rates by treatment regimen

Summary of annualized bleeding rates by treatment regimen
Full Analysis Set
Page 1 of 1

	Treatment regimen		
	Episodic (N=22)	Prophylactic (N=28)	ITI (N=0)
Number of patients with an efficacy period	22	28	0
Overall			
n	22	28	0
Mean	2.13	1.58	
SD	2.525	1.524	
Median	0.21	1.24	
25th, 75th pctl.	0.00, 5.00	0.00, 2.49	
Min, Max	0.0, 6.8	0.0, 5.4	
0	11 (50.0%)	8 (28.6%)	0
>0-5	6 (27.3%)	18 (64.3%)	0
>5-10	5 (22.7%)	2 (7.1%)	0
>10-20	0	0	0
>20	0	0	0

Annualized Bleeding Rate (ABR) by type of bleeding episode

The median **spontaneous ABR** was 0 in both regimens and **traumatic ABR** was 0.0 and 0.91 in episodic and prophylactic treatment regimens, respectively. Further details are summarized in the table below.

Table 6: Summary of annualised bleeding rate by type of bleed and treatment regimen

Summary of annualized bleeding rate by type of bleed and treatment regimen
Full Analysis Set
Page 1 of 3

	Treatment regimen		
	Episodic (N=22)	Prophylactic (N=28)	ITI (N=0)
Number of patients with an efficacy period	22	28	0
Type of bleed			
Spontaneous			
n	22	28	0
Mean	1.11	0.24	
SD	1.730	0.615	
Median	0.00	0.00	
25th, 75th pctl.	0.00, 2.26	0.00, 0.00	
Min, Max	0.0, 5.6	0.0, 2.6	
0	13 (59.1%)	23 (82.1%)	0
>0-5	7 (31.8%)	5 (17.9%)	0
>5-10	2 (9.1%)	0	0
>10-20	0	0	0
>20	0	0	0
Traumatic			
n	22	28	0
Mean	0.72	1.13	
SD	1.318	1.257	
Median	0.00	0.91	
25th, 75th pctl.	0.00, 1.62	0.00, 1.80	
Min, Max	0.0, 4.5	0.0, 5.4	
0	16 (72.7%)	9 (32.1%)	0
>0-5	6 (27.3%)	18 (64.3%)	0
>5-10	0	1 (3.6%)	0
>10-20	0	0	0
>20	0	0	0
Unknown			
n	22	28	0
Mean	0.30	0.21	
SD	1.104	0.667	
Median	0.00	0.00	
25th, 75th pctl.	0.00, 0.00	0.00, 0.00	
Min, Max	0.0, 5.0	0.0, 2.6	
0	20 (90.9%)	24 (85.7%)	0
>0-5	2 (9.1%)	4 (14.3%)	0
>5-10	0	0	0
>10-20	0	0	0
>20	0	0	0

Number of Injections for Resolution of a Bleeding Episode by Treatment Regimen

Analysis of the number of injections required for resolution of a bleeding episode by treatment regimen resulted in a median number of injections of 1 (range 1 to 31) and 1 (range 1 to 4) for the episodic and prophylactic regimens, respectively, with only a single injection required to resolve a bleeding episode: 23 episodes (85.2%) and 51 episodes (87.9%) for the episodic and prophylactic regimens, respectively. Bleeding episodes that were treated with non-study medication were included in the determination of the number of injections required to resolve the bleeding episode but not in either the average dose per injection or the total dose required.

The number of bleeding episodes that required ⩽2 injections for resolution was 24 (88.9%) and 56 (96.6%) for the episodic and prophylactic regimens, respectively.

Overall, 3 subjects experienced bleeding episodes requiring >3 injections for resolution these 2 subjects were on episodic treatment regimen and 1 subject switched from episodic to prophylactic treatment regimen.

Summary of Dose for resolution of Bleeding Episodes

Analysis of the dose of rFIXFc that was required for resolution of bleeding episodes by treatment regimen resulted in a median average dose per injection of 88.50 and 71.92 IU/kg for bleeding episodes in the episodic and prophylactic regimens, respectively. Further details are provided in the table below.

Table 7: Summary of dose (IU/kg) of rFIXFc for resolution of bleeding episodes by treatment regimen

Summary of dose (IU/kg) of rFIXFc for resolution of bleeds by treatment regimen
Full Analysis Set

	Treatment regimen		
	Episodic (N=22)	Prophylactic (N=28)	ITI (N=0)
Number of patients with an efficacy period	22	28	0
Per bleeding episode			
Average dose per injection (IU/kg)			
n (a)	27	58	0
Mean	90.82	79.48	
SD	32.789	36.384	
Median	88.50	71.92	
25th, 75th pctl.	68.97, 114.68	52.45, 100.81	
Min, Max	41.7, 178.6	23.3, 181.8	
Total dose (IU/kg) (b)			
N	27	58	0
Mean	306.17	93.07	
SD	735.744	64.532	
Median	91.74	78.74	
25th, 75th pctl.	68.97, 136.36	53.57, 104.90	
Min, Max	41.7, 3042.1	23.3, 459.8	
Per patient			
Average dose per injection (IU/kg) (c)			
n (d)	11	20	0
Mean	84.26	79.07	
SD	30.429	30.818	
Median	83.71	75.11	
25th, 75th pctl.	59.49, 117.00	57.74, 85.95	
Min, Max	44.6, 135.7	46.5, 167.9	
Total dose (IU/kg) (e)			
n	11	20	0
Mean	433.74	92.06	
SD	903.168	45.954	
Median	95.79	77.03	
25th, 75th pctl.	59.49, 149.55	65.65, 103.19	
Min, Max	44.6, 3042.1	46.5, 226.4	

NOTE 1: Abbreviation: pctl. = percentile
2: Based on the efficacy period. The efficacy period begins with the first prophylactic dose of rFIXFc and ends with the last dose (regardless of the reason for dosing). Surgery/rehabilitation periods are not included in the efficacy period.
3: Patients are included in each treatment regimen they participated in for the duration of time on that regimen and as such may appear in more than one treatment regimen.
(a) n = total number of bleeding episodes.
(b) For each bleeding episode, the total dose is the sum of the doses (IU/kg) administered across all injections given to treat that bleeding episode.
(c) The average dose per injection (IU/kg) used to resolve each bleed is averaged across all bleeding episodes per patient. Descriptive statistics are displayed for this per-patient average.
(d) n = number of patients with a bleeding episode.
(e) The total dose (IU/kg) used to resolve each bleed is averaged across all bleeding episodes per patient. Descriptive statistics are displayed for this per-patient average.

Subjects' Assessments of Response to rFIXFc Injections for Treatment of Bleeding Episodes by Treatment Regimen

Subject's assessment of response to each injection of rFIXFc for each bleeding episode was analyzed by treatment regimen and is summarized in the table below.

Table 8: Summary of subject's assessment pf responses to rFIXFc injections for the treatment of bleeding episodes by treatment regimen

Summary of patient's assessment of response to rFIXFc injections for the treatment of bleeding episodes by treatment regimen
Full Analysis Set

	Treatment regimen		
	Episodic (N=22)	Prophylactic (N=28)	ITI (N=0)
Number of patients with an efficacy period	22	28	0
Each injection			
Based on injections with an evaluation			
n (a)	22	57	0
Excellent or Good	22(100.0%)	50(87.7%)	0
Excellent	15(68.2%)	30(52.6%)	0
Good	7(31.8%)	20(35.1%)	0
Moderate	0	6(10.5%)	0
None	0	1(1.8%)	0
Based on all injections			
n (b)	80	74	0
Excellent or Good	22(27.5%)	50(67.6%)	0
Excellent	15(18.8%)	30(40.5%)	0
Good	7(8.8%)	20(27.0%)	0
Moderate	0	6(8.1%)	0
None	0	1(1.4%)	0
Response not provided	58(72.5%)	17(23.0%)	0
First injection for each bleeding episode			
Based on injections with an evaluation			
n (a)	5	43	0
Excellent or Good	5(100.0%)	37(86.0%)	0
Excellent	5(100.0%)	28(65.1%)	0
Good	0	9(20.9%)	0
Moderate	0	5(11.6%)	0
None	0	1(2.3%)	0
Based on all injections			
n (b)	27	58	0
Excellent or Good	5(18.5%)	37(63.8%)	0
Excellent	5(18.5%)	28(48.3%)	0
Good	0	9(15.5%)	0
Moderate	0	5(8.6%)	0
None	0	1(1.7%)	0
Response not provided	22(81.5%)	15(25.9%)	0

NOTE 1: 'None' means that there was no improvement, not that the patient did not provide a response.
2: Based on the efficacy period. The efficacy period reflects the sum of all intervals of time during which patients are treated with rFIXFc according to the treatment regimens of the study excluding surgical/ rehabilitation periods and large injection intervals (>28 days).
3: Patients are included in each treatment regimen they participated in for the duration of time on that regimen and as such may appear in more than one treatment regimen.
(a) n = number of injections (or bleeding episodes as appropriate) with a response. Percentages are based on this number during the efficacy period.
(b) n = number of injections (or bleeding episodes as appropriate) reported whether or not a response was provided. Percentages are based on this number during the efficacy period.

Investigator's Global Assessment of the Response to rFIXFc

This assessment was performed every 12 weeks during the study. The majority of Investigators' global assessments of response were "excellent" or "effective" at all timepoints. Of the total number of responses, 33 responses (100.0%) were excellent for subjects on the episodic regimen, 152 responses (95.6%) were excellent for subjects on the prophylactic regimen, and overall 185 responses (96.4%) were excellent. Combining "excellent" and "effective," the global assessments of response was 33 responses (100.0%) for subjects on the episodic regimen, 159 responses (100.0%) for subjects on the prophylactic regimen, and overall 192 responses (100.0%).

Total Annualized rFIXFc Consumption

The median annualized rFIXFc consumption by treatment regimen was 203.2 IU/kg (range 0 to 5719 IU/kg) and 3175.0 IU/kg (range 2544 to 13164 IU/kg) on the episodic and prophylactic treatment regimens, respectively. The overall median annualized rFIXFc consumption was 2673.3 IU/kg (range 0 to 10507 IU/kg).

Table 9: summary of annualised rFIXFc consumption (IU/kg) by treatment regimen

Summary of annualized rFIXFc consumption (IU/kg) by treatment regimen
Full Analysis Set
Page 1 of 1

	Treatment regimen			
	Episodic (N=22)	Prophylactic (N=28)	ITI (N=0)	Overall (N=33)
Number of patients with an efficacy period	22	28	0	33
Annualized consumption (IU/kg)				
n	22	28	0	33
Mean	790.1	3616.8		2540.4
SD	1510.16	1935.41		1902.76
Median	203.2	3175.0		2673.3
25th, 75th percentile	0.0, 840.5	2919.0, 3629.8		1723.6, 3123.2
Min, Max	0, 5719	2544, 13164		0, 10507

NOTE 1: Annualized consumption is the total rFIXFc (IU/kg) received during the efficacy period extrapolated to a 1-year interval of time.
2: The efficacy period reflects the sum of all intervals of time during which patients are treated with rFIXFc according to the treatment regimens of the study excluding surgical/rehabilitation periods and large injection intervals (>28 days).
3: Patients are included in each treatment regimen they participated in for the duration of time on that regimen and as such may appear in more than one treatment regimen. Each patient is counted only once in the overall column.

Incremental Recovery (IR)

The one-stage clotting (aPTT) assay was used for this analysis. The IR values observed overall were consistent in the episodic and prophylactic treatment groups. The IR for the baseline PK profile of subjects on the episodic regimen of 0.7 IU/dL per IU/kg (0.63 to 0.78 IU/dL per IU/kg [median (25th – 75th)]) was same in comparison to the prophylactic regimen, 0.7 IU/dL per IU/kg (0.68 to 0.77 IU/dL per IU/kg). IR remained stable throughout the study, with both regimens exhibiting similar IR values for the duration (through Week 120).

Health outcomes (exploratory endpoint)

Throughout all study visits, there was a very small number of subjects who completed Questions 2, 3, 4, and 5 (refers to questions listed in section "Methods, exploratory endpoints") of the health outcomes questionnaires. Thus, the responses to these questions are not suitable for summarizing meaningful observations.

Question 1 (How many times the child's injection was administered by different persons?) had larger numbers of responses, particularly for subjects in the prophylactic regimen at Follow-Up Weeks 24, 48, and 72. Subjects received various numbers of infusions by caregivers or visiting home nurses or at clinic. For those who went to the clinic to get their infusions, varying proportions of subject families had difficulty in getting to the clinic. No consistent result patterns emerged across the different follow-up visits.

Other results

No subjects were eligible for ITI and therefore no response was assessed.

No subject had undergone major surgery during the study and so no Investigator's assessment, no blood loss, no rFIXFc consumption or no injection was required.

There were minor surgeries performed in 16 subjects. The most common surgery performed was for port placement.

Safety results

The primary objective of the study was to evaluate the safety of rFIXFc in previously untreated subjects with severe hemophilia B. The primary endpoint is the occurrence of inhibitor development.

The Nijmegen-modified Bethesda assay was performed by the central laboratory to detect neutralizing inhibitors to rFIXFc. A positive inhibitor was defined as an inhibitor test result of ≥0.60 BU/mL that was confirmed by a second test result of ≥0.60 BU/mL from a separate sample, drawn 2 to 4 weeks after the date when the original sample was drawn. The date of the inhibitor was the date of the sample with the first positive test result, which was subsequently confirmed.

The total subject-years followed on the study was 57.51 years with a total of 2233 EDs. Overall, the number of subjects with at least 50 EDs was 21 (63.6%), at least 75 EDs was 18 (54.5%), and at least 100 EDs was 11 (33.3%). Overall, the median number of EDs was 76 days (range 1 to 137 days).

Key safety result

Of 33 subjects in the Safety Analysis Set with at least 1 subsequent inhibitor test result or who had an inhibitor, 1 subject (3.03% [95% CI: 0.08%, 15.76%]) developed a low-titer inhibitor to rFIXFc during the study.

Adverse events

Adverse events (AEs) were coded using MedDRA Version 20.1. Subjects who experienced multiple events in a SOC (system organ class) or PT (preferred term) were counted only once in the incidence of that SOC or PT. The term TEAE is used to refer to those AEs that appeared or worsened after Day 1 in Study 998HB303, excluding AEs that emerged during major surgical/ rehabilitation periods. The term AE is used to describe non-TEAEs or a combination of TEAEs and non-TEAEs. The same principle is applied to TESAEs.

The total number of TEAEs reported was 387 from 57.51 total patient-years followed and 2233 total EDs. Of the 33 subjects who received at least 1 dose of rFIXFc during the study, 30 (90.9%) subjects had at least 1 TEAE and 2 (6.1%) subjects had at least 1 TEAE that was assessed as related to rFIXFc treatment by the Investigator. Of the 33 subjects treated with at least 1 dose of rFIXFc, 1 (3.0%) subject discontinued treatment and/or the study due to an AE.

During episodic treatment, 14 of 22 (63.6%) subjects had at least 1 TEAE; however no subject had TEAE that was assessed as related to rFIXFc treatment by the Investigator. During prophylactic treatment, 27 of 28 (96.4%) subjects had at least 1 TEAE and 2 (7.1%) subjects had at least 1 TEAE that was assessed as related to rFIXFc treatment by the Investigator.

Table 10: overall summary of rFIXFc treatment-emergent adverse events by treatment regimen

Overall summary of rFIXFc treatment-emergent adverse events by treatment regimen
Safety Analysis Set
Page 1 of 2

	Treatment regimen				
	Episodic (N=22)	Prophylactic (N=28)	ITI (N=0)	Surgery subgroup (a) (N=0)	Overall (N=33)
Number of patients treated with rFIXFc	22	28	0	0	33
Total number of TEAEs	106	263	0	0	387
Total patient-years followed	14.25	42.20	0	0	57.51
Total exposure days	93	2103	0	0	2233
Patients with at least one TEAE, n (%)	14 (63.6%)	27 (96.4%)	0	0	30 (90.9%)
Patients with at least one related TEAE (b), n (%)	0	2 (7.1%)	0	0	2 (6.1%)
Patients who discontinued treatment and/or the study due to an AE, n (%)	0	1 (3.6%)	0	0	1 (3.0%)
Total number of TESAEs	24	27	0	0	58
Patients with at least one TESAE, n (%)	9 (40.9%)	14 (50.0%)	0	0	23 (69.7%)
Patients with at least one related TESAE (b), n (%)	0	1 (3.6%)	0	0	1 (3.0%)
Number of deaths, n (%)	0	0	0	0	0

NOTE 1: Abbreviations: TESAE = treatment-emergent serious adverse event
2: Patients are included in each treatment regimen they participated in for the duration of time on that regimen and as such may appear in more than one treatment regimen.
3: Percentages are based on the number of patients in each treatment regimen or overall.
4: Total patient-years is the cumulative sum of time in years that patients were followed during the study; time during major surgical rehabilitation periods is not included within the treatment groups.
5: An exposure day is a 24-hour period in which one or more rFIXFc injections are given. Exposure days during major surgical rehabilitation periods are not included within the treatment groups.
(a) Includes AEs emergent during the major surgical/rehabilitation period; these AEs are not included in the treatment groups but are included in the overall column.
(b) Related includes AEs with the relationship missing.

Of the 33 subjects treated with rFIXFc in the study, 30 (90.9%) reported at least 1 TEAE in any SOC. The SOC with the highest incidence of TEAEs was infections and infestations (26 [78.8%] subjects).

The most common TEAE PTs within the infections and infestation SOC (reported for ≥10% of subjects overall) were nasopharyngitis (11 [33.3%] subjects); upper respiratory tract infection (7 [21.2%] subjects); and ear infection, otitis media, pharyngitis, varicella, and viral infection (4 [12.1%] subjects each).

Other SOCs with a TEAE incidence of ≥10% were general disorders and administration site conditions (16 [48.5%] subjects), gastrointestinal disorders (15 [45.5%] subjects), skin and subcutaneous tissue disorders (14 [42.4%]); injury, poisoning and procedural complications (13 [39.4%] subjects); respiratory, thoracic and mediastinal disorders (12 [36.4%] subjects),surgical and medical procedures (9 [27.3%] subjects), investigations (7 [21.2%] subjects), blood and lymphatic system disorders (5 [15.2%] subjects), vascular disorders (5 [15.2%] subjects), metabolism and nutrition disorders (5 [15.2%] subjects), nervous system disorders (5 [15.2%] subjects), ear and labyrinth disorders (4 [12.1%]subjects), musculoskeletal and connective tissue (4 [12.1%] subjects), psychiatric disorders (4 [12.1%] subjects), and reproductive system and breast disorders (4 [12.1%] subjects).

- The most common TEAE PTs within the general disorders and administration site conditions SOC was pyrexia (14 [42.4%] subjects).
- The most common TEAE PTs within the gastrointestinal disorders SOC were teething (6 [18.2%] subjects), diarrhoea (5 [15.2%] subjects), and vomiting (4 [12.1%] subjects).
- The most common TEAE PT within the skin and subcutaneous tissue disorders were dermatitis diaper (4 [12.1%] subjects) and eczema (3 [9.1%] subjects).

- The most common TEAE PT within the injury, poisoning, and procedural complications SOC were fall (8 [24.2%] subjects) and head injury (7 [21.2%] subjects).
- The most common TEAE PT within the respiratory, thoracic, and mediastinal disorders SOC were cough and rhinorrhoea with 6 (18.2%) subjects, each.
- The most common TEAE PT within the surgical and medical procedures SOC was central venous catheterisation (9 [27.3%] subjects).
- None of the TEAEs within the investigations SOC occurred in more than 10% of subjects. The most common PT was blood alkaline phosphatase increased (3 [9.1%] subjects).
- None of the TEAEs within the blood and lymphatic system disorders SOC occurred in more than 10% of subjects.
- None of the TEAEs within the vascular disorders SOC occurred in more than 10% of subjects, with poor venous access (3 [9.1%] subjects) and hematoma (2 [6.1%] subjects) experienced by the subjects.
- The most common TEAE PT within the metabolism and nutritional disorders SOC was iron deficiency (3 [9.1%] subjects).
- Middle ear effusion (2 [6.1%] subjects) was the most common TEAE PT within the ear and labyrinth disorders SOC.
- Haemarthrosis (2 [6.1%] subjects) was the most commonly observed TEAE PT within the musculoskeletal and connective tissue disorders SOC.
- None of the TEAEs within the psychiatric disorders occurred in more than 10% of subjects; with irritability (2 [6.1%] subjects) as the common TEAE PT.
- None of the TEAEs within the reproductive system and breast disorders SOC occurred in more than 10% of subjects. The most common PT was balanoposthitis (2 [6.1%] subjects).

The most common TEAE PTs reported for subjects during episodic treatment were nasopharyngitis (6 [27.3%] subjects), pyrexia (5 [22.7%] subjects), fall (4 [18.2%] subjects), and teething (4 [18.2%] subjects).

The most common TEAE PTs reported for subjects during prophylactic treatment were pyrexia (9 [32.1%] subjects), upper respiratory tract infection (7 [25.0%] subjects), cough (6 [21.4%] subjects), fall (5 [17.9%] subjects), head injury (5 [17.9%] subjects), central venous catheterization (5 [17.9%] subjects), teething (4 [14.3%] subjects), nasopharyngitis (4 [14.3%] subjects), pharyngitis (4 [14.3%] subjects), and rhinorrhea (4 [14.3%] subjects).

Factor IX inhibition was reported for 1 (3.6%) subject during prophylactic treatment.

Overall, the majority of TEAEs were categorized as mild (326 events), with 48 TEAEs assessed as moderate, and 13 assessed as severe. Of the 33 subjects treated with rFIXFc, 9 (27.3%) subjects had at least 1 TEAE classified a severe and mild, each, and 12 (36.4%) subjects had at least 1 TEAE classified as moderate.

- Episodic: Severe in 5 (22.7%) subjects, moderate in 1 (4.5%) subjects, and mild in 8 (36.4%) subjects

- Prophylactic: Severe in 5 (17.9%) subjects, moderate in 12 (42.9%) subjects, and mild in 10 (35.7%) subjects

Nine subjects experienced 13 TEAEs assessed by the Investigator as severe (see Table 28 below). Accidental exposure to product, central venous catheterisation, compartment syndrome, croup infectious, Factor IX inhibition, fall, head injury, immune thrombocytopenic purpura, lower respiratory tract infection, spinal cord hematoma, subdural haematoma, and syncope were reported in 1 (3.0%) subject each.

Of the 13 TEAEs reported as severe, 12 were reported as serious.

Of the 13 TEAEs reported as severe, 1 TEAE was assessed as related to rFIXFc treatment by the Investigator (1 report of Factor IX inhibition was reported in one Subject).

Adverse events evaluated as treatment-related by the investigator

Overall, of the 387 reported TEAEs, a total of 5 TEAEs reported in 2 (6.1%) subjects were assessed by the Investigator as related to treatment with rFIXFc:

- Events of injection site erythema resolved and were assessed as related to the study treatment.
- Inhibitor development, hypersensitivity.

Serious Adverse Events

A total of 58 TESAEs was reported in 33 subjects, with 23 (69.7%) subjects experiencing at least 1 TESAE and 1 (3.0%) subject experiencing at least 1 TESAE that was assessed as related to rFIXFc treatment by the Investigator (see table 29 below). During episodic treatment, 9 of 22 (40.9%) subjects experienced a total of 24 TESAEs; and during prophylactic treatment, 14 of 28 (50.0%) subjects experienced a total of 27 TESAEs. The SOCs with the highest incidence of TESAEs were surgical and medical procedures (9 [27.3%] subjects), infections and infestations (8 [24.2%] subjects), injury, poisoning, and procedural complications (7 [21.2%] subjects), blood and lymphatic system disorders (3 [9.1%] subjects]), and nervous system disorders (3 [9.1%] subjects). A higher incidence of TESAEs in the injury, poisoning, and procedural complications SOC were reported in subjects on episodic treatment (4 [18.2%] subjects) compared with prophylactic treatment (2 [7.1%] subjects).

The incidence of individual TESAEs reported by at least 2 subjects were central venous catheterization (9 [27.3%] subjects), fall (5 [15.2%] subjects), head injury (3 [9.1%] subjects), and poor venous access (3 [9.1%] subjects). The remaining TESAEs occurred in 1 (3.0%) subject each.

Of the 58 TESAEs, 56 were assessed by the Investigator as unrelated to rFIXFc and 2 were assessed by the Investigator as related to rFIXFc (1 TESAE each of Factor IX inhibition and hypersensitivity for one Subject), which resulted in withdrawal of study treatment. None of the TESAEs was associated with a fatal outcome.

Table 11: summary of rFIXFc treatment emergent serious adverse events by treatment regimen

Summary of rFIXFc treatment-emergent serious adverse events by treatment regimen
Safety Analysis Set

System organ class Preferred term	Treatment regimen Episodic (N=22)	 Prophylactic (N=28)	 ITI (N=0)	 Overall (N=33)
Number of patients treated with rFIXFc	22	28	0	33
Total number of TESAEs	24	27	0	58
Number of patients with at least one TESAE	9 (40.9%)	14 (50.0%)	0	23 (69.7%)
Blood and lymphatic system disorders	0	3 (10.7%)	0	3 (9.1%)
Anemia	0	1 (3.6%)	0	1 (3.0%)
Factor IX inhibition	0	1 (3.6%)	0	1 (3.0%)
Immune thrombocytopenic purpura	0	1 (3.6%)	0	1 (3.0%)
Congenital, familial and genetic disorders	0	1 (3.6%)	0	1 (3.0%)
Phimosis	0	1 (3.6%)	0	1 (3.0%)
Gastrointestinal disorders	0	1 (3.6%)	0	2 (6.1%)
Inguinal hernia	0	0	0	1 (3.0%)
Tongue hemorrhage	0	1 (3.6%)	0	1 (3.0%)
General disorders and administration site conditions	0	0	0	1 (3.0%)
Vessel puncture site hematoma	0	0	0	1 (3.0%)
Immune system disorders	0	1 (3.6%)	0	1 (3.0%)
Hypersensitivity	0	1 (3.6%)	0	1 (3.0%)
Infections and infestations	1 (4.5%)	7 (25.0%)	0	8 (24.2%)
Croup infectious	0	1 (3.6%)	0	1 (3.0%)
Gastroenteritis	1 (4.5%)	0	0	1 (3.0%)
Infusion site pustule	0	1 (3.6%)	0	1 (3.0%)
Lower respiratory tract infection	0	1 (3.6%)	0	1 (3.0%)
Respiratory tract infection	0	1 (3.6%)	0	1 (3.0%)
Staphylococcal bacteremia	0	1 (3.6%)	0	1 (3.0%)
Viral infection	0	1 (3.6%)	0	1 (3.0%)
Viral rash	0	1 (3.6%)	0	1 (3.0%)
Injury, poisoning and procedural complications	4 (18.2%)	2 (7.1%)	0	7 (21.2%)
Accidental exposure to product	1 (4.5%)	0	0	1 (3.0%)
Craniocerebral injury	1 (4.5%)	0	0	1 (3.0%)
Face injury	0	0	0	1 (3.0%)
Fall	4 (18.2%)	0	0	5 (15.2%)
Head injury	1 (4.5%)	2 (7.1%)	0	3 (9.1%)
Skull fracture	1 (4.5%)	0	0	1 (3.0%)
Subdural hematoma	1 (4.5%)	0	0	1 (3.0%)
Musculoskeletal and connective tissue disorders	1 (4.5%)	0	0	2 (6.1%)
Compartment syndrome	1 (4.5%)	0	0	1 (3.0%)
Hemarthrosis	0	0	0	1 (3.0%)
Nervous system disorders	1 (4.5%)	2 (7.1%)	0	3 (9.1%)
Coma	0	1 (3.6%)	0	1 (3.0%)
Febrile convulsion	0	1 (3.6%)	0	1 (3.0%)
Spinal cord hematoma	1 (4.5%)	0	0	1 (3.0%)
Tongue biting	0	1 (3.6%)	0	1 (3.0%)
Reproductive system and breast disorders	0	1 (3.6%)	0	1 (3.0%)
Prepuce redundant	0	1 (3.6%)	0	1 (3.0%)
Surgical and medical procedures	2 (9.1%)	5 (17.9%)	0	9 (27.3%)
Central venous catheterization	2 (9.1%)	5 (17.9%)	0	9 (27.3%)
Vascular disorders	2 (9.1%)	2 (7.1%)	0	4 (12.1%)
Hematoma	1 (4.5%)	0	0	1 (3.0%)
Poor venous access	1 (4.5%)	2 (7.1%)	0	3 (9.1%)

NOTE 1: Patients are included in each treatment regimen they participated in for the duration of time on that regimen and as such may appear in more than one treatment regimen.
2: Percentages are based on the number of patients in each treatment regimen or overall.
3: Using the MedDRA Version 20.1 dictionary.
4: Patients are counted once if they report multiple events in the same system organ class or preferred term.
5: Does not include SAEs emergent during major surgical/rehabilitation periods.

Death

There were no deaths in the study.

Vascular Thrombotic Events

No subject reported vascular thrombotic events during the study in both the treatment groups.

Hypersensitivity and Allergic Reactions

One subject experienced a TESAE of hypersensitivity during the study which was assessed as serious and related tor the study treatment by the Investigator.

Fifteen AEs in 10 patients (e.g. rash, eczema, erythema) were medically reviewed for possible allergic events and considered as not related to treatment.

Overdose

There was one overdose event reported for 1 subject during the study without clinical consequence.

Clinical Laboratory Results

Clinical laboratory evaluations included hematology (WBC count and differential, RBC, hemoglobin, hematocrit, and platelet count) and blood chemistry (sodium, potassium, chloride, total protein, total bilirubin, GGT, ALT, AST, ALP, BUN, serum creatinine, and glucose).

According to the MAH no clinically meaningful patterns or trends were observed in abnormalities of hematology.

According to the MAH no clinically meaningful patterns or trends were observed in abnormalities of blood chemistry.

Anti-rFIXFc Binding Antibody

Of the 33 subjects, no subject, including inhibitor subjects, were positive for anti-rFIXFc antibodies prior to treatment with rFIXFc. Of the 33 subjects evaluated, 32 (97.0%) subjects were negative at all post-dose assessments. Of the 33 subjects evaluated, 1 (3.0%) subject was positive for anti-rFIXFc antibodies at any time after rFIXFc treatment (see key safety result).

Vital signs & physical examination

In summary, there was no apparent clinically meaningful pattern or consistent trend in vital signs observed, including increase in blood pressure or temperature.

The abnormal physical examination findings were typical of what is expected for the general hemophilia population with findings reported in the extremities/joints, musculoskeletal, and skin body systems.

Discontinuation due to adverse events

One of 33 subjects (3.0%) treated with rFIXFc discontinued due to 2 TEAEs of hypersensitivity and Factor IX inhibition, both assessed as serious.

2.3.3. Discussion on clinical aspects

The MAH submitted the final Clinical Study Report of the ALPROLIX Study 998HB303 (PUPs B) performed in paediatric, previously untreated patients (PUPs). This submission is done to meet the requirement of Art. 46 to submit paediatric data within 6 months from End of Study. During the assessment of this P46 procedure, the MAH submitted a type II variation in order to update the Product Information, based on the same study results.

In Study 998HB303 safety and efficacy of rFIXFc (Alprolix) were investigated in PUPs with severe hemophilia B defined as ≤2 IU/dL (≤2 %).

The primary study endpoint was the occurrence of inhibitor development.

Secondary endpoints included annualized bleeding rates, assessments of responses to treatment with Alprolix for bleeding episodes, and the number of injections and dose needed to resolve bleeding episodes, the total number of EDs per subject per year, Alprolix consumption, and incremental recovery.

All subjects were male, with an overall median age of 0.60 (range 0.08 to 2). Most subjects (78.8%) were <1 year of age.

Overall, exposure over the period of at least 50 exposure days (EDs) for a minimum of 20 subjects was reached and hence, the requirements of the "Guideline on the clinical investigation of recombinant and human plasma-derived factor IX products" (EMA/CHMP/BPWP/144552/2009) are met for deleting the statement in section 4.2 of the SmPC on the lack of data in PUPs. Of note, this guideline is currently under revision. The draft guideline does not foresee the requirement for formal PUP studies anymore.

Initially, it was planned that the study will end when at least 40 subjects have reached at least 100 EDs with Alprolix. This was changed to 20 subjects with at least 50 EDs through an amendment and in order to align with the revised EU paediatric investigational plan.

Prophylactic and episodic treatment regimens were assessed in a total of 33 patients (full and safety analysis set). Six patients discontinued, resulting in 27 patients who completed the study (of which 20 had an exposure of at least 50 EDs).

Of the 33 subjects in the analysis set, 11 subjects were started in the prophylaxis arm, 22 in the episodic treatment arm. At the investigator's discretion 17/22 patients were switched from the episodic to the prophylactic treatment arm. The last prescribed dosing frequency for each subject was twice weekly (1 subject), every 5 days (1 subject), every 7 days (23 subjects), every 14 days (2 subjects) and on-demand (1 subject). Throughout the study report, results are presented for the episodic and prophylactic treatment arm, however, at the end of the study the majority of patients were in the prophylactic treatment arm (n= 28 at EOS). The rationale behind switching from episodic to prophylactic treatment is fully understood, however, the results from the episodic arm need to be interpreted cautiously due to short duration for the majority of the subjects and the limited number of subjects at the end of study in this treatment arm.

The study population, overall study design and the number of study participants are considered acceptable.

Safety:

Inhibitor development occurred in 1/33 subjects. Treatment-related hypersensitivity was reported in the same subject, a coincidence commonly seen with Factor IX therapy. From a total of 58 TESAEs reported in 23/33 subjects (70 %), these two TESAEs were the only two assessed as related to treatment by the Investigator.

Inhibitor development against FIX products with related hypersensitivity is a known risk in haemophilia B treatment. This is also reflected in the current version of the SmPC of Alprolix by general statements in accordance with the FIX Core SmPC. The MAH agreed to add the occurrence of inhibitor with related hypersensitivity during the PUP study to the tabulated list of adverse reactions in section 4.8 of the SmPC. The respective type II variation procedure is currently under evaluation (Procedure No. EMEA/H/C/004142/II/0029).

From the subject disposition the following data initially gave rise to concern that detection of inhibitors was hampered by the low completion of study visits: Key visits were those in which inhibitor tests were performed. Most subjects completed the Week 12 visit (31, 93.9%), Week 24 visit (29, 87.9%), Week 36 visit (29, 87.9%), Week 48 visit (28, 84.8%), Week 60 visit (24, 72.7%), Week 72 visit (19, 57.6%), and approximately half of all subjects (16, 48.5%) achieved Week 84 visit. Approximately half of the subjects (17, 51.5%) completed the 10-ED inhibitor test visit, 15 subjects (45.5%) completed the 20-ED inhibitor test visit, and 14 subjects (42.4%) completed the 50-ED inhibitor test visit. The MAH clarified that while a considerable high number of subjects did not complete the 20 and 50 ED milestone visits for inhibitor testing, all subjects reaching 20 EDs (n=26) and 50 EDs (n=21) were tested for inhibitor at least once after the milestone. Therefore, the detection of potential inhibitor development was possible.

Due to the low number of patients the precision of the incidence is low (3.03% [95% CI: 0.08%, 15.76%]) and therefore no firm conclusions on the inhibitor frequency can be drawn. However, as inhibitor development is a known risk and can be expected in PUPs, no concerns arise from the study results in this regard.

The total number of TEAEs reported was 387 from 57.51 total patient-years followed and 2233 total EDs. The most common TEAEs observed (incidence ≥ 10%) were, in descending order of incidence, pyrexia, nasopharyngitis, central venous catheterization, fall, upper respiratory tract infection, head injury, cough, rhinorrhea, teething, diarrhea, vomiting, ear infection, otitis media, pharyngitis, varicella, viral infection, and dermatitis diaper. Apart from 3 episodes of injection site erythema in a single subject and the two events described above (inhibitor development, hypersensitivity) none of the TEAEs were related to treatment by the Investigator. Overall, the number and nature of (related) TEAEs does not give rise to concern. The MAH agreed to add injection site erythema to the tabulated list of adverse reactions in section 4.8 of the SmPC (currently under evaluation as part of a type II variation request).

No vascular thrombotic events, anaphylaxis, or anti-drug-antibodies were reported. Overdose in a single subject was not of clinical consequence. No clinically meaningful patterns in abnormalities of hematology (e.g. WBC/ RBC/ platelet count, haematocrit, haemoglobin) and blood chemistry (e.g. ALT, AST, glucose, sodium, potassium could be identified. Likewise, vital signs including increase in blood pressure or temperature were normal. No deaths occurred.

Efficacy:

Bleeding rates were low with a mean ABR of 1.58 (range 0.0 to 5.4) in the prophylactic treatment arm and 2.13 (range 0.0 to 6.8) in the episodic treatment arm. Only descriptive statistics were used which is considered acceptable for this kind of study where the primary objective was investigation of safety.

The majority of bleeding episodes was resolved by a single injection. However, two patients experienced bleeding episodes. In light of the prolonged duration of those two bleeding episodes (approx. 1-1.5 months) the apparently high numbers of injections required for resolution appear justified. Of note, duration of a bleeding episode was defined as starting from the first sign of a bleed, and ending no more than 72 hours after the last injection to treat the bleed, within which any symptoms of bleeding at the same location, injections less than or equal to 72 hours apart, are considered the same bleeding episode.

The median dose per bleeding episodes was higher than that observed in the previously submitted studies in PTPs. Although this might be explained by the increased clearance in younger patients the MAH agreed to add these results in section 5.1 of the SmPC (currently under evaluation as part of a type II variation request).

Consumption data do not give rise to concern: The median annualized rFIXFc consumption was 203.2 IU/kg (range 0 to 5719 IU/kg) in the episodic treatment arm and 3175.0 IU/kg (range 2544 to 13164 IU/kg) in the prophylaxis treatment arm. The overall median annualized rFIXFc consumption was reported as 2673.3 IU/kg (range 0 to 10507 IU/kg). The used 4-point scale for the patient´s (caregiver/parents) assessment of haemostatic response was the same as used during the pivotal studies submitted for MAA and is therefore considered acceptable. For all injections of rFIXFc with an evaluation, 22 injections (100%) in the episodic treatment arm and 50 injections (87.7%) in the prophylaxis treatment arm, respectively, were assessed as excellent or good. For all injections, a response of excellent or good was reported for 22 (27.5%) and 50 injections (67.6%). For a high number of injections no response was provided: 58 (72.5%) in the episodic treatment arm and 17 (23.0%) in the prophylactic treatment arm, respectively. This was explained by initial difficulties in data collection via an electronic patient diary and the fact that a single subject (998HB303-818-901; see above) accounted for more than half of the responses not given in the episodic treatment arm. While this strongly limits the interpretation of the result, the investigator's assessment of response did not indicate concerns regarding haemostatic efficacy. The latter has been demonstrated as part of the marketing authorisation procedure. Moreover, safety/immunogenicity was the primary objective of this paediatric study under assessment, thus no further issue is made on the reliability of patient's response data.

3. Rapporteur's overall conclusion and recommendation

Safety and tolerability of Alprolix in PUPs seem to be largely comparable with the data generated in previously treated patients. The MAH agreed to update section 4.8 and 5.1 of the SmPC in order to include inhibitor development, hypersensitivity and injection site erythema as well as information on dose per bleeding episode. These changes are dealt with as part of a separate type II variation request which was submitted on 03 April 2020 while this P46 report was under assessment (Procedure No. EMEA/H/C/004142/II/0029).

The MAH was asked to clarify several issues related to uncertainties on safety and efficacy which have been resolved sufficiently.

Overall, the data presented do not indicate any new safety or efficacy aspects which may alter the benefit risk profile.

☒ **Fulfilled:**

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The MAH is asked to provide any follow-up data in one patient who discontinued the study due to inhibitor development, if available.
2. The MAH is asked for clarification why a considerable high number of subjects did not complete the visits for inhibitor testing. Furthermore, a discussion is awaited whether detection of any inhibitors potentially occurring during the study was possible in light of the poor adherence to study visits.
3. The MAH is asked to discuss the following two bleeding episodes in two subjects in more detail and to explain the high number of injections needed for resolution:
    - Case 1: spontaneous subdural hematoma
    - Case 2: spontaneous internal bleeding
4. The MAH should commit to submit a variation to update the Product Information:
    - The occurrence of an inhibitor with related hypersensitivity during the PUP study should be added in the tabulated list of adverse reactions in section 4.8 of the SmPC.
    - Injection site erythema should be added in the tabulated list of adverse reactions in section 4.8 of the SmPC.
    - Information on dose per bleeding episode might be added in section 5.1 of the SmPC.
5. The median annualized rFIXFc consumption was 203.2 IU/kg (range 0 to 5719 IU/kg) in the episodic treatment arm and 3175.0 IU/kg (range 2544 to 13164 IU/kg) in the prophylaxis treatment arm. The overall median annualized rFIXFc consumption was reported as 2673.3 IU/kg (range 0 to 10507 IU/kg). Clarification is needed regarding discrepancies in ranges (shown as min and max values) of the overall median annualized consumption.
6. No patient response was provided for a high number of injections: 58 (72.5%) in the episodic treatment arm and 17 (23.0%) in the prophylactic treatment arm, respectively. The MAH is asked to clarify why no reports were received for such a high number of bleeding episodes and to discuss the interpretability of results.

The timetable is a 30 day response timetable with clock stop.

5. MAH responses to Request for supplementary information

Question 1:

The MAH is asked to provide any follow-up data in one patient who discontinued the study due to inhibitor development, if available.

MAH responses:

The MAH provided a full description of the case narrative.

Assessor's comments:

The MAH provides a brief narrative on the request for follow-up data of one patient who discontinued the study due to inhibitor development against FIX.

Issue resolved.

Question 2:

The MAH is asked for clarification why a considerable high number of subjects did not complete the visits for inhibitor testing. Furthermore, a discussion is awaited whether detection of any inhibitors potentially occurring during the study was possible in light of the poor adherence to study visits.

MAH responses:

Please note that the percentages for ED Milestone Visits presented in CSR Section 10.1 are based on the total number of subjects in the Safety analysis set, rather than on the number of subjects reaching each milestone.

To optimize detection of any inhibitor development during the study, subjects were routinely tested for inhibitor and anti-rFIXFc antibody formation at each clinic visit (see CSR Section 9.5.4.3.1 Inhibitor testing). Tests and assessments performed at Screening and Baseline Incremental Recovery visit are presented in CSR Table 3, and assessments at Interim study visits every 12 (±2) weeks are shown in CSR Table 4. Inhibitor test results for all subjects are provided in CSR Listing 16.2.8.8, and subjects who developed inhibitors in CSR Listing 16.2.8.10.

In addition, testing for inhibitors was also conducted at the time of ED milestones (CSR Section 9.5.4.3.1). If these did not align with a scheduled study visit, an additional ED Milestone Visit was scheduled to complete this testing. Additional unscheduled testing could also be performed as needed if clinically indicated. The assessments performed at ED milestone visits are presented in CSR Table 5. A summary of patients attending key study visits (*e.g.* ED milestone visits) is presented in CSR Table 16.2.1.2.

Of the 28 subjects that reached 10 EDs (CSR Table 16), 27 were tested for inhibitor at least once after the milestone (derived from CSR Table 24). All subjects reaching 20 EDs (n=26) and 50 EDs (n=21) were tested for inhibitor at least once after the milestone.

Therefore, based on the rigorous protocol schedule of inhibitor testing and the opportunity to perform inhibitor testing at any time during the study based on clinical status, the MAH believes that these measures allowed for accurate detection of inhibitor development during the study.

Assessor's comments:

The MAH reiterates that inhibitor testing was performed adequately throughout the study in order to detect potential inhibitor development. Measurements were performed at screening, baseline, scheduled visits (every 12 ±2 weeks) and unscheduled visits (if clinically indicated). Although only 15 subjects (45.5%) completed the 20-ED inhibitor test visit, and 14 subjects (42.4%) completed the 50-ED inhibitor test visit, the MAH states that all subjects reaching 20 and 50 ED were tested at least once after the milestone. This is considered adequate in terms of inhibitor monitoring over time/ exposure.

Issue resolved.

Question 3:

The MAH is asked to discuss the following two bleeding episodes in two subjects in more detail and to explain the high number of injections needed for resolution:

- Case 1: spontaneous subdural hematoma
- Case 2: spontaneous internal bleeding

MAH responses:

According to the study protocol Section 10.2.3.1, a bleeding episode starts from the first sign of a bleed, and ends no more than 72 hours after the last injection to treat the bleed, within which any symptoms of bleeding at the same location, injections less than or equal to 72 hours apart, are considered the same bleeding episode.

The study protocol, Section 5.3 and Appendix A, specified the rFIXFc dosing guidelines to be followed in the event of CNS bleeding episodes. Injection dose and frequency was to be individually selected in order to maintain the necessary 60%–100% peak plasma Factor IX activity levels, and taking into account lower rFIXFc recoveries observed in young children. This requirement resulted in a relatively high number of injections needed for resolution in the two subjects referenced above, compared with the overall rates observed in the study. The clinical details are summarized below.

Case 1: spontaneous subdural hematoma

Case 2: spontaneous internal bleeding

Assessor's comments:

The MAH explains that a bleeding episode "starts from the first sign of a bleed, and ends no more than 72 hours after the last injection to treat the bleed, within which any symptoms of bleeding at the same location, injections less than or equal to 72 hours apart, are considered the same bleeding episode". Dosage and intervals aimed at maintaining adequate (in case of CNS manifestations 60%–100%) peak plasma Factor IX activity levels. In case of the two serious events in two different subjects of spontaneous subdural hematoma (26 injections required for resolution) and spontaneous internal bleeding (31 injections required for resolution) it is acknowledged that these events lasted for about 1.5 and 1 months, respectively, thus explaining the high number of injections needed.

Issue resolved.

Question 4:

The MAH should commit to submit a variation to update the Product Information:

- The occurrence of an inhibitor with related hypersensitivity during the PUP study should be added in the tabulated list of adverse reactions in section 4.8 of the SmPC.
- Injection site erythema should be added in the tabulated list of adverse reactions in section 4.8 of the SmPC.
- Information on dose per bleeding episode might be added in section 5.1 of the SmPC.

MAH responses:

A variation to update SmPC and PIL texts based on the study results was submitted by the MAH on 8 April 2020. The proposed changes include:

- Addition of factor IX inhibition, hypersensitivity and injection site erythema to the tabulated list of adverse reactions in SmPC section 4.8.
- Information on dose per bleeding episode in SmPC section 5.1.

Assessor's comments:

The MAHs agrees to update the SmPC (and corresponding PIL sections) to adequately reflect the events of factor IX inhibition, hypersensitivity, injection site erythema (tabulated list of AEs in section 4.8) and information on dose per bleeding episode (section 5.1).

As meanwhile the MAH has requested a type II variation, further comments on proposed SmPC changes are dealt with in the corresponding assessment report (Procedure No. EMEA/H/C/004142/II/0029)

Therefore, as part of this P46 procedure, no further comments are made.

Issue resolved.

Question 5:

The median annualized rFIXFc consumption was 203.2 IU/kg (range 0 to 5719 IU/kg) in the episodic treatment arm and 3175.0 IU/kg (range 2544 to 13164 IU/kg) in the prophylaxis treatment arm. The overall median annualized rFIXFc consumption was reported as 2673.3 IU/kg (range 0 to 10507 IU/kg). Clarification is needed regarding discrepancies in ranges (shown as min and max values) of the overall median annualized consumption.

MAH responses:

The annualized rFIXFc consumption is calculated based on rFIXFc consumption and the duration of each regimen/period. The calculation is detailed in the Statistical Analysis Plan Section 6.6.1.4.

It should be noted that for each patient, the Overall period covers the combined time on episodic and prophylactic regimens. The annualized consumption for a patient in the episodic regimen would usually be expected to be lower than the annualized consumption in the prophylactic regimen, unless the patient is experiencing frequent bleeding episodes. The overall annualized consumption is then expected to fall between the annualized consumption for the episodic and prophylactic regimens, respectively.

The minimum annualized consumption could thus be lower for episodic than the overall and likewise maximum consumption for prophylactic could indeed be higher than maximum annualized consumption combined. Also, a patient with an annualized consumption 0 on episodic regimen and who is not transitioning to a prophylactic regimen, would have an overall annualized consumption of 0. There are thus no discrepancies in the ranges of overall annualized consumption.

Assessor's comments:

The MAH clarified how annualized consumption data were calculated and that there are no discrepancies in the ranges of overall annualized consumption. This explanation can be followed.

Issue resolved.

Question 6:

No patient response was provided for a high number of injections: 58 (72.5%) in the episodic treatment arm and 17 (23.0%) in the prophylactic treatment arm, respectively. The MAH is asked to clarify why no reports were received for such a high number of bleeding episodes and to discuss the interpretability of results.

MAH responses:

For individual bleeding episodes treated at the study site, the assessment of response to bleeding episodes were to be done by the Investigator in the eCRF. For other episodes, the assessments were to be done by the subject in the electronic patient diary (EPD).

Subjects (or caregivers) were instructed to enter data about the injection as soon as possible after an injection while the treatment response to a bleeding episode were to be assessed approximately 8 to 12 hours after an injection. At the start of the study, the EPD did not allow users who had already entered data about the injection to return at a later timepoint to rate the treatment response. This was inconvenient for users and led to missing data. The system was updated in late 2017 to allow entry of the patient's assessment of treatment response at a later time point.

The lack of data entry for individual bleeding episodes has an impact on the response frequency, especially for the episodic regimen. It is most clearly seen for subject 818-901 where no assessment was entered during the bleeding episode that is further described in the response to Question 3 (CSR Listing 16.2.7.2). This single bleeding episode with 31 injections thus accounts for more than half of the 58 (72.5%) "Response not provided" in the episodic regimen shown in CSR Table 21.

The main reason for "No response given" was a lack of data entry from individual subjects due to the inherent difficulties in collecting patient assessments in this type of study. Despite these limitations, the MAH believes the available data is representative for the study population and allows for adequate interpretation and assessment.

Assessor's comments:

The MAH explains that the lack of subjects' response to a high number of injections (72.5% in the episodic treatment arm and 23.0% in the prophylactic treatment arm, respectively) is due issues in data collection via the electronic patient diary (EPD). Many patients did not provide treatment responses to a bleeding episode, as the assessment window of 8 to 12 hours after injection was inconvenient at the start of the study. This was amended to allow data entry at a later time point.

While this is acknowledged, it is unclear from the MAH's response what exactly is meant with "a later time point" and in how far later data entry impacted on the accuracy of responses given. The MAH further outlines that lack of data entry in a single subject (requiring 31 injections to treat a bleeding episode) accounted for more than half of the 72.5% "responses not provided" in the episodic arm. It is noted, that the quality of data collection limits meaningful conclusions on patients responses to rFIXFc injections. However, given that i) the investigator's assessment of response did not indicate concerns regarding haemostatic efficacy, ii) the latter has been demonstrated as part of the marketing authorisation procedure and iii) safety/immunogenicity was the primary objective of this paediatric study under assessment, no further issue is made on the reliability of patients' response data.

Issue resolved.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Alprolix Active substance: eftrenonacog alfa

Study title	Study number	Date of completion	Date of submission of final study report
Single Dose IV and Paravenous LocalTolerance Study of Lyophilized rFIXFc in New Zealand White Rabbits	ASL00018	2010-04-13	2015-06-04
4-Week IV Dose Toxicity and PK Study of FIXFc in Rats Followed by a 4-Week Recovery Period	N102010	2008-07-16	2015-06-04
5-Week IV Dose Toxicity and PK Study of FIXFc in Cynomolgus Monkeys Followed by a 4-week Recovery Period	N102011	2008-07-11	2015-06-04
Evaluation of the Thrombogenic Potential of FIXFc Using the Wessler Stasis Model in New Zealand White Rabbits	N102013	2008-08-06	2015-06-04
27-Week IV Dose Toxicity and PK Study of FIXFc in Cynomolgus Monkeys Followed by a 4-Week Recovery Period	N102015	2009-07-02	2015-06-04
Evaluation of Thrombogenic Potential of FIXFc Phase 3a DP Using the Wessler Stasis Model in New Zealand White Rabbits	N102018-B	2009-07-20	2015-06-04
Pilot Repeat Dose Study of FIXFc in Cynomolgus Monkeys	N-FIX-002A	2007-06-22	2015-06-04
Pilot Repeat Dose Study of FIXFc in Rats and Immunization with FIXFc for Control Antibodies	N-FIX-003	2007-04-06	2015-06-04
Pharmacokinetic Analysis of Single Intravenous Dose FIXFc Phase 1/2a DP and FIXFc Phase 3 DP in Cynomolgus Monkeys	N-FIX-006	2009-08-20	2015-06-04
Pharmacokinetic Analysis of rFIXFc 5000 L Lyophilized Drug Product and rFIXFc 15000 L Lyophilized Drug Product Administered as a Single Intravenous Dose in Cynomolgus Monkeys	N-FIX-008-R2	2010-07-23	2015-06-04
Pharmacokinetic Analysis of rFIXFc 5000 L Lyophilized Drug Product and rFIXFc 15000 L Lyophilized Drug Product Administered as a Single Intravenous Dose in FIX-deficient Mice	N-FIX-009-R1	2010-07-23	2015-06-04
Efficacy Comparison of rFIXFc 5000 L Lyophilized Drug Product and 15000 L Lyophilized Drug Product by Whole Blood Rotation Thromboelastometry in FIX-deficient Mice	N-FIX-010-R1	2010-06-30	2015-06-04
Pharmacokinetic Analysis of rFIXFc Lyophilized Drug Product and BeneFIX® After a Single Intravenous Dose of 200 IU/kg in HemB Mice	N-FIX-011	2011-08-15	2015-06-04
Characterization of FIXFc for a Hemophilic Dog Study, and the Pharmacodynamics and Pharmacokinetics of FIXFc in Hemophilic Dogs	R-FIX-014	2007-04-03	2015-06-04
Pharmacokinetics of Factor IX-Fc Monomer and BeneFIX in Normal and Factor IX-Deficient Rodents	R-FIX-015	2005-01-28	2015-06-04
Efficacy of FIXFc Monomer and BeneFIX in FIX-Deficient Mice	R-FIX-017	2005-10-31	2015-06-04
Pharmacokinetics of FIXFc (13.1 c40 & 6B6 c28) in Rodents	R-FIX-023	2007-04-13	2015-06-04
Pharmacokinetics of FIXFc and BeneFIX in Human FcRn Transgenic (Tg) and FcRn Knockout Mice	R-FIX-025	2007-05-22	2015-06-04
Supplemental Report R-FIX-026 for study N102011	R-FIX-026	2008-01-28	2015-06-04
Comparability of Pharmacokinetics and Pharmacodynamics of FIXFc Phase 1/2a DP and Phase 3 DP after a Single IV Dose in FIXdeficient Mice	R-FIX-027	2009-06-26	2015-06-04
Acute Efficacy of rFIXFc in the Tail Clip Bleeding Model of Hemophilia B Mice	R-FIX-031-R1	2011-08-08	2015-06-04
Recombinant FIX Fc Fusion Protein: Prophylactic Efficacy in Hemophilia B Mouse Tail Vein Transection Model	R-FIX-032-R1	2012-02-08	2015-06-04
Placental Transfer of rFIXFc in Pregnant Female Factor IX-Deficient (HemB) Mice	R-FIX-048	2014-11-03	2015-06-04

Clinical studies

Product Name: Alprolix Active substance: efmoroctocog alfa

Study title	Study number	Date of completion	Date of submission of final study report
A Phase I/IIa Safety and Pharmacokinetic Study of Intravenous FIXFc in Previously Treated Hemophilia B Patients	SYN-FIXFc-07-001	2009-10-26	2015-06-04
B-LONG: An Open-label, Multi-center Evaluation of the 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 Hemophilia B	998HB102	2012-07-29	2015-06-04
An Open-label, Multicenter Evaluation of Safety, Pharmacokinetics, and Efficacy of Recombinant Coagulation Factor IX Fc Fusion Protein, BIIB029, in the Prevention and Treatment of Bleeding Episodes in Pediatric Subjects With Hemophilia B	9HB02PED	2014-11-24	2015-06-04
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 Hemophilia B	9HB01EXT	Data cut-off: 2014-10-17 Study completion: 2017-10-31	2015-06-04 2018-04-27
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 Hemophilia B	998HB303	2019-08-20	2020-02-xx