21 February 2019
EMA/210117/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Alprolix

International non-proprietary name: eftrenonacog alfa

Procedure No. EMEA/H/C/004142/II/0021

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion [2]**
☐	Start of procedure:	02 Oct 2018	02 Oct 2018	☐
☐	CHMP Rapporteur Assessment Report	05 Nov 2018	05 Nov 2018	☐
☐	PRAC Rapporteur Assessment Report	12 Nov 2018	12 Nov 2018	☐
☐	PRAC members comments	16 Nov 2018	n/a	☐
☐	CHMP members comments	19 Nov 2018	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	20 Nov 2018	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	22 Nov 2018	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report [3]	27 Nov 2018	27 Nov 2018	☐
☐	Start of written procedure	27 Nov 2018	27 Nov 2018	☐
☐	Request for Supplementary Information	29 Nov 2018	29 Nov 2018	☐
☐	Submission deadline	20/12/2018	20/12/2018	
☐	Start of procedure:	24/12/2018	24/12/2018	☐
☐	CHMP Rapporteur Assessment Report	28/01/2019	28/01/2019	☐
☐	CHMP members comments	11/02/2019	N/A	☐
☐	Updated CHMP Rapporteur Assessment Report	14/02/2019	N/A	☐
☐	Start of written procedure	19/02/2019	19/02/2019	☐
☒	Opinion	21/02/2019	21/02/2019	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair.

List of abbreviations

Abbreviation	Definition
ABR	Annualized bleeding rate
ADA	Anti-rFIXFc drug antibody
ADR	Adverse drug reaction
AE	Adverse event
BU	Bethesda unit
CSR	Clinical study report
ED	Exposure day
EMA	European Medicines Agency
EOT	End of Treatment
EU	European Union
Fc	Fragment crystallizable
FIX	Coagulation factor IX
HEK	293H Human embryonic kidney cells 293
IgG1	Immunoglobulin G1
IU	International unit
i.v.	Intravenous
MAH	Marketing authorization holder
NGNA	N-glycolylneuraminic acid
PK	Pharmacokinetic(s)
PTP	Previously treated patient
PUP	Previously untreated patient
rFIXFc	Recombinant human coagulation factor IX Fc fusion protein
SAE	Serious adverse event
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
US	United States of America
USPI	United States product insert
WFH	World Federation of Hemophilia

Procedure resources	
CHMP Rapporteur:	Andrea Laslop
PRAC Rapporteur:	Brigitte Keller-Stanislawski

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Swedish Orphan Biovitrum AB (publ) submitted to the European Medicines Agency on 29 August 2018 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB

Update of sections 4.8 and 5.1 of the SmPC to include new clinical efficacy and safety data on long-term treatment with Alprolix. The submission includes integrated evaluation of data from the extension study 9HB01EXT (BYOND) which was submitted in a previous P46 procedure and the pivotal parent studies. The PL is updated accordingly. The RMP (v.1.4) is updated to reflect the completion of the mentioned study and to comply with the latest template. In addition, the MAH took the opportunity to update the product information to comply with the latest version of the “Excipients in the labelling and package leaflet of medicinal products for human use"guideline. The list of local representatives has been updated and other minor editorial changes have been included in the PL.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

The MAH conducted a Phase 3, open-label, multicentre, extension study (study 9HB01EXT; BYOND) comprising 120 previously treated male subjects with haemophilia B (congenital factor IX [FIX] deficiency). The objectives of the study were to evaluate the long-term safety of recombinant factor IX Fc fusion protein (rFIXFc) and its efficacy in the prevention and treatment of bleeding episodes, as routine prophylaxis, and for perioperative management.

Subjects enrolled in the extension study had completed one of two preceding pivotal studies of rFIXFc: either Study 9HB02PED (Kids-B-LONG; subjects <12 years of age) or Study 998HB102 (B-LONG; subjects ≥12 years of age). Participation in Study 9HB01EXT would allow subjects to remain on treatment with rFIXFc until commercially available.

Inhibitor surveillance over the period of 100 EDs for each subject was carried out following the “Guideline on the clinical investigation of recombinant and human plasma-derived factor IX products” (EMA/CHMP/BPWP/144552/2009).

The complete clinical study report of the extension study (study 9HB01EXT; BYOND) has already been previously submitted as an Article 46 paediatric submission (EMEA/H/C/004142/P46 005) in order to meet the deadline to provide paediatric data within 6 months from End of Study. The data presented did not reveal any new safety or efficacy aspects which may have altered the benefit risk profile. However, at the time of submission of the Art.46 procedure the results of an integrated analysis of the extension study with the two parent studies was not available and hence, no final conclusions concerning long-term safety and efficacy could be drawn.

As previously agreed upon, the MAH has submitted the final data package including the results of the integrated analysis within this Type II variation.

Overall, the efficacy data generated in the extension study proved to be broadly comparable with the respective results obtained in the parent studies. With regards to the perioperative management an integrated analysis of the haemostatic response during surgery and postoperatively was performed. Results from this analysis continue to support the use of rFIXFc in the perioperative setting as haemostatic response was rated good or excellent in 100% of the major surgeries assessed. In addition, in 80 % of the major surgeries a single injection of rFIXFc was sufficient to maintain haemostasis during surgery. Comparing the other main efficacy results (e.g. ABRs, number of injections to control a BE, total annualized rFIXFc consumption) with those already submitted in the previous Article 46 paediatric submission (EMEA/H/C/004142/P46 005), no changes were observed.

An integrated safety analysis of data pooled from the completed extension study 9HB01EXT and its two parent studies (998HB102 and 9HB02PED) has also been submitted. The integrated safety data set comprised a total of 153 subjects: 120 subjects who participated in the extension study and additional 33 subjects who completed one of the two parent studies but did not enrol into the extension study. The primary endpoint of the extension study was the development of inhibitors. None of the 153 subjects developed an inhibitor. Type and incidence of the AEs observed in the extension and the two parent studies were found to be consistent with what is expected for the general haemophilia B population. 2 TESAEs were assessed by the Investigators as related to rFIXFc treatment. However, both events resolved and did not lead to discontinuation from the study. There were no identified tolerability issues. No deaths occurred, no reports of anaphylaxis or hypersensitivity events were reported. No new ADRs emerged and no new safety signals were reported. Altogether, the integrated safety analysis did not reveal any unusual findings or new safety concerns for Alprolix.

According to the new safety and efficacy data available from the extension study and its integrated analysis with the two parent studies, updates of sections 4.8 and 5.1 of the SmPC were proposed by the MAH. In section 4.8 only some minor changes were proposed (e.g. among other things: changes of the total number of exposure days), in section 5.1 the results of the extension study were proposed to be included. As overall the new data (derived from the extension study) were not found to impact the already known efficacy and safety profile of Alprolix, the MAH was reminded that a detailed reflection of these data in the SmPC was not considered necessary and should be avoided. According to the SmPC guideline statements should be brief and precise and only limited information relevant to the prescriber should be presented in PI. Therefore, the MAH was requested to revise the proposed updates in section 4.8. and in particular in section 5.1 of the SmPC. The MAH complied with the request and revised both sections accordingly. Hence, section 5.1 was shortened significantly and now only contains the main efficacy results of the extension study. Furthermore, the MAH amended section 5.1 in order to improve readability. The new proposals made by the MAH for sections 4.8 and 5.1 are considered acceptable.

Originally, the efficacy results for the 11 patients aged ≥12 to <18 years at entry to the preceding study 998HB102 were not presented separately in the dossier and no information was provided what treatment arms these patients were assigned to. It was acknowledged that these efficacy analyses were not specifically required in the Alprolix PIP. However, as already outlined in the previous Article 46 procedure these data were considered necessary in order to draw final conclusions also for this age cohort. Upon request, the MAH provided the main efficacy data (ABR, Annualized Joint Bleeding Rate and Annualized rFIXFc consumption) now also for this age cohort. The results of this subgroup (a total of 9 patients at the end) are largely similar with those obtained for the other age subgroups. It is acknowledged that the number of patients is deemed too low to include data in the SmPC.

Overall, the efficacy data generated in the extension study are broadly comparable with the respective results obtained in the parent studies indicating that Alprolix is effective as prophylaxis and for treatment

of bleeding episodes in both adult and paediatric patients with severe haemophilia B. Long-term treatment for more than 5 years has shown that Alprolix exhibits an acceptable safety profile and is well-tolerated in children, adolescents and adults with haemophilia B.

To summarise, the data presented did not indicate any new safety or efficacy aspects which may alter the benefit risk profile. The benefit risk balance of Alprolix remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB

Update of sections 4.8 and 5.1 of the SmPC to include new clinical efficacy and safety data on long-term treatment with Alprolix. The submission includes integrated evaluation of data from the extension study 9HB01EXT (BYOND) which was submitted in a previous P46 procedure and the pivotal parent studies. The PL is updated accordingly. In addition, the MAH took the opportunity to update the product information to comply with the latest version of the “Excipients in the labelling and package leaflet of medicinal products for human use"guideline. The list of local representatives has been updated and other minor editorial changes have been included in the PL.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA and IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

Scope

Please refer to the Recommendations section above

Summary

Section 4.8 of the SmPC (Undesirable effects) was updated to include that: ‘Adverse events were monitored for a total of 561 subject-years. The total number of exposure days was 26,106 with a median of 165 (range 1-528)’.

Section 5.1 of the SmPC (pharmacodynamic properties) was updated to include the results from the long-term study (study III):

‘Out of 123 subjects who completed Study I, 93 were enrolled in Study III (extension study) with median total follow-up time of 6.5 years.
(…)

Prophylaxis fixed weekly and individualised intervals:

Median weekly dose for subjects in the fixed weekly arm was 45.17 IU/kg (interquartile range (IQR) 38.1-53.7) in Study I. The corresponding median Median Annualised Bleeding Rates (ABR) in subjects evaluable for efficacy were 2.95 (interquartile range 1.01-4.35) and remained similar throughout Study III (1.85 (IQR: 0.76-4.0)). Subjects had a median of 0.38 (IQR: 0.00-1.43) spontaneous joint bleeds in Study III.

For subjects in the individualised interval arm of, the median dosing interval was 12.53 days (IQR: 10.4-13.4) in Study I. The corresponding median ABR was 1.38 (IQR: 0.00-3.43) and remained similar throughout Study III (1.85 (IQR: 0.76-4.0).

Dosing intervals and factor consumption remained similar in Study III (extension study) compared to Study I for both prophylactic regimens.

(...)

Perioperative management (surgical prophylaxis):
A total of 35 major surgical procedures were performed and assessed in 22 subjects (21 adults and adolescents, and 1 paediatric patient <12 years of age) in Study I and Study III. Of the 35 major surgeries, 28 surgeries (80.0%) required a single pre-operative dose to maintain haemostasis during surgery. The median average dose per injection to maintain hemostasis during surgery was 94.7 IU/kg (range: 49 to 152 IU/kg). The total dose on the day of surgery ranged from 49 to 341 IU/kg and the total dose in the 14 day perioperative period ranged from 60 to 1947 IU/kg.

The haemostatic response was rated as excellent or good in 100 % of major surgeries.

For subjects in the individualised interval arm of, the median dosing interval was 12.53 days (IQR: 10.4-13.4) in Study I. The corresponding median ABR was 1.38 (IQR: 0.00-3.43) and remained similar throughout Study III (1.85 (IQR: 0.76-4.0).
Dosing intervals and factor consumption remained similar in Study III (extension study) compared to Study I for both prophylactic regimens.

(...)
Paediatric population
(...)Out of 30 patients having completed Study II, 27 enrolled to Study III (extension study). The median time on Study II+III was 2.88 years and median number of exposure days was 166.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Recombinant factor IX Fc fusion protein (rFIXFc) is a long-acting, fully recombinant, fusion protein comprising human coagulation factor IX covalently linked to the dimeric Fc domain of human immunoglobulin G1 with no intervening sequence, and produced by recombinant DNA technology. This type of construct has been termed a monomeric Fc fusion protein.

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 (Figure 1). rFIXFc was developed to have a longer half-life while maintaining the activity profile of FIX as a treatment for hemophilia B. The rFIXFc drug substance (DS) is produced in human embryonic kidney 293 (HEK-293) cells.

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

The rFIXFc clinical development program was designed to evaluate the rFIXFc in order to address the unmet medical need for a safe and effective hemophilia B therapy that can be administered less frequently than the conventional FIX products.

The clinical development program consists of 4 completed studies in previously treated patients (PTPs) and 1 ongoing study in previously untreated patients (PUPs).

Completed studies:

- Study SYN-FIXFc-07-001 was a phase 1/2a dose-escalation study in adults ≥18 years of age to evaluate the safety and PK of rFIXFc.
- Study 998HB102 (B-LONG) was a pivotal phase 3 study to evaluate the safety, PK and efficacy of rFIXFc in adults and adolescents ≥12 years of age.
- Study 9HB02PED (Kids-B-LONG) was a pivotal phase 3 study to evaluate the safety, PK and efficacy of rFIXFc in children <12 years of age.
- Study 9HB01EXT (BYOND) was a phase 3 extension study to evaluate long-term safety and efficacy of eligible subjects previously enrolled in the parent studies 998HB102 or 9HB02PED.

Ongoing study:

- Study 998HB303 (PUP-B) is a phase 3 study to evaluate the safety and efficacy of rFIXFc in PUPs with severe hemophilia B.

The original marketing authorization application for rFIXFc was based on the results from one Phase 1/2a dose escalation study (SYN-FIXFc-07-001) and the two pivotal Phase 3 studies (9HB02PED and

998HB102), plus interim data from the long-term extension study 9HB01EXT (data cut-off October 17, 2014).

As of October 31, 2017, the long-term extension study 9HB01EXT has been completed. This was an open-label, multicenter, long-term study of intravenous administration of rFIXFc in PTPs with hemophilia B who had completed studies 998HB102 or 9HB02PED (hereafter referred to as parent studies). The objectives of the study were to evaluate the long-term safety and efficacy of rFIXFc in the treatment of bleeding episodes, as routine prophylaxis and for perioperative management.

Study 9HB01EXT was designed to meet the EMA guideline (EMA 2011) on the clinical investigation of recombinant and human plasma-derived FIX products for a postmarketing investigation of at least 50 subjects followed for at least 100 EDs to monitor long-term efficacy and safety, in particular immunogenicity.

The complete clinical study report of the extension study (study 9HB01EXT; BYOND) has already previously been submitted as an Article 46 paediatric submission (EMEA/H/C/004142/P46 005) in order to meet the deadline to provide paediatric data within 6 months from End of Study. The data presented did not reveal any new safety or efficacy aspects which may alter the benefit risk profile. However, at the time of submission of the Art.46 procedure the results of an integrated analysis of the extension study with the two parent studies were not available preventing to draw final conclusions concerning long-term safety and efficacy.

As previously agreed upon, the MAH submitted the final data package via the current Type II variation.

The SmPC updates in section 4.8 and 5.1 (please refer to Attachment 1 for details) proposed in this variation are results of the integrated evaluation of data from the extension study and the two pivotal parent studies.

6. Clinical Efficacy aspects

6.1. Methods – analysis of data submitted

Study 9HB01EXT was a Phase 3, open-label, multicenter, long-term extension study of IV administration of rFIXFc in male PTPs with hemophilia B who had completed any of the following studies (also referred to as parent studies):

- Study 998HB102 (B-LONG; adults and adolescents ≥12 years of age)
- Study 9HB02PED (Kids-B-LONG; children <12 years of age)

Study 9HB01EXT was designed to meet the EMA guideline (EMA 2011) on the clinical investigation of recombinant and human plasma-derived FIX products for a post-marketing investigation of at least 50 subjects followed for at least 100 EDs to monitor efficacy and safety, in particular immunogenicity.

Study results were summarized in the final CSR and submitted to the EMA as a paediatric Article 46 submission (Alprolix – P46 005 – EMEA/H/C/004142/P46/005) on April 26, 2018.

To further evaluate the efficacy of long-term treatment with rFIXFc, an integrated analysis of perioperative management in subjects from studies 998HB102, 9HB02PED, and 9HB01EXT was performed.

Summaries of parent studies

Study 998HB102 was a Phase 3, open-label, multicenter study that evaluated the safety, PK, and efficacy of rFIXFc in 123 adult and adolescent PTPs ≥12 years of age with severe hemophilia B (defined as ≤2 IU/dL [≤2 %] endogenous FIX) and at least 100 prior EDs to a FIX product.

Study 998HB102 showed that rFIXFc has a half-life of 82 hours, which is 2.43-fold longer than BeneFIX®. rFIXFc was effective in the control of bleeding with >90 % acute bleeding episodes controlled with a single injection. rFIXFc was effective in each of 2 routine prophylaxis regimens (a weekly, fixed-interval, personalized dose regimen and a fixed-dose [100 IU/kg], personalized, interval regimen) with >80 % reduction in ABR relative to episodic treatment.

The median weekly dose during the last 6 months on study in the weekly prophylaxis arm was 40.7 IU/kg. The median dosing interval during the last 6 months on study in the individualized interval prophylaxis arm (dosed at 100 IU/kg) was 13.8 days. rFIXFc was effective when used for perioperative management, with 100 % of major surgeries having excellent or good hemostasis.

Study 9HB02PED was a Phase 3, open-label, multicenter study that evaluated the safety, PK, and efficacy of rFIXFc in pediatric PTPs with severe hemophilia B (defined as ≤2 IU/dL [≤2 %] endogenous FIX) and at least 50 prior EDs to a FIX product.

A total of 30 subjects (15 subjects <6 years of age and 15 subjects 6 to <12 years of age) were enrolled and treated with rFIXFc in the study. rFIXFc had prolonged half-life and reduced CL in comparison with prestudy FIX Sobi Alprolix (rFIXFc) products. Subjects who administered rFIXFc prophylactically had a low ABR; median ABR was 1.09 in the <6 years of age cohort and 2.13 in the 6 to <12 years of age cohort. rFIXFc was highly effective in treating bleeding episodes, with nearly all (91.7 %) of bleeds controlled with either 1 or 2 injections of rFIXFc, with 75.0 % resolved with a single injection.

Overall, the AE profile in the completed studies in PTPs was generally consistent with that expected in patients with hemophilia B and also consistent across the patient populations evaluated in the parent studies. No inhibitor development was observed in the studies in PTPs.

While ADA was detected in a small number of phase 3 subjects at some point, the presence of an ADA-positive test result did not have an observed clinical effect on the safety of subjects, and ADA in this context is still exploratory. There were no serious allergic AEs or serious vascular thrombotic events in either of the phase 3 parent studies.

Study 9HB01EXT

Design and investigational plan

The open-label, multicenter, long-term study 9HB01EXT of rFIXFc in PTPs with hemophilia B was a global study and was offered to those sites in countries participating in the parent studies.

Male subjects of all ages with severe hemophilia B who had completed any of the parent studies were eligible for enrolment. The End of treatment visit of the previous study served as the Screening visit for the extension. Assessments performed at this visit were used to confirm eligibility for participation in the study. Subjects from study 9HB02PED were assigned to 1 of 2 age cohorts (<6 or 6 to <12 years of age) at the Screening visit for the parent study; subjects continued in their parent study-assigned age cohorts throughout study 9HB01EXT unless otherwise stated.

Study visits were scheduled at 6-month (±2 weeks) intervals following the completion of Visit 1. Unscheduled visits occurred as deemed necessary by the investigator. For subjects who underwent

surgery, postoperative clinic visits were more frequent. For subjects that underwent major surgery, a visit was required 1 to 2 weeks after surgery; this was not required for minor surgery.

Scheduled visits included safety and efficacy assessments and FIX activity measurements to assess trough and peak (recovery) levels. In addition, the site contacted study subjects and/or caregivers by telephone on a bimonthly basis to review AEs, treatment compliance, and use of concomitant medications and therapies. Subjects were followed through at least 100 EDs to rFIXFc in total across parent and extension study. All subjects had the opportunity to continue in this study for up to 4 years.

Study population /Sample size

To be eligible to participate in this study, candidates were required to meet the following eligibility criteria at the time of signing the informed consent at Visit 1 of the study, or at the EOT Visit of the previous study.

Main Inclusion Criteria:

- Ability to understand the purpose and risks of the study and ability to provide signed and dated informed consent and authorization to use protected health information in accordance with national and local subject privacy regulations. Parental or guardian consent was required for subjects who were less than 18 years of age or unable to give consent, or as applicable per local laws. Subjects who are less than 18 years of age may provide assent in addition to the parental/guardian consent, if appropriate.
- Subjects who had completed either Study 998HB102 or Study 9HB02PED (two parent studies for Study 9HB01EXT).

Main Exclusion Criteria:

- Confirmed high-titer inhibitor (≥5.00 BU/mL).
- Current enrolment in any other clinical study.
- Inability to comply with study requirements.
- Other unspecified reasons that, in the opinion of the Investigator or Biogen Idec Inc., make the subject unsuitable for enrolment.

As this was an extension study, the **sample size** was based on the planned sample sizes of Study 998HB102 (N = 100) and Study 9HB02PED (N = 20).

Objectives

Primary Objective:

- The primary objective of the study was to evaluate the long-term safety of rFIXFc in subjects with hemophilia B.

Secondary Objective:

- The secondary objective of the study was to evaluate the efficacy of rFIXFc in the prevention and treatment of bleeding episodes in subjects with hemophilia B.

Endpoints

Primary Endpoint

The primary endpoint was the occurrence of inhibitor development.

Secondary Endpoints

- The annualized number of bleeding episodes (spontaneous and traumatic) per subject.
- The annualized number of spontaneous joint bleeding episodes per subject.
- The total number of days of exposure per subject per year.
- The consumption of rFIXFc as total dose per kg per subject per year.
- Physician's global assessment of the subject's response to his treatment regimen using a 4-point scale.
- Subject's/caregiver's assessment of response to the treatment of bleeding episodes using a 4-point scale.

Major Surgery Endpoints

The major surgery endpoints are as follows:

- Investigator/Surgeon assessment of hemostatic response to surgery using the 4-point bleeding response scale.
- Number of injections and dose per injection to maintain hemostasis during the surgical period.
- Estimated blood loss (mL) during surgery and the Postoperative Period.
- Number of blood product units transfused during surgery.

Additional assessments

- Number of injections and dose of rFIXFc to resolve a bleeding episode
- Time to injection to treat a bleeding episode: time from last injection and time between first and second injections
- Hemophilia Joint Health Score (HJHS)
- Patient-Reported outcomes
- Hemophilia-Related Health Economic Parameters

Treatments

rFIXFc (BIIB029) was supplied in a kit containing several components: a vial of lyophilized drug, the diluent syringe, a filter device vial adapter, and a winged injection set. The lyophilized powder was provided in clear glass vials containing 250, 500, 1000, 2000, or 3000 IU of rFIXFc (nominal strengths). The drug product was reconstituted with a diluent syringe containing 5 mL of 0.325% sodium chloride for IV administration.

Subjects 12 years of age or older followed either a weekly (modified) prophylaxis, an individualized prophylaxis, a personalized prophylaxis, or an on-demand regimen based on the subject's clinical profile and on PK profiles and dosing levels from the parent rFIXFc study. Subjects were allowed to change from a prophylaxis regimen to on-demand and from on-demand to prophylaxis during the study.

Subjects <12 years of age received a prophylactic regimen and did not have the option to change to on-demand treatment until reaching the age of 12 years, at which time they could use any of the 4 treatment regimens.

All treatment regimen changes were discussed between the Investigator and the subject (and parent/guardian, as applicable). All treatment regimen changes required the approval of the Sponsor Medical Monitor.

rFIXFc was administered over several minutes by slow IV injection. The rate of administration was determined by the subject's comfort level. Any missed doses were to be taken as soon as possible or per the instructions of the Investigator.

Treatment was self-administered as follows:

- **Weekly prophylaxis** (all ages): doses of approximately 20 IU/kg to 100 IU/kg every 7 days. The dose was based on the subject's clinical profile observed in the parent rFIXFc study and his individual PK profile, trough, and/or peak (recovery) values.
- **Individualized prophylaxis**: doses of approximately 100 IU/kg every 8 to 16 days, or 2 times per month. The dosing interval was based on the subject's clinical profile observed in the parent rFIXFc study, and his individual PK, trough, and/or peak (recovery) values.
- **Personalized prophylaxis**: If optimal prophylaxis dosing could not be achieved using either of the above options, the Investigator could further personalize dosing to meet the needs of individual subjects. The Investigator could consider the following personalized dosing options:
    - Addition of "prevention" doses prior to strenuous activity.
    - Targeting a FIX trough level of >5%, if warranted by the bleeding history and/or activity level.
    - Dosing 2 times per week, e.g., 25 IU/kg twice weekly versus 50 IU/kg once weekly, for subjects likely to have better control with such a regimen. For paediatric subjects <12 years of age, the dose could have been adjusted up to 100 IU/kg twice weekly.
- **Episodic (on-demand) treatment**: The individual dose of rFIXFc to treat bleeding episodes was based on the subject's clinical condition, type and severity of the bleeding event, and if indicated, FIX levels. A subject's PK profile and dosing levels from the parent study could also be used to guide dosing decisions. Subjects <12 years of age who were entering from another rFIXFc study were not offered this option, but could opt to receive episodic treatment when they reached the age of 12 years during the study.

To ensure the accuracy of inhibitor testing, subjects following a prophylaxis regimen were required to schedule clinic visits 72 hours after their previous dose of rFIXFc, whenever possible.

Duration of Treatment and Follow-Up:

Treatment Period:

Subjects were expected to be followed through at least 100 EDs to rFIXFc. Subjects first dosed with rFIXFc when <12 years of age were to be followed to at least 100 EDs even if rFIXFc become commercially available.

All subjects had the opportunity to continue in this study for up to 4 years or until rFIXFc became commercially available in the applicable participating country.

Follow-Up Period:

A final study visit was conducted approximately 14 (+7) days after treatment with the last dose of study drug rFIXFc. This follow-up visit was not required if a subject ended his participation in the extension study to enrol into another rFIXFc study.

Statistical methods and considerations

Analysis Populations

- **All-enrolled analysis set**: All subjects who consented to participate in study 9HB01EXT.
- **Full analysis set (FAS)**: Subjects who received at least 1 dose of rFIXFc in study 9HB01EXT. Analyses of efficacy were performed on the Full analysis set.
- **Safety analysis set**: subjects who received at least 1 dose of rFIXFc in study 9HB01EXT.
- **Surgery subgroup**: subjects who had undergone major surgery or had major surgical/rehabilitation periods.

Statistical and Analytical Plan

Because the subjects from study 998HB102 and study 9HB02PED were in different age groups (i.e., ≥12 years of age for study 998HB102 and <12 years of age for study 9HB02PED) and could therefore have different safety and efficacy profiles, analyses were performed for each population of subjects. For subjects from study 9HB02PED, the age cohorts (<6 years old and 6 to <12 years old) were based on the ones used in study 9HB02PED.

Summaries of study 9HB01EXT data were produced using standard summary statistics. Continuous variables were summarized using descriptive statistics. Categorical variables were summarized by counts and percentages.

The efficacy period for each regimen reflected the sum of all intervals of time during which subjects were treated with rFIXFc according to the treatment regimens of the study, excluding major and minor surgical/rehabilitation periods and large injection intervals (>42 days within a prophylactic treatment regimen). All subjects with an efficacy period were included in the efficacy analysis. Information on bleeding episodes was used to derive the secondary efficacy endpoints.

An impact analysis was performed to evaluate the potential impact on the study results of the absence of documented subject confirmation for those categories of EPD data changes for which it was required. The impact assessment included the evaluation of key study endpoints after data were reset to their original values.

Analyses of integrated data

Surgery data from the parent studies 998HB102 and 9HB02PED and the extension study 9HB01EXT were integrated to describe treatment during and after surgery and to evaluate haemostatic response. The results were summarized using descriptive statistics.

6.2. Results

Recruitment / Number analysed

The subject disposition is displayed in Table 1.

Table 1. Summary of Disposition (All-Enrolled Analysis Set)

Number of subjects in each analysis set	Subjects (<12 years of age) from Study 9HB02PED	Subjects (≥12 years of age) from Study 998HB102	All subjects in Study 9HB01EXT
All-enrolled Analysis Set n/m (%) (a)	27/30 (90.0%)	93/123 (75.6%)	120/153 (78.4%)
Full Analysis Set (b)	27 (100.0%)	93 (100.0%)	120 (100.0%)
Subjects in 9HB01EXT (c) in:			
Weekly prophylaxis	23	51	74
Individualized prophylaxis	5	31	36
Personalized prophylaxis	2	17	19
Episodic	0	15	15
Subjects with an efficacy period	27 (100.0%)	93 (100.0%)	120 (100.0%)
Weekly prophylaxis	23	51	74
Individualized prophylaxis	5	31	36
Personalized prophylaxis	2	16	18
Episodic	0	15	15
Safety Analysis Set (b)	27 (100.0%)	93 (100.0%)	120 (100.0%)
Surgery subgroup (d)	1 (3.7%)	15 (16.1%)	16 (13.3%)
Completion status			
Completed (e)	23 (85.2%)	75 (80.6%)	98 (81.7%)

Discontinued prematurely	4 (14.8%)	18 (19.4%)	22 (18.3%)
Lack of efficacy	0	1 (1.1%)	1 (0.8%)
Lost to follow-up	0	3 (3.2%)	3 (2.5%)
Other	1 (3.7%)	10 (10.8%)	11 (9.2%)
Physician decision	2 (7.4%)	0	2 (1.7%)
Withdrawal by subject	1 (3.7%)	4 (4.3%)	5 (4.2%)

NOTE: 1: Except for the percentages noted in footnote (a), all percentages are based on the number of subjects in the All-enrolled Analysis Set in corresponding columns. 2: All-enrolled Analysis set consists of subjects who consent to participate in 9HB01EXT. (a) n = number of subjects enrolled in study 9HB01EXT from each parent study and overall; m = total number of subjects enrolled in each parent study and overall; percentages are based on m. (b) Subjects who have received at least one dose of rFIXFc. (c) Subjects 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 9HB01EXT treatment regimen. (d) Subjects who have undergone major surgery or have major surgical/rehabilitation periods during this study. (e) Completed means ended participation in the study without premature discontinuation.

Source: Table 6 – Clinical Study Report, Study 9HB01EXT

Demographic and other baseline characteristics

The demographic and baseline characteristics of the subjects enrolled in study 9HB01EXT are summarized in Table 2.

Table 2. Summary of demographic and baseline characteristics in study 9HB01EXT by parent studies (Safety analysis set)

	9HB02PED		998HB102
	<6 years old age cohort (N=13)	6 to 12 years old age cohort (N=14)	(N=93)
Age (years)[a]			
Median	3	9.5	29.0
Min, max	3,5	7, 12	13, 63
Race			
White	10 (76.9 %)	9 (64.3 %)	47 (50.5 %)
Black/African American	1 (7.7 %)	1 (7.1 %)	9 (9.7 %)
Asian	2 (15.4 %)	3 (21.4 %)	27 (29.0 %)
Other	0	1 (7.1 %)	10 (10.8 %)
Geographic location[b]			
Europe	4 (30.8 %)	7 (50.0 %)	23 (24.7 %)
North America	8 (61.5 %)	4 (28.6 %)	23 (24.7 %)
Other	1 (7.7 %)	3 (21.4 %)	47 (50.5 %)

Source: CSR 9HB01EXT, Table 7, and Table 8.
Note 1: Race was taken from the parent study.
Note 2: Percentages are based on the number of subjects with nonmissing data in each treatment regimen/subgroup or overall.
[a] Age at the time of informed consent for study 9HB01EXT.
[b] Europe includes Belgium, Germany, France, United Kingdom, Italy, Poland, Russia, and Sweden. North America includes Canada and the United States. Other countries include Australia, Brazil, China, Hong Kong, India, Japan, and South Africa.

Table 3 (made by the assessor) gives an overview of the subject distribution by age group per treatment regimen in the Safety Analysis Set.

Table 3. The following table (made by the assessor) gives an overview of the subject distribution by age group per treatment regimen in the Safety Analysis Set.

Subject distribution in Study 9HB01EXT by age group per treatment regimen[a] Safety Analysis Set						
Age group[b] (Years)	Weekly prophylaxis	Individualized prophylaxis	Personalised prophylaxis	Episodic	Surgery subgroup[1]	Overall[a]
Number of subjects from the paediatric Study 9HB02PED						
< 6	13	0	1	0	0	13
≥6 to <12	10	5	1	0	1	14
Number of subjects from Study 998HB102						
≥ 12	51	31	17	15	15	93

NOTE 1: Subjects in the surgery subgroup are also counted in their treatment regimen in which they participated. Surgery subgroup includes subjects who have undergone major surgery or have major surgical/rehabilitation periods during this study.

(a) Subjects 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 9HB01EXT treatment regimen. Each subject is counted only once in the overall column. (b) Age at the time of informed consent for 9HB01EXT.

Source: Tables 7 and 8, Clinical Study Report - Study 9HB01EXT

Efficacy evaluation

The study evaluated the efficacy of rFIXFc in the prevention and treatment of bleeding, routine prophylaxis, and perioperative management and reached the following conclusions:

Annualized Bleeding Rate (ABR)

In Study 9HB01EXT, the ABR was summarized by treatment regimen for subjects from Study 998HB102, and by age cohort (<6 years old and 6 to <12 years old) and treatment regimen for subjects from Study 9HB02PED. Subjects were included in the summary of more than 1 treatment regimen if their regimen changed during the study.

Subjects from Study 998HB102

The median ABR was 1.85 (interquartile range [IQR]: 0.76, 4.00) for subjects on individualized prophylaxis; 2.26 (IQR: 0.40, 5.16) for subjects on weekly prophylaxis; 2.91 (IQR: 1.14, 5.36) for subjects on personalized prophylaxis; and 11.64 (IQR: 5.12, 18.54) for subjects on episodic treatment.

2 of 31 subjects (6.5%) on individualized prophylaxis, 9 of 51 subjects (17.6%) on weekly prophylaxis, 3 of 16 subjects (18.8%) on personalized prophylaxis, and 3 of 15 subjects (20.0%) on episodic treatment had no bleeding episodes reported during the Efficacy Period; all 3 of these subjects were on an episodic regimen for a short period of time (≤0.02 years) before changing to weekly or individualized prophylaxis. 24 of 31 subjects (77.4%) on individualized prophylaxis, 29 of 51 subjects (56.9%) on weekly prophylaxis, and 9 of 16 subjects (56.3%) on personalized prophylaxis had an ABR of >0 to 5 bleeding episodes per year during the Efficacy Period. 5 subjects had an ABR of more than 20 bleeding episodes per year during the Efficacy Period. 3 of these subjects were on episodic treatment, and 2 were on prophylaxis (1 subject each from individualized and weekly prophylaxis).

Considering the secondary efficacy endpoint, **annualized number of spontaneous joint bleeding episodes**, the median rate was 0.38 with 25th and 75th percentiles (IQR: 0.00, 1.43) for subjects on individualized prophylaxis; 0.38 (IQR: 0.00, 2.25) for subjects on weekly prophylaxis; 0.30 (IQR: 0.00, 1.37) for subjects on personalized prophylaxis; and 2.15 (IQR: 0.58, 11.68) for subjects on episodic treatment. The median rates for **traumatic joint bleeding** were 0.25 (IQR: 0.00, 1.33), 0.00 (IQR: 0.00, 0.95), 0.44 (0.00, 1.42) and 0.61 (0.00, 3.50) for subjects on individualized, weekly, and personalized prophylaxis, and episodic treatment, respectively.

Subjects from Study 9HB02PED:

- <6 years of age cohort: There were no subjects on individualized prophylaxis in this age cohort. The median ABR was 1.04 (IQR of 0.00 and 2.28) for weekly prophylaxis (13 subjects) and 0.54 for personalized prophylaxis (1 subject only).
- 6 to <12 years of age cohort: The median ABR was 3.69 for individualized prophylaxis (5 subjects), 1.14 (IQR: 0.54, 2.34) for weekly prophylaxis (10 subjects) and 3.13 for personalized prophylaxis (1 subject only).

For subjects on individualized prophylaxis, no subjects had 0 bleeding episodes, 3 of 5 subjects (60.0%) in the 6 to <12 years of age cohort had an ABR of >0 to 5 bleeding episodes per year during the Efficacy Period, 1 subject had an ABR >10 bleeding episodes per year. For subjects on weekly prophylaxis, 5 subjects had 0 bleeding episodes, and 2 subjects had ABR >10 bleeding episodes per year in the <6 years of age cohort, and 2 subjects had 0 bleeding episodes, and 1 subject had ABR >10 in the 6 to <12 years of age cohort. The subjects on personalized prophylaxis (1 subject in the <6 years old cohort and 1 subject in the 6 to <12 years old cohort) had an ABR of >0 to 5 bleeding episodes per year during the Efficacy Period.

4 subjects had an ABR of more than 10 episodes per year (2 in each age cohort).

For the **annualized number of spontaneous joint bleeding episodes**, the median rates were 0.00 (IQR: 0.00, 0.29) for subjects in the 6 to <12 years old cohort on individualized prophylaxis; the median rates for **traumatic joint bleeding** was 0.74 (0.00, 0.85) in the 6 to <12 years of age cohort. There were no subjects on individualized prophylaxis in the <6 years old cohort. For subjects in the <6 years old cohort on weekly prophylaxis, the median rates were 0.00 (IQR: 0.00, 1.06) for spontaneous joint bleeding and 0.00 (IQR: 0.00, 0.99) for traumatic joint bleeding. In the 6 to <12 years old cohort on weekly prophylaxis, the median rates were 0.00 (IQR: 0.00, 1.40) for spontaneous joint bleeding and 0.27 (IQR: 0.00, 0.62) for traumatic joint bleeding. The 1 subject on personalized prophylaxis in the 6 to <12 years old cohort had ABR of 3.13 for traumatic joint bleeding and no spontaneous joint bleeding. The subject on personalized prophylaxis in the <6 years old cohort had no joint bleeding episodes.

For the mean ABR values please refer to the assessment report of the previous Article 46 procedure (EMEA/H/C/004142/P46 005).

Treatment of bleeding episodes

- ***Number of Injections and Dose of rFIXFc to Resolve a Bleeding Episode (BE)***

Subjects from Study 998HB102

Analysis per BE showed that 1 injection of rFIXFc was adequate to resolve 85.9% of BEs in subjects receiving individualized prophylaxis, 84.6% for those receiving weekly prophylaxis, 88.0% for those receiving personalized prophylaxis, and 94.9% for those receiving an episodic regimen, with 96.5%, 96.9%, 97.3%, and 98.9% controlled with ≤2 injections of rFIXFc, respectively. The median number of injections required for resolution of a BE was consistently 1.0 regardless of the treatment regimen.

For resolution of each BE with individualized, weekly, personalized, and episodic treatments, the median dose per injection was 34.39, 50.39, 51.96, and 40.05 IU/kg, respectively, and the median total dose was 36.59, 51.78, 54.87, and 40.54 IU/kg, respectively.

21 subjects had BEs requiring more than 3 injections for resolution (8, 8, 3, and 2 subjects on individualized, weekly, personalized, and episodic treatments, respectively).

Subjects from Study 9HB02PED

1 injection of rFIXFc was adequate to resolve 93.3% of BEs in subjects receiving weekly prophylaxis in the <6 years of age cohort. The 1 subject receiving personalized prophylaxis in the <6 years of age cohort required 3 injections of rFIXFc to resolve the BE. BEs were controlled by ≤2 injections in 98.7% of subjects in subjects receiving weekly prophylaxis in the <6 years of age cohort.

In the 6 to <12 years of age cohort, 1 injection of rFIXFc was adequate to resolve 86.7% and 84.8% of BEs in subjects receiving weekly and individualized prophylaxis, respectively. BEs were controlled by ≤2 injections in the 6 to <12 years of age cohort in 96.7% and 97.0% of subjects receiving weekly and individualized prophylaxis, respectively. The 1 subject receiving personalized prophylaxis in the 6 to <12 years of age cohort required 2 injections of rFIXFc to resolve 2 bleeding episodes and >3 injections to resolve 1 BE.

For weekly prophylaxis in the <6 years of age cohort, the median dose per injection to treat a BE was 58.82 IU/kg, and the median total dose to treat a bleeding episode was 58.82 IU/kg. For weekly prophylaxis in the 6 to <12 years of age cohort, the median dose per injection to treat a BE was 60.85 IU/kg, and the median total dose to treat a BE was 91.60 IU/kg.

For individualized prophylaxis in the 6 to <12 years of age cohort, the median dose per injection to treat a BE was 42.46 IU/kg, and the median total dose to treat a BE was 49.12 IU/kg. For personalized prophylaxis in the 6 to <12 years of age cohort, the median dose per injection to treat a BE was 97.11 IU/kg, and the median total dose to treat a BE was 207.97 IU/kg.

1 subject in the weekly prophylaxis in the <6 years of age cohort, and 1 subject in the personalized prophylaxis regimen in the 6 to <12 years of age cohort had BEs requiring more than 3 injections for resolution.

Assessment of response to rFIXFc treatment

A range of 74 % to 97 % of rFIXFc first injections across all parent studies and all treatment arms were rated by the subject as producing excellent or good responses for treatment of bleeding. The physician's global assessment of the subject's response to their rFIXFc regimen was considered mostly excellent (78.0 %) and effective (21.0 %). No response was assessed as ineffective at any visit.

- ***Subject's assessment of response to rFIXFc for bleeding***

Subjects assessed response to treatment using a 4-point scale of excellent, good, moderate, and none ('none' meaning no improvement).

Subjects from Study 998HB102

In subjects enrolled from study 998HB102, 342 (74.2 %), 336 (87.0 %), 135 (75.8 %), and 603 (97.1 %) of first injections with an evaluation for response were rated as excellent or good by the subjects receiving weekly prophylaxis, individualized prophylaxis, personalized prophylaxis, and on-demand treatment, respectively.

Subjects from Study 9HB02PED

In subjects enrolled from study 9HB02PED, 60 (81.1 %) and 47 (82.5 %) of first injections with an evaluation were rated as excellent or good by the subjects receiving weekly prophylaxis in the <6 years old cohort and the ≥6 to <12 years old cohort, respectively. For subjects receiving individualized prophylaxis, 25 (80.6 %) of first injections evaluated for response were rated as excellent or good by the subjects in the 6 to <12 years of age cohort.

- ***Physician's assessment of subject's global response to rFIXFc for bleeding***

The global assessment was an overall assessment at each scheduled postbaseline visit of a subject's response to his assigned rFIXFc regimen since his last visit. A 4-point scale was used: excellent, effective, partially effective, and ineffective.

Subjects from Study 998HB102

Of a total of 815 visits during the study for subjects from study 998HB102, the Physician's assessment of the subject's global response to their rFIXFc regimen was excellent for 622 visits (76.3 %), effective for 184 visits (22.6 %), and partially effective for 9 visits (1.1 %). There were no subjects whose response to the regimen was assessed as ineffective at any visit.

Subjects from Study 9HB02PED

Of a total of 151 visits during the study for subjects from study 9HB02PED, 131 visits (86.8 %) were rated by physicians as excellent, 19 (12.6 %) were rated as effective, and 1 (0.7 %) were rated as partially effective. No responses were assessed as ineffective.

Total Annualized rFIXFc Consumption

Subjects from Study 998HB102

For subjects who enrolled from Study 998HB102, the median annualized consumption of rFIXFc during the Efficacy Period was as follows:

- 2598.0 IU/kg (range: 1154 IU/kg to 6687 IU/kg) for subjects who selected weekly prophylaxis (N = 51)
- 2894.8 IU/kg (range: 1143 IU/kg to 7410 IU/kg) for subjects who selected individualized prophylaxis (N = 31)
- 3671.2 IU/kg (range: 1289 IU/kg to 8209 IU/kg) for subjects who selected personalized prophylaxis (N = 16)
- 595.6 IU/kg (range: 0 IU/kg to 2346 IU/kg) for subjects who were treated episodically (N = 15)

Subjects from Study 9HB02PED

Of the subjects enrolled from Study 9HB02PED in the <6 years of age cohort, 13 subjects were assigned to a weekly prophylaxis regimen. The median annualized consumption during the Efficacy Period for these subjects was 3382.5 IU/kg (range: 2334 IU/kg to 4464 IU/kg). For the 1 subject in the <6 years of age cohort assigned to personalized prophylaxis, the annualized consumption for the Efficacy Period was 3331.7 IU/kg.

For subjects from Study 9HB02PED in the 6 to <12 years of age cohort, the median annualized rFIXFc consumption during the Efficacy Period was as follows:

- 3212.0 IU/kg (range: 2312 IU/kg to 4986 IU/kg) for subjects who selected weekly prophylaxis (N = 10)

- 3700.7 IU/kg (range: 2745 IU/kg to 6656 IU/kg) for subjects who selected individualized prophylaxis (N = 5)
- 8931.2 IU/kg for 1 subjects who received personalized prophylaxis

For the mean values please refer to the assessment report of the previous Article 46 procedure (EMEA/H/C/004142/P46 005).

Prophylactic dosing and dosing interval

Subjects from Study 998HB102 in Study 9HB01EXT

The median dosing interval for subjects who participated in a weekly, individualized, and personalized prophylaxis regimen was 6.99, 13.61, and 6.61 days, respectively.

The median weekly dose for subjects was 48.46 IU/kg, 50.76 IU/kg, and 68.23 IU/kg, for weekly, individualized, and personalized prophylaxis, respectively.

Subjects from Study 9HB02PED in Study 9HB01EXT

The median dosing interval for subjects from study 9HB02PED on weekly prophylaxis was 7.00 days for the <6 years of age cohort. In the 6 to <12 years of age cohort, the median dosing interval was 7.02 days for subjects on weekly prophylaxis and 10.20 days for subjects on individualized prophylaxis. There was only 1 subject on personalized prophylaxis in the <6 years of age cohort, and 1 subject in the 6 to <12 years of age cohort: the dosing intervals for these subjects were 4.50 days and 4.11 days, respectively.

The median weekly dose for subjects on weekly prophylaxis in the <6 years of age cohort was 64.64 IU/kg. In the 6 to <12 years of age cohort, the median weekly dose for subjects was 59.96 IU/kg for weekly prophylaxis and 67.70 IU/kg for individualized prophylaxis.

Compliance

Of 113 subjects receiving prophylactic treatment in study 9HB01EXT and participating in the efficacy period, 108 subjects (95.6 %) were compliant with their prescribed dose, 111 subjects (98.2 %) were compliant with the prescribed dosing interval, and 106 subjects (93.8 %) were compliant with both the prescribed dose and the prescribed dosing interval.

Comparison and analyses of results across studies

a) Perioperative management

Hemostatic response during surgery and postoperatively was evaluated in **an analysis of integrated efficacy data** from studies 998HB102, 9HB02PED, and 9HB01EXT. Hemostasis was postoperatively assessed by the investigator/surgeon using a 4-point scale of excellent, good, fair, and poor/none.

In the analysis of integrated data, the surgery subgroup consisted of 34 subjects who had undergone major surgery or had major surgical/rehabilitation periods during study 9HB01EXT.

Of the 35 major surgeries performed, 33 surgeries in 22 subjects were assessed for hemostatic response. Hemostasis was rated by the investigator/surgeon as excellent (n = 29) or good (n = 4) in all 33 major surgeries. The majority of surgeries were orthopedic procedures with knee replacement as the most common surgery.

Of the 35 major surgeries, 28 (80.0 %) required a single injection of rFIXFc to maintain hemostasis during surgery, 4 (11.4 %) required 2 injections, 1 (2.9 %) required 3 injections, and 1 (2.9 %) required 4 injections. There was no record of injections given for 1 major surgery.

The median average dose per injection was 94.7 IU/kg (range: 49 to 152 IU/kg). The total dose on the day of surgery ranged from 49 to 341 IU/kg, and the total dose in the 14-day perioperative period ranged from 60 to 1947 IU/kg.

Although no specific objectives were specified for minor surgeries, information on minor surgeries and the hemostatic responses was collected in the extension study. Minor surgery results were consistent with those for major surgery. Data were collected on 62 minor surgeries in 37 subjects. Assessment of response was available for 38 of the 62 minor surgeries; hemostasis was assessed as excellent or good in all of them.

b) Comparison of efficacy endpoints across parent and extension studies

The parent studies 998HB102 and 9HB02PED and the extension study 9HB01EXT have key efficacy endpoints in common. Results of these endpoints are presented in Table 4 for study 998HB102 and in Table 5 for study 9HB02PED, and serve as basis for comparisons between the parent studies and the extension study.

Surgery endpoints are also common between the parent studies and the extension study. Surgery events are reported as they occur, i.e., cumulatively over the course of both studies, and results are therefore presented in the analysis of integrated data above.

Table 4. Summary of key efficacy endpoints in study 998HB102 and study 9HB01EXT

	Study 998HB102			Study 9HB01EXT - Subjects from 998HB102			
	Weekly (N=63)	Individualized (N=29)	On demand (N=27)	Weekly (N=51)	Individualized (N=31)	Personalized (N=17)	On demand (N=15)
Median ABR (IQR)	2.95 (N=61) (1.01, 4.35)	1.38 (N=26) (0.00, 3.43)	17.69 (10.77, 23.24)	2.26 (0.40, 5.16)	1.85 (0.76, 4.00)	2.91 (1.14, 5.36)	11.64 (5.12, 18.54)
Median weekly dose (IU/kg) (min, max)	45.17 (25.0, 74.3)	d	NA	48.46 (21.3, 105.6)	50.76 (17.1, 141.3)	68.23 (22.4, 145.7)	NA
Median dosing interval (days) (min, max)	c	12.53 (7.8, 15.9)	NA	6.99 (6.7, 7.8)	13.61 (3.5, 21.3)	6.61 (3.3, 14.2)	NA
Number of injections to resolve bleed							
≤2	94.0 %	97.0 %	98.8 %	96.9 %	96.5 %	97.3 %	98.9 %
1	85.0 %	85.1 %	93.5 %	84.6 %	85.9 %	88.0 %	94.9 %
Dose/injection to resolve bleed (min, max)							
Median (IU/kg)	47.11 (16.6, 99.1)	44.78 (14.3, 110.1)	45.98 (7.9, 111.1)	50.39 (7.1, 112.4)	34.39 (11.8, 106.5)	51.96 (13.8, 91.6)	
Total (IU/kg)	51.47 (16.6, 263.9)	49.62 (14.3, 223.0)	46.58 (7.9, 228.1)	51.78 (7.1, 779.1)	36.59 (11.8, 591.8)	54.87 (13.8, 558.9)	
Subject's assessment of trmt[a]							
Excellent/good	78.8 %	74.6 %	87.1 %	74.2 %	87.0 %	75.8 %	97.1 %
Moderate	18.6 %	22.2 %	11.9 %	20.8 %	10.9 %	21.9 %	2.6 %
None/No response	2.6 %	3.2 %	1.0 %	5.0 %	2.1 %	2.2 %	0.3 %
Physician's assessment of trmt response[b]							
Excellent		71.0 %			76.3 %		
Effective		27.8 %			22.6 %		
Partially effective		1.2 %			1.1 %		

Source: CSR 998HB102: Table 19, Table 22, Table 25, Table 26, Table 64, Table 65, and Table 94. CSR 9HB01EXT: Table 12, Table 14, Table 15, Table 17, Table 18, Table 39, and Table 41.
Abbreviations: ABR, Annualized bleeding rate; IQR, Interquartile range; IU, International unit; Min, Minimum; Max, Maximum; NA, Not applicable; Trmt, Treatment.
[a] Percentages are based on the number of first injections for a bleeding episode with an evaluation.
[b] Total responses across all treatment arms. In study 998HB102, percentages are based on the number of subjects with nonmissing observations for the by-visit summaries and on the total number of responses from Week 4 through Week 52 for the total number of scale responses in each arm and overall. In study 9HB01EXT, percentages are based on the number of subjects with nonmissing observations for the by-visit summaries and on the number of responses across all scheduled study visits for the total number of scale responses.
[c] Fixed weekly interval.
[d] Given as monthly prophylactic dose (244.66 [196.4, 396.1] IU/kg) in CSR 998HB102, Table 67.

Source - Table 2.7.3-6 – Summary of Clinical Efficacy

Table 5. Summary of key efficacy endpoints in study 9HB02PED and study 9HB01EXT

	Study 9HB02PED		Study 9HB01EXT - Subjects from 9HB02PED				
	<6 years old	6 <12 years old	<6 years old		6 <12 years old		
	Individualized (N=15)	Individualized (N=15)	Weekly (N=13)	Personalized (N=1)	Weekly (N=10)	Individualized (N=5)	Personalized (N=1)
Median ABR (IQR)	1.09 (0.00, 2.90)	2.13 (0.00, 4.17)	1.04 (0.00, 2.28)	0.54 (0.54, 0.54)	1.14 (0.54, 2.34)	3.69 (3.54, 5.21)	3.13 (3.13, 3.13)
Median weekly dose (IU/kg) (min, max)	59.40 (31.0, 68.6)	57.78 (46.5, 110.1)	64.64 (41.2, 82.5)	59.66 (59.7, 59.7)	59.96 (44.2, 81.8)	67.70 (49.6, 139.2)	156.72 (156.7, 156.7)
Median dosing interval (days) (min, max)	6.99 (6.9, 10.8)	6.99 5.9, 8.1)	7.00 (6.8, 7.2)	4.5 (4.5, 4.5)	7.02 (6.9, 7.5)	10.20 (5.2, 13.2)	4.11 (4.1, 4.1)
Number of injections to resolve bleed							
≤2	95.5 %	89.5 %	98.7 %	c	96.7 %	97.0 %	d
1	86.4 %	68.4 %	93.3 %		86.7 %	84.8 %	
Dose/injection to re-solve bleed (min, max)							
Median (IU/kg)	63.70 (30.1, 133.3)	62.92 (16.7, 122.7)	58.82 (22.6, 159.6)	63.29 (63.3, 63.3)	60.85 (20.0, 138,2)	42.46 (19.6, 99.5)	97.11 (93.0, 104.0)
Total (IU/kg)	65,37 (30.1, 266.7)	89.77 (16.7, 362.7)	58.82 (22.6, 170.2)	189.87 (189.9, 189.9)	91.60 (20.0, 209.2)	49.12 (19.6, 248.8)	207.97 (186.0, 388.4)
Subject's assessment of trmt[a]							
Excellent/good	89.5 %	88.2 %	81.1 %	0	82.5 %	80.6 %	50.0 %
Moderate	5.3 %	11.8 %	18.9 %	100.0 %	10.5 %	3.2 %	50.0 %
None	5.3 %	0	0	0	7.0 %	16.1 %	0
Physician's assessment of trmt response[b]							
Excellent	87.9 %				86.8 %		
Effective	12.1 %				12.6 %		
Partially effective	0				0.7 %		

Source: CSR 9HB02PED: Table 17, Table 21, Table 22, Table 23, Table 46, Table 47, and Table 79. CSR 9HB01EXT: Table 13, Table 14, Table 16, Table 19, Table 20, Table 40, and Table 42.
Abbreviations: ABR, Annualized bleeding rate; IQR, Interquartile range; IU, International unit; Min, Minimum; Max, Maximum; NA, Not applicable; Trmt, Treatment.
[a] Percentages are based on the number of first injections for a bleeding episode with an evaluation.
[b] In study 9HB02PED, percentages are based on the number of subjects with nonmissing observations for the by-visit summaries and on the number of responses from Week 12 through Week 50 for the total number of scale responses in each age cohort or overall.. In study 9HB01EXT, percentages are based on the number of subjects with nonmissing observations for the by-visit summaries and on the number of responses across all scheduled study visits for the total number of scale responses.
[c] The one subject in the <6 years old cohort on personalized prophylaxis required 3 injections of rFIXFc to resolve the bleeding episode.
[d] The one subject in the 6 <12 years old cohort on personalized prophylaxis required 2 injections of rFIXFc to resolve 2 bleeds and >3 injections to resolve 1 bleed.

Source - Table 2.7.3-7 – Summary of Clinical Efficacy

Analysis of clinical information relevant to dosing recommendations

The dosing recommendations in the initial Marketing Authorization Application remain clinically current.

Persistence of efficacy and/or tolerance effects

Persistence of efficacy with rFIXFc in adults, adolescents, and children has been evaluated in the extension study 9HB01EXT.

6.3. Discussion

The MAH submitted a Type II variation application to update the Alprolix Product Information as a result of new clinical efficacy and safety data on long-term treatment with Alprolix. The SmPC updates proposed in this variation are results of an integrated evaluation of data obtained from the extension study 9HB01EXT (BYOND) and the two pivotal parent studies (998HB102 and 9HB02PED). The clinical study report of the extension study 9HB01EXT has already been submitted in April 2018 as an Article 46 paediatric submission (EMEA/H/C/004142/P46 005) in order to meet the deadline to provide paediatric data within 6 months from End of Study.

The extension trial, Study 9HB01EXT, was performed to evaluate the long-term safety and efficacy of recombinant factor IX Fc fusion protein (rFIXFc) in the treatment of bleeding episodes, as routine prophylaxis, and for perioperative management in adult and paediatric subjects. The study included

previously treated male patients with hemophilia B who completed either Study 998HB102 (B-LONG; adult and adolescents ≥12 years of age) or study 9HB02PED (Kids-B-LONG: children < 12 years of age).

Inhibitor surveillance over the period of 100 EDs for each subject was carried out following the "Guideline on the clinical investigation of recombinant and human plasma-derived factor IX products" (EMA/CHMP/BPWP/144552/2009).

A total of 120 subjects were included in the Full Analysis Set (FAS) and Per Protocol Analysis Set (PPAS). Of these, 93 subjects had transitioned from pivotal Study 998HB102 (subjects ≥12 years of age) and 27 from Study 9HB02PED (13 subjects <6 years of age; 14 subjects 6 to < 12 years of age).

The key efficacy and surgery endpoints of the extension trial and the parent studies were the same. Key efficacy endpoints included assessment of annualized bleeding rates (ABRs) during routine prophylaxis and assessment of response to bleeding episodes (BEs). Surgery events were reported as they occur, i.e., cumulatively over the course of both studies, presented as integrated analysis.

Treatment was self-administered as weekly, individualized, or personalized prophylaxis, or as episodic treatment. Subjects ≥12 years of age were able to switch from 1 regimen to another at scheduled or unscheduled visits during the study according to the investigator´s discretion. Subjects <12 years of age were prescribed a prophylactic regimen (weekly, personalized, or individualized) and did not have the option to change to episodic treatment until they turned 12 years of age.

Of the 120 subjects in the FAS, 74 subjects were included in the weekly prophylaxis arm (51 subjects from Study 998HB102, 23 subjects from Study 9HB02PED), 36 subjects participated in the individualized prophylaxis arm (31 subjects from Study 998HB102, 5 subjects from Study 9HB02PED), 18 subjects participated in the personalized prophylaxis arm (16 subjects from Study 998HB102, 2 subjects from Study 9HB02PED), and 15 subjects were treated episodically (all from Study 998HB102).

In the analysis of integrated data, the surgery subgroup consisted of 34 subjects who had undergone major surgery or had major surgical/rehabilitation periods during study 9HB01EXT. Of the 35 major surgeries performed, 33 surgeries in 22 subjects were assessed for hemostatic response.

Most subjects were ≥12 years of age (n=93), 11 of these patients were ≥12 to < 18 years of age at the start of the parent study. 14 subjects were 6 to < 12 years of age and 13 subjects were <6 years of age at the start of the parent study.

Overall, ABRs and dosing intervals during prophylaxis were in a range similar to those observed over the course of the preceding phase 3 trials.

Similar to the parent studies, the majority of bleeding episodes (BEs) were resolved by ≤2 injections of rFIXFc in the extension study. These results seem to be consistent with the Physician´s global assessment of subject´s response to rFIXFc, which was considered mostly excellent (78%) or effective (21%); 1.0% were considered classified as partially effective. There were no subjects whose response to the rFIXFc regimen was assessed as ineffective at any visit.

However, in contrast to the preceding trials several subjects (21 subjects from 998HB102 and 2 subjects from Study 9HB02PED) needed ≥3 injections to control a BE. Narratives of the subjects who required more than 3 injections to treat a BE and for those who exhibited more than 10 ABRs were provided. Available information on these patients is considered comprehensible and thus, no concerns regarding efficacy arise.

Total annualized rFIXFc consumption also remained similar to that in the preceding studies.

Hemostatic response during surgery and postoperatively was evaluated in an analysis of integrated efficacy data from studies 998HB102, 9HB02PED, and 9HB01EXT. 33 (out of 35) major surgeries in 22

subjects were assessed for hemostatic response. Hemostasis was rated by the investigator/surgeon as excellent or good in 100% of the major surgeries. The majority of them (80%) required a single injection of rFIXFc to maintain hemostasis during surgery. Overall, the data of the integrated analysis continue to support the efficacy of rFIXFc in maintaining hemostasis in the perioperative setting.

Conclusion on Efficacy

Altogether, the efficacy data generated in the extension study are broadly comparable with the respective results obtained in the parent studies indicating that Alprolix is effective as prophylaxis and for treatment of bleeding episodes in both adult and paediatric patients with severe hemophilia B. With regards to the perioperative management an integrated analysis of the hemostatic response during surgery and postoperatively was performed. Results from this analysis continue to support the use of rFIXFc in the perioperative setting. Comparing the other main efficacy results (e.g. ABRs, number of injections to control a BE, total annualized rFIXFc consumption) with those already submitted in the previous Article 46 paediatric submission (EMEA/H/C/004142/P46 005), no changes were observed.

The MAH proposed to update Section 5.1 of the SmPC according to the new efficacy data available from the extension study and its integrated analysis with the two parent studies. As overall, the new data (derived from the extension study) did not impact the already known efficacy and safety profile of Alprolix, a detailed reflection of these data in the SmPC was not considered necessary. The MAH was reminded that according to the SmPC guideline statements should be kept brief and precise presenting only limited information relevant to the prescriber. Therefore, the MAH was requested to revise the proposed updates in Section 5.1 of the SmPC. The MAH complied with the request and completely revised Section 5.1. Only the main efficacy results are now proposed to be included and in addition, the whole section was amended and shortened to improve readability. The new proposals made by the MAH are considered acceptable.

Originally, the efficacy results for the 11 patients aged ⩾12 to <18 years at entry to the pre-ceding study 998HB102 were not presented separately in the dossier and no information was provided what treatment arms these patients were assigned to. It was acknowledged that these efficacy analyses were not specifically required in the Alprolix PIP. However, the MAH was requested to provide these data in order to draw a final conclusion concerning efficacy also for this age cohort. The MAH has already been requested to present these data in the previous procedure (EMEA/H/C/004142/P46 005). However, at that time it was considered acceptable that these data would be presented within the current procedure. Upon request, the MAH presented data on the Annualized Bleeding Rate (ABR), the Annualized Joint Bleeding rate, and the Annualized rFIXFc consumption also for this subpopulation. Overall, the results seem broadly comparable with those obtained for the other age cohorts (‹ 12 year olds and adults). It is acknowledged that the number of patients (a total 9 patients in the end) is deemed too low to include data in the SmPC.

7. Clinical Safety aspects

This submission contains integrated safety data from the completed extension Study 9HB01EXT and its 2 parent studies (998HB102 and 9HB02PED).

7.1. Methods – analysis of data submitted

Exposure to the drug

The safety data previously reported were derived from the 2 completed parent (originating) studies, i.e., the Phase 3 study in adults and adolescents ≥12 years of age (998HB102) and the Phase 3 study in children <12 years of age (9HB02PED), integrated with interim data, as of the data cut-off of 17 October 2014, from the ongoing extension study (9HB01EXT) for subjects who further enrolled into this study. The extension study (9HB01EXT) was completed on 31 October 2017.

Exposure (duration of dosing to rFIXFc, total exposure days, and total number of injections per subject) was summarized cumulatively from the parent study (998HB102 and 9HB02PED) to the extension study (9HB01EXT).

Exposure days (EDs) were defined as the 24-hour period in which 1 or more rFIXFc injections were given. The total number of EDs to rFIXFc are summarized categorically (<50, 50 - <100, 100 - <150, 150 - <200, 200 - <250, etc.) by parent study and by age. The total number of EDs and total number of injections per subject are summarized using descriptive statistics.

Safety Assessments for Pooled Studies

Data from the following assessments in the 3 completed studies were pooled for this integrated analysis to evaluate the safety of rFIXFc: inhibitor (neutralizing anti-FIX antibody) development, serious adverse events (SAEs), AEs, and anti-rFIXFc binding antibody development. Concomitant therapy and procedures, haematology, blood chemistry, and vital signs are not included in the integrated analysis; these are included in the respective clinical study reports.

Statistical Methods and Considerations, Integrated Presentation

Analyses of safety data for the integrated analysis are based on the Safety Analysis Set, which was defined as all subjects who received at least 1 dose of rFIXFc in either parent (originating) study.

The Surgery Subgroup is defined as all subjects who underwent a major surgery after the first dose of study treatment in 1 of the 2 parent studies or in Study 9HB01EXT.

For analyses of data by age category, age at the time of informed consent in the parent study and age at the end of the study participation were used to include subjects into the appropriate age categories. Age data presented in the listings are the ages at the time of informed consent in the parent study. Age categories defined by the age of the subject at the time of informed consent in the parent study include: <6 years, 6 to <12 years, 12 to <18 years, and ≥18 years. Age categories defined by age at end of the study (end of parent study for subjects who did not enrol into the extension study and end of extension study for those who did) include: <65 years and ≥65 years.

Analysis of Adverse Events

Definition and Reporting of Adverse Events

An AE was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that did not necessarily have a causal relationship with this treatment.

Any AE experienced by the subject from the time of the first dose of study treatment to the follow-up visit after the last dose of rFIXFc was recorded, regardless of the severity of the event or its relationship to study treatment. AEs that occurred prior to the first dose of study treatment were also recorded, if they were reported.

Bleeding episodes were not considered AEs in this subject population. Bleeding episodes that met a serious criterion (defined in the following section) were to be reported as SAEs. All bleeding episodes were captured in the electronic patient diary.

Definition and Reporting of Serious Adverse Events (SAEs)

Any SAE experienced by the subject after signing the informed consent form and through end of study (last visit) was recorded, regardless of the severity of the event or its relationship to study treatment.

Any SAE that was ongoing when the subject completed the study or discontinued from the study was monitored by the Investigator until the event resolved, stabilized, or returned to baseline status.

As specified by the protocol for each of the 3 studies included in the integrated analysis, the following AEs were considered medically important and were to be reported as SAEs:

- Development of an inhibitor defined as a positive result (confirmed by results from a second independent sample taken within 2 to 4 weeks) from the central laboratory.
- Development of a Grade 2 or higher allergic reaction (hypersensitivity [bronchospasm or anaphylaxis]) in association with administration of rFIXFc (based on the Recommendations for Grading of Acute and Subacute Toxic Effects on the World Health Organization [WHO] scale).
- Development of a vascular thrombotic event in association with the administration of rFIXFc, except for IV injection site thrombophlebitis.

For Study 998HB102, major surgery was not required to be reported as an SAE. For Study 9HB02PED, a change was made with Protocol Version 3 (07 March 2013) to indicate that major surgeries should be reported as SAEs to optimize collection of safety information. There were no major surgeries during Study 9HB02PED. For the extension study (9HB01EXT), a change was made with Protocol Version 4 (13 November 2013) to indicate that major surgeries should be reported as SAEs. For 3 major surgeries (in 3 subjects) during the extension study (9HB01EXT), in accordance with the protocol version in effect at the time, the major surgery was not reported as an SAE.

Definition of Treatment-Emergent Adverse Events

All analyses of AEs were based on the principle of treatment emergence to rFIXFc. An AE was regarded as treatment-emergent to rFIXFc if it was present prior to receiving the first injection of rFIXFc and subsequently worsened in severity, or was not present prior to receiving the first injection but subsequently appeared before either the subject's last visit on study or the follow-up telephone call (or the date of withdrawal/lost to follow up), whichever occurred later. The primary focus of analyses or summaries of AEs is on the rFIXFc treatment-emergent adverse events (TEAEs) and the term TEAE will refer to those events, excluding events that emerge during the perioperative management period (surgical/rehabilitation period) for a major surgery, which are discussed separately.

Adverse Events by Exposure Day Interval

To identify potential trends among AEs occurring with longer duration of exposure to rFIXFc across each parent study and the extension study, AEs were grouped by ED intervals. For a given ED interval, the number of subjects who were monitored for AEs during that ED interval was presented along with the incidence of AEs with an onset during that ED interval. For the number of subjects meeting the interval definition, subjects were counted only once for a given ED interval but could be counted more than once

across ED intervals. For AE incidence, subjects were counted in an ED interval if the onset of the reported AE was in that ED interval. For example, a subject with a total of 120 EDs who had a single AE with onset on the 40th ED would appear in the row for the number of subjects meeting the interval definition in the <50, 50 to <100, and 100 to <150 columns, but would only appear in the rows for AE incidence (number of subjects with at least 1 TEAE and subsequent rows) in the <50 column.

Further factors determined the handling of AEs that spanned multiple ED intervals, AEs that had multiple onset times, and AEs occurring during follow-up. AEs that started in 1 ED interval and continued to another were counted only in the interval in which the AE onset date fell. AEs that had more than 1 onset during the same ED interval were counted only once. AEs that had multiple onsets during different ED intervals were counted in each respective interval. AEs that occurred during the follow-up period were considered treatment emergent and were counted in the subject's last ED interval.

Adverse Events by Severity

The Investigator assessed the severity of each AE as mild, moderate, or severe according to the following classifications:

Mild: Symptoms barely noticeable to subject or did not make subject uncomfortable; did not influence performance or functioning; prescription drug was not ordinarily needed for relief of symptoms but might have been given because of personality of subject.

Moderate: Symptoms of a sufficient severity to make subject uncomfortable; performance of daily activity was influenced; subject was able to continue in study; treatment for symptoms might have been needed.

Severe: Symptoms caused severe discomfort; symptoms caused incapacitation or significant impact on subject's daily life; severity might have caused cessation of treatment with study treatment; treatment for symptoms might have been given or subject was hospitalized.

A subject was counted once for each SOC and PT based on the AE with the greatest severity within that SOC and PT, respectively.

Adverse Events by Relationship to Study Treatment

In Study 998HB102, the Investigators assessed the relationship of each AE to study treatment as possibly related, related, unlikely related, or unrelated according to the following classifications:

Unrelated: Any event that did not follow a reasonable temporal sequence from administration of study treatment AND that was likely to have been produced independently by the subject's clinical state or other modes of therapy administered to the subject.

Unlikely: Any event that did not follow a reasonable temporal sequence from administration of study treatment OR that was likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.

Possibly: Any event that followed a reasonable temporal sequence from administration of study treatment OR that followed a known response pattern to the suspected drug AND that could not have been reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Related: Any event that followed a reasonable temporal sequence from administration of study treatment AND that followed a known response pattern to the suspected drug AND that recurred with re-challenge, AND/OR was improved by stopping the drug or reducing the dose.

In Studies 9HB02PED and 9HB01EXT, the Investigators assessed the relationship of each AE to study treatment as related or unrelated according to the following classifications:

Not related: An AE was considered "not related" to the use of the investigational drug if there was not a possibility that the event had been caused by the product under investigation. Factors pointing toward this assessment included, but were not limited to the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the AE (e.g., the event occurred before administration of drug), or the presence of a more likely alternative explanation for the AE.

Related: An AE was considered "related" to the use of the investigational drug if there was a possibility that the event may have been caused by the product under investigation. Factors that pointed toward this assessment included, but were not limited to a positive re-challenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of an alternative explanation for the AE.

Adverse Events During the Surgical/Rehabilitation Period

The perioperative management period (surgery/rehabilitation period) was defined as starting from the first dose of rFIXFc given for the surgery (i.e., the presurgery dose) to 1 minute before the first regular prophylactic dose after the last day of postoperative care/rehabilitation (or the last day of rehabilitation for subjects in Arm 4 of Study 998HB102), or the end of study for a subject if the overall end of study was declared before the subject's end of postoperative care/rehabilitation.

Because they most often represented AEs that led to the surgical procedure, AEs that occurred during a major surgical/rehabilitation period with an onset date on the day the surgical/rehabilitation period started or on the day of the surgery were included in the overall AE summaries; however, they were not included with AEs that occurred during major surgical/rehabilitation periods. This is consistent with the handling of these AEs in Studies 9HB02PED and 9HB01EXT, whereas Study 998HB102 had included these AEs with AEs that occurred during the surgical period.

Analysis of Hematology and Blood Chemistry

Laboratory test data presented in the integrated analysis include inhibitor test results and anti-rFIXFc antibody data. These analyses include data from each parent study (Studies 998HB102 and 9HB02PED) integrated with final results from Study 9HB01EXT for subjects who further enrolled into the extension study. Hematology and blood chemistry test data are not presented as part of the integrated analysis.

Analysis of Inhibitor and Anti-rFIXFc Binding Antibody

Formation of an inhibitor was defined as a neutralizing antibody value ≥0.6 Bethesda Units (BU)/mL that was confirmed upon testing of a second sample within 2 to 4 weeks, based on the central laboratory test results, consistent with regulatory guidance.7 A low-titer inhibitor was defined as a value ≥0.6 and <5.0 BU/mL and a high-titer inhibitor was defined as a value ≥5.0 BU/mL. An exact 95% confidence interval (CI) for the proportion of subjects with a confirmed inhibitor was calculated using the Clopper-Pearson method for a binomial proportion. Results from blood samples collected during surgical/rehabilitation periods for determining the presence of an inhibitor were included in this analysis. Inhibitor results are summarized by parent study and overall.

Anti-drug (rFIXFc) binding antibody (ADA), which is distinguished from neutralizing antibody (inhibitor), was assessed by an electrochemiluminescent assay (ECLA), which is approximately 70- to 80-fold more sensitive than the Nijmegen-modified Bethesda assay. The development of ADAs was assessed as the number and percentage of subjects negative throughout the studies, positive at any time after treatment with rFIXFc, and positive at the final evaluation. Percentages were based on the number of subjects who were antibody negative prior to treatment with rFIXFc and had at least 1 post-baseline antibody evaluation for the referenced timepoint or time interval. Baseline was assessed prior to the first dose of rFIXFc during the parent studies (Study 998HB102 and Study 9HB02PED). ADA data from all 3 studies are included in this analysis. Results from blood samples collected during surgical/rehabilitation periods for determining the presence of ADAs were also included in this analysis.

7.2. Results

Overall Extent of Exposure

The integrated safety data set includes data from 153 subjects with a median total duration on rFIXFc treatment of 188.31 weeks, including 126 subjects treated for ≥1 year, 107 subjects treated for ≥2 years, 96 subjects treated for ≥3 years, 67 subjects treated for ≥4 years, and 53 subjects treated for ≥5 years. The median total exposure days (EDs) was 165.0 with 128 of the 153 subjects achieving ≥50 EDs of cumulative exposure and 109 subjects achieving ≥100 EDs, with a total exposure of 26,106 EDs for the integrated data set. Retention in the clinical development program was high, with 120 of 153 eligible subjects (78.4%) entering the extension study and 98 of 120 subjects (81.7%) completing the extension study. Adverse events were monitored for a total of 560.64 subject-years.

Disposition, Integrated Presentation

Disposition data for subjects from the Phase 3 parent (originating) study in adults and adolescents ≥12 years of age (998HB102) and the Phase 3 parent study in children <12 years of age (9HB02PED) were integrated with data from Study 9HB01EXT for subjects who enrolled in the extension study.

An integrated summary of disposition by age cohort, based on age at the time of informed consent in the parent study, is presented in Table 6. An integrated summary of disposition by age at the end of study (end of the parent study for subjects who did not enroll into the extension study and end of the extension study for those who did) is presented in Table 7. A total of 123 subjects were dosed with rFIXFc in the completed Study 998HB102 and 30 subjects were dosed with rFIXFc in the completed Study 9HB02PED, for a total of 153 subjects in the integrated presentation. Of subjects dosed with rFIXFc, 93 subjects (75.6%) from the completed Study 998HB102 and 27 subjects (90.0%) from the completed Study 9HB02PED, enrolled in the extension study (9HB01EXT) for a total of 120 subjects in 9HB01EXT.

Overall, 15 subjects were <6 years of age at first enrollment, 15 were 6 to <12 years of age, 11 were 12 to <18 years of age, and 112 were ≥18 years of age (Table 6). 6 subjects were ≥65 years of age at the end of study (Table7).

Twenty-two subjects, 21 initially enrolled in Study 998HB102 and 1 initially enrolled in Study 9HB02PED, underwent a total of 35 major surgeries during their participation in the parent or extension study and are included in the surgery subgroup.

Table 6: Cumulative summary of disposition for all subjects enrolled in studies 998HB102, 9HB02PED and 9HB01EXT by age at start of parent study, Safety Analysis Set

	Parent study				
	Study 9HB02PED		Study 998HB102		
	<6 years (N=15)	6 to <12 years (N=15)	12 to <18 years (N=11)	>= 18 years (N=112)	Total (N=153)
Number of subjects dosed (a)	15 (100.0%)	15 (100.0%)	11 (100.0%)	112 (100.0%)	153 (100.0%)
Completion status					
Completed (b)	13 (86.7%)	14 (93.3%)	11 (100.0%)	104 (92.9%)	142 (92.8%)
Discontinued prematurely	2 (13.3%)	1 (6.7%)	0	8 (7.1%)	11 (7.2%)
Adverse event	0	0	0	2 (1.8%)	2 (1.3%)
Lost to follow-up	1 (6.7%)	1 (6.7%)	0	1 (0.9%)	3 (2.0%)
Physician decision	1 (6.7%)	0	0	0	1 (0.7%)
Protocol violation	0	0	0	2 (1.8%)	2 (1.3%)
Withdrawal by subject	0	0	0	3 (2.7%)	3 (2.0%)
Study 9HB01EXT					
Number of subjects enrolled (c)	13 (86.7%)	14 (93.3%)	11 (100.0%)	82 (73.2%)	120 (78.4%)
Number of subjects dosed (d)	13 (86.7%)	14 (93.3%)	11 (100.0%)	82 (73.2%)	120 (78.4%)
Current status					
Not enrolled in study 9HB01EXT (e)	2 (13.3%)	1 (6.7%)	0	30 (26.8%)	33 (21.6%)
Completed study 9HB01EXT (b)	11 (73.3%)	12 (80.0%)	8 (72.7%)	67 (59.8%)	98 (64.1%)
Discontinued prematurely from study 9HB01EXT	2 (13.3%)	2 (13.3%)	3 (27.3%)	15 (13.4%)	22 (14.4%)
Lack of efficacy	0	0	0	1 (0.9%)	1 (0.7%)
Lost to follow-up	0	0	0	3 (2.7%)	3 (2.0%)
Other	1 (6.7%)	0	3 (27.3%)	7 (6.3%)	11 (7.2%)
Physician decision	0	2 (13.3%)	0	0	2 (1.3%)
Withdrawal by subject	1 (6.7%)	0	0	4 (3.6%)	5 (3.3%)
For major surgeries occurring during studies 998HB102, 9HB02PED, or 9HB01EXT (f)					
Number of subjects in the surgery subgroup (g)	0	1 (6.7%)	1 (9.1%)	20 (17.9%)	22 (14.4%)
Number of major surgeries	0	1	3	31	35

Note 1: Unless stated otherwise, percentages are based on the number of subjects dosed.
(a) The Safety Analysis Set consists of subjects who received at least one dose of rFIXFc.
(b) Completed means ended participation in the study without premature discontinuation. Subjects who discontinued participation in the study because the study was stopped by the Sponsor are considered to have completed the study.
(c) All subjects who consented to participate in study 9HB01EXT.
(d) Subjects who received at least one dose of rFIXFc in study 9HB01EXT.
(e) Subjects who were in study 998HB102 or 9HB02PED, but were not enrolled in study 9HB01EXT.
(f) Includes major surgeries after first dose of study drug.
(g) Surgery subgroup is defined as subjects who had a major surgery after the first dose of study drug.

Source: Table 16 – Summary of Clinical Safety

Table 7: Cumulative summary of disposition for all subjects enrolled in studies 998HB102, 9HB02PED and 9HB01EXT by age at end of study Safety Analysis Set

	Parent study			
	Study 9HB02PED	Study 998HB102		
	<65 years (N=30)	<65 years (N=117)	>=65 years (N=6)	Total (N=153)
Number of subjects dosed (a)	30 (100.0%)	117 (100.0%)	6 (100.0%)	153 (100.0%)
Completion status				
Completed (b)	27 (90.0%)	109 (93.2%)	6 (100.0%)	142 (92.8%)
Discontinued prematurely	3 (10.0%)	8 (6.8%)	0	11 (7.2%)
Adverse event	0	2 (1.7%)	0	2 (1.3%)
Lost to follow-up	2 (6.7%)	1 (0.9%)	0	3 (2.0%)
Physician decision	1 (3.3%)	0	0	1 (0.7%)
Protocol violation	0	2 (1.7%)	0	2 (1.3%)
Withdrawal by subject	0	3 (2.6%)	0	3 (2.0%)
Study 9HB01EXT				
Number of subjects enrolled (c)	27 (90.0%)	90 (76.9%)	3 (50.0%)	120 (78.4%)
Number of subjects dosed (d)	27 (90.0%)	90 (76.9%)	3 (50.0%)	120 (78.4%)
Current status				
Not enrolled in study 9HB01EXT (e)	3 (10.0%)	27 (23.1%)	3 (50.0%)	33 (21.6%)
Completed study 9HB01EXT (b)	23 (76.7%)	73 (62.4%)	2 (33.3%)	98 (64.1%)
Discontinued prematurely from study 9HB01EXT	4 (13.3%)	17 (14.5%)	1 (16.7%)	22 (14.4%)
Lack of efficacy	0	1 (0.9%)	0	1 (0.7%)
Lost to follow-up	0	3 (2.6%)	0	3 (2.0%)
Other	1 (3.3%)	9 (7.7%)	1 (16.7%)	11 (7.2%)
Physician decision	2 (6.7%)	0	0	2 (1.3%)
Withdrawal by subject	1 (3.3%)	4 (3.4%)	0	5 (3.3%)
For major surgeries occurring during studies 998HB102, 9HB02PED, or 9HB01EXT (f)				
Number of subjects in the surgery subgroup (g)	1 (3.3%)	19 (16.2%)	2 (33.3%)	22 (14.4%)
Number of major surgeries	1	30	4	35

Note 1: Unless stated otherwise, percentages are based on the number of subjects dosed.
(a) The Safety Analysis Set consists of subjects who received at least one dose of rFIXFc.
(b) Completed means ended participation in the study without premature discontinuation. Subjects who discontinued participation in the study because the study was stopped by the Sponsor are considered to have completed the study.
(c) All subjects who consented to participate in study 9HB01EXT.
(d) Subjects who received at least one dose of rFIXFc in study 9HB01EXT.
(e) Subjects who were in study 998HB102 or 9HB02PED, but were not enrolled in study 9HB01EXT.
(f) Includes major surgeries after first dose of study drug.
(g) Surgery subgroup is defined as subjects who had a major surgery after the first dose of study drug.

Source: Table 17 – Summary of Clinical Safety

Duration of Dosing, Integrated Presentation

The duration of dosing is summarized by parent study in Table 8, by age cohort based on age at the time of informed consent in the parent study in Table 9, and by age cohort at the end of study (end of parent study for subjects who did not enroll into the extension study and end of extension study for those who did) in Table 10.

Table 8: Cumulative Summary of Duration of Dosing With rFIXFc for All Subjects Enrolled in Studies 998HB102, 9HB02PED and 9HB01EXT by Parent Study

	Parent study		
	Study 9HB02PED (N=30)	Study 998HB102 (N=123)	Total (N=153)
Cumulative number of weeks on rFIXFc (a)			
At least 13 weeks	30 (100.0%)	119 (96.7%)	149 (97.4%)
At least 26 weeks	29 (96.7%)	117 (95.1%)	146 (95.4%)
At least 39 weeks	27 (90.0%)	112 (91.1%)	139 (90.8%)
At least 52 weeks	26 (86.7%)	100 (81.3%)	126 (82.4%)
At least 65 weeks	26 (86.7%)	93 (75.6%)	119 (77.8%)
At least 78 weeks	26 (86.7%)	91 (74.0%)	117 (76.5%)
At least 91 weeks	26 (86.7%)	90 (73.2%)	116 (75.8%)
At least 104 weeks	18 (60.0%)	89 (72.4%)	107 (69.9%)
At least 117 weeks	17 (56.7%)	89 (72.4%)	106 (69.3%)
At least 130 weeks	16 (53.3%)	87 (70.7%)	103 (67.3%)
At least 143 weeks	15 (50.0%)	86 (69.9%)	101 (66.0%)
At least 156 weeks	15 (50.0%)	81 (65.9%)	96 (62.7%)
At least 169 weeks	14 (46.7%)	78 (63.4%)	92 (60.1%)
At least 182 weeks	13 (43.3%)	69 (56.1%)	82 (53.6%)
At least 195 weeks	13 (43.3%)	60 (48.8%)	73 (47.7%)
At least 208 weeks	9 (30.0%)	58 (47.2%)	67 (43.8%)
At least 221 weeks	9 (30.0%)	57 (46.3%)	66 (43.1%)
At least 234 weeks	2 (6.7%)	55 (44.7%)	57 (37.3%)
At least 247 weeks	1 (3.3%)	55 (44.7%)	56 (36.6%)
At least 260 weeks	0	53 (43.1%)	53 (34.6%)
At least 273 weeks	0	45 (36.6%)	45 (29.4%)
At least 286 weeks	0	41 (33.3%)	41 (26.8%)
At least 299 weeks	0	39 (31.7%)	39 (25.5%)
At least 312 weeks	0	28 (22.8%)	28 (18.3%)
At least 325 weeks	0	8 (6.5%)	8 (5.2%)
Total weeks on rFIXFc			
n	30	123	153
Mean	151.13	196.42	187.54
SD	72.252	111.330	106.158
Median	149.95	189.28	188.31
Min, Max	16.9, 251.1	<1, 337.7	<1, 337.7

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

Source: Table 3 – Summary of Clinical Safety

Table 9: Cumulative summary of duration of dosing with rFIXFc for all subjects enrolled in studies 998HB102, 9HB02PED and 9HB01EXT by age at start of parent study (Safety Analysis Set)

	Age cohort (years old)				
	<6 (N=15)	6 to <12 (N=15)	12 to <18 (N=11)	>= 18 (N=112)	Total (N=153)
Cumulative number of weeks on rFIXFc (a)					
At least 13 weeks	15 (100.0%)	15 (100.0%)	11 (100.0%)	108 (96.4%)	149 (97.4%)
At least 26 weeks	14 (93.3%)	15 (100.0%)	11 (100.0%)	106 (94.6%)	146 (95.4%)
At least 39 weeks	13 (86.7%)	14 (93.3%)	11 (100.0%)	101 (90.2%)	139 (90.8%)
At least 52 weeks	12 (80.0%)	14 (93.3%)	11 (100.0%)	89 (79.5%)	126 (82.4%)
At least 65 weeks	12 (80.0%)	14 (93.3%)	11 (100.0%)	82 (73.2%)	119 (77.8%)
At least 78 weeks	12 (80.0%)	14 (93.3%)	11 (100.0%)	80 (71.4%)	117 (76.5%)
At least 91 weeks	12 (80.0%)	14 (93.3%)	11 (100.0%)	79 (70.5%)	116 (75.8%)
At least 104 weeks	6 (40.0%)	12 (80.0%)	11 (100.0%)	78 (69.6%)	107 (69.9%)
At least 117 weeks	5 (33.3%)	12 (80.0%)	11 (100.0%)	78 (69.6%)	106 (69.3%)
At least 130 weeks	5 (33.3%)	11 (73.3%)	11 (100.0%)	76 (67.9%)	103 (67.3%)
At least 143 weeks	5 (33.3%)	10 (66.7%)	11 (100.0%)	75 (67.0%)	101 (66.0%)
At least 156 weeks	5 (33.3%)	10 (66.7%)	10 (90.9%)	71 (63.4%)	96 (62.7%)
At least 169 weeks	4 (26.7%)	10 (66.7%)	9 (81.8%)	69 (61.6%)	92 (60.1%)
At least 182 weeks	3 (20.0%)	10 (66.7%)	7 (63.6%)	62 (55.4%)	82 (53.6%)
At least 195 weeks	3 (20.0%)	10 (66.7%)	7 (63.6%)	53 (47.3%)	73 (47.7%)
At least 208 weeks	1 (6.7%)	8 (53.3%)	6 (54.5%)	52 (46.4%)	67 (43.8%)
At least 221 weeks	1 (6.7%)	8 (53.3%)	6 (54.5%)	51 (45.5%)	66 (43.1%)
At least 234 weeks	0	2 (13.3%)	6 (54.5%)	49 (43.8%)	57 (37.3%)
At least 247 weeks	0	1 (6.7%)	6 (54.5%)	49 (43.8%)	56 (36.6%)
At least 260 weeks	0	0	6 (54.5%)	47 (42.0%)	53 (34.6%)
At least 273 weeks	0	0	6 (54.5%)	39 (34.8%)	45 (29.4%)
At least 286 weeks	0	0	6 (54.5%)	35 (31.3%)	41 (26.8%)
At least 299 weeks	0	0	5 (45.5%)	34 (30.4%)	39 (25.5%)
At least 312 weeks	0	0	5 (45.5%)	23 (20.5%)	28 (18.3%)
At least 325 weeks	0	0	2 (18.2%)	6 (5.4%)	8 (5.2%)
Total weeks on rFIXFc					
n	15	15	11	112	153
Mean	117.61	184.65	251.92	190.97	187.54
SD	62.215	67.345	76.929	112.935	106.158
Median	101.87	223.02	290.18	188.51	188.31
Min, Max	16.9, 225.0	37.0, 251.1	155.0, 327.4	<1, 337.7	<1, 337.7

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

Source: Table 18 – Summary of Clinical Safety

Table 10: Cumulative summary of duration of dosing with rFIXFc for all subjects enrolled in studies 998HB102, 9HB02PED and 9HB01EXT by age at end of study

	Age cohort (years old)		
	<65 (N=147)	>=65 (N=6)	Total (N=153)
Cumulative number of weeks on rFIXFc (a)			
At least 13 weeks	143 (97.3%)	6 (100.0%)	149 (97.4%)
At least 26 weeks	140 (95.2%)	6 (100.0%)	146 (95.4%)
At least 39 weeks	133 (90.5%)	6 (100.0%)	139 (90.8%)
At least 52 weeks	122 (83.0%)	4 (66.7%)	126 (82.4%)
At least 65 weeks	116 (78.9%)	3 (50.0%)	119 (77.8%)
At least 78 weeks	114 (77.6%)	3 (50.0%)	117 (76.5%)
At least 91 weeks	113 (76.9%)	3 (50.0%)	116 (75.8%)
At least 104 weeks	104 (70.7%)	3 (50.0%)	107 (69.9%)
At least 117 weeks	103 (70.1%)	3 (50.0%)	106 (69.3%)
At least 130 weeks	101 (68.7%)	2 (33.3%)	103 (67.3%)
At least 143 weeks	99 (67.3%)	2 (33.3%)	101 (66.0%)
At least 156 weeks	94 (63.9%)	2 (33.3%)	96 (62.7%)
At least 169 weeks	90 (61.2%)	2 (33.3%)	92 (60.1%)
At least 182 weeks	80 (54.4%)	2 (33.3%)	82 (53.6%)
At least 195 weeks	72 (49.0%)	1 (16.7%)	73 (47.7%)
At least 208 weeks	66 (44.9%)	1 (16.7%)	67 (43.8%)
At least 221 weeks	65 (44.2%)	1 (16.7%)	66 (43.1%)
At least 234 weeks	56 (38.1%)	1 (16.7%)	57 (37.3%)
At least 247 weeks	55 (37.4%)	1 (16.7%)	56 (36.6%)
At least 260 weeks	52 (35.4%)	1 (16.7%)	53 (34.6%)
At least 273 weeks	44 (29.9%)	1 (16.7%)	45 (29.4%)
At least 286 weeks	40 (27.2%)	1 (16.7%)	41 (26.8%)
At least 299 weeks	38 (25.9%)	1 (16.7%)	39 (25.5%)
At least 312 weeks	27 (18.4%)	1 (16.7%)	28 (18.3%)
At least 325 weeks	8 (5.4%)	0	8 (5.2%)
Total weeks on rFIXFc			
n	147	6	153
Mean	189.90	129.71	187.54
SD	105.814	107.119	106.158
Median	189.28	87.27	188.31
Min, Max	<1, 337.7	48.4, 317.9	<1, 337.7

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

Source: Table 19 – Summary of Clinical Safety

Injections and Days of Exposure (Integrated Presentation)

The number of rFIXFc injections and EDs is summarized by parent study in Table 11, by age at the time of informed consent in the parent study in Table 12, and by age at the end of study (end of parent study for subjects who did not enroll into the extension study and end of extension study for those who did) in Table 13.

Table 11: Cumulative Summary of Injections and Days of Exposure to rFIXFc for All Subjects Enrolled in Studies 998HB102, 9HB02PED and 9HB01EXT by Parent Study

	Parent study		
	Study 9HB02PED (N=30)	Study 998HB102 (N=123)	Total (N=153)
Total exposure days (a)			
<50	3 (10.0%)	22 (17.9%)	25 (16.3%)
50-<100	1 (3.3%)	18 (14.6%)	19 (12.4%)
100-<150	10 (33.3%)	12 (9.8%)	22 (14.4%)
150-<200	6 (20.0%)	25 (20.3%)	31 (20.3%)
200-<250	8 (26.7%)	11 (8.9%)	19 (12.4%)
250-<300	2 (6.7%)	8 (6.5%)	10 (6.5%)
300-<350	0	17 (13.8%)	17 (11.1%)
350-<400	0	6 (4.9%)	6 (3.9%)
400-<450	0	2 (1.6%)	2 (1.3%)
450-<500	0	1 (0.8%)	1 (0.7%)
500-<550	0	1 (0.8%)	1 (0.7%)
n	30	123	153
Mean	152.4	175.1	170.6
SD	72.64	122.84	114.89
Median	165.5	165.0	165.0
Min, Max	18, 256	1, 528	1, 528
Total number of injections per subject			
n	30	123	153
Mean	154.4	178.2	173.6
SD	73.77	125.51	117.36
Median	168.0	166.0	167.0
Min, Max	18, 262	1, 555	1, 555
Sum	4632	21924	26556

NOTE 1: Percentages are based on numbers of subjects dosed with rFIXFc in each parent study or overall.
(a) An exposure day is a 24-hour period in which one or more rFIXFc injections are given. All injections over the study course are counted.

Source: Table 4 – Summary of Clinical Safety

Table 12: Cumulative summary of injections and days of exposure to rFIXFc for all subjects enrolled in studies 998HB102, 9HB02PED and 9HB01EXT by age at start of parent study

	Age cohort (years old)				
	<6 (N=15)	6 to <12 (N=15)	12 to <18 (N=11)	>= 18 (N=112)	Total (N=153)
Total exposure days (a)					
<50	2 (13.3%)	1 (6.7%)	0	22 (19.6%)	25 (16.3%)
50-<100	1 (6.7%)	0	0	18 (16.1%)	19 (12.4%)
100-<150	7 (46.7%)	3 (20.0%)	2 (18.2%)	10 (8.9%)	22 (14.4%)
150-<200	2 (13.3%)	4 (26.7%)	3 (27.3%)	22 (19.6%)	31 (20.3%)
200-<250	2 (13.3%)	6 (40.0%)	1 (9.1%)	10 (8.9%)	19 (12.4%)
250-<300	1 (6.7%)	1 (6.7%)	1 (9.1%)	7 (6.3%)	10 (6.5%)
300-<350	0	0	3 (27.3%)	14 (12.5%)	17 (11.1%)
350-<400	0	0	1 (9.1%)	5 (4.5%)	6 (3.9%)
400-<450	0	0	0	2 (1.8%)	2 (1.3%)
450-<500	0	0	0	1 (0.9%)	1 (0.7%)
500-<550	0	0	0	1 (0.9%)	1 (0.7%)
n	15	15	11	112	153
Mean	124.4	180.5	236.6	169.0	170.6
SD	71.37	64.44	88.93	124.34	114.89
Median	104.0	197.0	240.0	163.0	165.0
Min, Max	18, 256	33, 256	107, 352	1, 528	1, 528
Total number of injections per subject					
n	15	15	11	112	153
Mean	126.3	182.5	238.7	172.3	173.6
SD	73.21	65.01	89.50	127.26	117.36
Median	105.0	199.0	250.0	164.5	167.0
Min, Max	18, 262	33, 260	107, 353	1, 555	1, 555
Sum	1895	2737	2626	19298	26556

NOTE 1: Percentages are based on numbers of subjects dosed with rFIXFc in each age cohort or overall.
(a) An exposure day is a 24-hour period in which one or more rFIXFc injections are given. All injections over the study course are counted.

Source: Table 20 – Summary of Clinical Safety

Table 13: Cumulative summary of injections and days of exposure to rFIXFc for all subjects enrolled in studies 998HB102, 9HB02PED and 9HB01EXT by age at end of study

	Age cohort (years old)		
	<65 (N=147)	>=65 (N=6)	Total (N=153)
Total exposure days (a)			
<50	24 (16.3%)	1 (16.7%)	25 (16.3%)
50-<100	16 (10.9%)	3 (50.0%)	19 (12.4%)
100-<150	22 (15.0%)	0	22 (14.4%)
150-<200	30 (20.4%)	1 (16.7%)	31 (20.3%)
200-<250	19 (12.9%)	0	19 (12.4%)
250-<300	9 (6.1%)	1 (16.7%)	10 (6.5%)
300-<350	17 (11.6%)	0	17 (11.1%)
350-<400	6 (4.1%)	0	6 (3.9%)
400-<450	2 (1.4%)	0	2 (1.3%)
450-<500	1 (0.7%)	0	1 (0.7%)
500-<550	1 (0.7%)	0	1 (0.7%)
n	147	6	153
Mean	173.0	113.2	170.6
SD	115.02	104.00	114.89
Median	166.0	68.0	165.0
Min, Max	1, 528	12, 282	1, 528
Total number of injections per subject			
n	147	6	153
Mean	175.8	118.8	173.6
SD	117.53	107.64	117.36
Median	167.0	74.5	167.0
Min, Max	1, 555	15, 297	1, 555
Sum	25843	713	26556

NOTE 1: Percentages are based on numbers of subjects dosed with rFIXFc in each age cohort or overall.
(a) An exposure day is a 24-hour period in which one or more rFIXFc injections are given. All injections over the study course are counted.

Source: Table 21 – Summary of Clinical Safety

Adverse events

Analysis of Adverse Events (Integrated Presentation)

This section and all the following AE subsections focus primarily on AEs that emerged during treatment with rFIXFc. In the following text, the term TEAE is used to refer to those AEs, excluding AEs that emerged during the perioperative management period (surgical/rehabilitation period) for major surgeries. The term AE will be used to describe non-TEAEs or a combination of TEAEs and non-TEAEs.

Detailed discussion of AEs includes the overall incidence of AEs for subjects from each of the parent studies and the total. For subjects from each of the parent studies and the total, more detailed analyses of AEs by SOC and PT, AEs by ED interval, AEs by severity, and AEs by relationship to study treatment are presented. Potential adverse drug reactions (ADRs) are also discussed.

Overview of Adverse Events

AEs were monitored for a total of 560.64 subject years (26,106 EDs) for the 153 subjects who received at least 1 dose of rFIXFc (Table 14), and AE data are included from a variety of dosing regimens. AEs that emerged during the perioperative management period for major surgeries are presented in the surgery subgroup columns and were counted in the total rFIXFc column of Table14.

Of the 153 subjects treated with rFIXFc, 138 subjects (90.2%) reported at least 1 TEAE (including AEs that emerged during the perioperative management period for a major surgery). Because the perioperative management period represents a unique clinical situation, AEs that emerged during the perioperative management period for major surgeries are discussed separately. Of the 153 subjects, 51

(33.3%) were reported to have experienced at least 1 treatment-emergent SAE (TESAE) with a total of 101 TESAEs. Two TESAEs were assessed by the Investigator as related to rFIXFc treatment. 15 subjects (9.8%) were reported to have experienced at least 1 related TEAE (an AE that was assessed by the Investigator as related to rFIXFc treatment). Three subjects (2.0%) were reported to have discontinued rFIXFc treatment or withdrawn from any of the studies due to a TEAE.

Overall, the incidence of TEAEs was similar between subjects enrolled in Study 9HB02PED (children <12 years of age) and Study 998HB102 (adults and adolescents ≥12 years of age), with TEAEs reported for 29 subjects (96.7%) and 108 subjects (87.8%), respectively. According to the MAH, differences in the incidence and types of AEs in subjects from the 2 studies are consistent with the applicable age groups.

Table 14: Cumulative overall summary of rFIXFc treatment-emergent adverse events for all subjects enrolled in studies 998HB102, 9HB02PED and 9HB01EXT, by parent study (Safety Analysis Set)

	Parent study		Surgery subgroup (a)		
	Study 9HB02PED (N=30)	Study 998HB102 (N=123)	Study 9HB02PED (N=1)	Study 998HB102 (N=21)	Total (N=153)
Total number of TEAEs	289	822	0	40	1151
Total subject-years followed	88.25	466.20	0.06	6.13	560.64
Total exposure days	4563	20887	10	652	26106
Subjects with at least one TEAE, n (%)	29 (96.7%)	108 (87.8%)	0	12 (57.1%)	138 (90.2%)
Subjects with at least one related TEAE (b), n (%)	1 (3.3%)	14 (11.4%)	0	0	15 (9.8%)
Subjects who discontinued treatment and/or the study due to a TEAE, n (%)	0	3 (2.4%)	0	0	3 (2.0%)
Total number of TESAEs	22	74	0	5	101
Subjects with at least one TESAE, n (%)	8 (26.7%)	43 (35.0%)	0	2 (9.5%)	51 (33.3%)
Subjects with at least one related TESAE (b), n (%)	0	2 (1.6%)	0	0	2 (1.3%)
Number of deaths, n (%)	0	0	0	0	0

NOTE 1: Abbreviations: TEAE = treatment-emergent adverse event, TESAE = treatment-emergent serious adverse event.
2: Percentages are based on the number of subjects dosed with rFIXFc in each parent study, surgery subgroup or overall.
3: For sequential PK subjects from study 998HB102, AEs emergent between the first on-study BeneFIX injection and the first on-study rFIXFc injection are not included. For subjects from study 9HB02PED, AEs emergent between the first prestudy FIX injection and the first rFIXFc injection for the PK group are not included.
4: Total subject-years is the cumulative sum of time in years that subjects were followed during the studies; time during major surgical rehabilitation periods is not included within the parent study columns, but is included in the total rFIXFc.
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 parent study columns, but are included in the total rFIXFc.
(a) Includes AEs emergent during major surgical/rehabilitation periods; these AEs are not included in the parent study columns, but are included in the total rFIXFc.
(b) Related includes all TEAEs with the relationship missing and for events from study 998HB102, those classified as 'Related' and 'Possibly related' on the eCRF.

Source: Table 6 – Summary of Clinical Safety

Common Adverse Events

The most frequently reported TEAEs (i.e., AEs that emerged during treatment with rFIXFc but excluding AEs that emerged during the perioperative management period for a major surgery), with an incidence ≥10% of the total, were nasopharyngitis (24.2%), fall (15.0%), headache (15.0%), arthralgia (13.1%), and influenza (11.1%). These AEs are typical of events that occur in the general hemophilia B population.

According to the MAH, among the frequently reported TEAEs, the incidences in the parent studies were similar and any differences are consistent with the applicable age groups.

Incidence of Adverse Events by System Organ Class and Preferred Term

Overall, of 153 subjects treated with rFIXFc, 137 subjects (89.5%) reported at least 1 TEAE in any SOC. The most frequently reported TEAEs by SOC were reported for infections and infestations (103 subjects [67.3%]). The remaining SOCs with an incidence of ≥10% were gastrointestinal disorders and injury, poisoning, and procedural complications (65 subjects each [42.5%]); musculoskeletal and connective tissue disorders (63 subjects [41.2%]); general disorders and administration site conditions (40 subjects [26.1%]); nervous system disorders (38 subjects [24.8%]); skin and subcutaneous tissue disorders (36 subjects [23.5%]); respiratory, thoracic, and mediastinal disorders (33 subjects [21.6%]); and investigations (19 subjects [12.4%]).

The most frequently reported TEAEs (≥10%) were nasopharyngitis (37 subjects [24.2%]), fall (23 subjects [15.0%]), headache (23 subjects [15.0%]), arthralgia (20 subjects [13.1%]), and influenza (17 subjects [11.1%]). These AEs were typical of events occurring in the general hemophilia population.

The TEAEs of nasopharyngitis and influenza were all assessed by the Investigator as mild to moderate in severity and unrelated to rFIXFc. In the majority of subjects, the TEAEs of fall, headache, and arthralgia were assessed as mild to moderate in severity and unrelated to rFIXFc. The TEAEs of fall and headache were reported as severe in 2 subjects each and the TEAE of arthralgia was reported as severe in 1. The TEAE of headache was reported as related to rFIXFc in 2 subjects. None of the fall or arthralgia TEAEs were assessed by the Investigator as related to rFIXFc treatment.

The incidence of TEAEs in the most frequently reported SOCs was generally similar in subjects from Studies 998HB102 and 9HB02PED. Among the frequently-reported SOCs, differences between subjects initially enrolled in Study 998HB102 and 9HB02PED were seen in gastrointestinal disorders (39.0% versus 56.7%), infections and infestations (65.0% versus 76.7%), injury, poisoning, and procedural complications (36.6% versus 66.7%), musculoskeletal and connective tissue disorders (43.9% versus 30.0%), nervous system disorders (27.6% versus 13.3%), and respiratory, thoracic, and mediastinal disorders (17.9% versus 36.7%).

Among the most frequently reported PTs (those reported for at least 5% of subjects overall), a difference in incidence of ≥10% between subjects initially enrolled in Study 998HB102 and Study 9HB02PED was seen for fall (7.3% versus 46.7%), pyrexia (4.9% versus 30.0%), vomiting (6.5% versus 23.3%), head injury (2.4% versus 20.0%), seasonal allergy (2.4% versus 20.0%), and viral infection (2.4% versus 20.0%). The differences are consistent with the applicable age groups. The incidences of other frequently reported PTs were similar between the 2 groups of subjects. For the remaining PTs, the relatively low incidences in each group precluded meaningful direct comparisons. Therefore, discussion of AEs and SAEs in the subsequent sections is focused on the total (subjects from both parent studies).

Adverse Events by Exposure Day Interval

Overall, of the 153 subjects in the integrated data set, all 153 were treated with rFIXFc and met the interval definition of exposure for the <50 ED interval. A total of 128 subjects had at least 50 EDs, 109 subjects had at least 100 EDs, 56 subjects had at least 200 EDs, and 27 subjects had at least 300 EDs. All intervals above 350 EDs had ≤10 subjects each.

The overall trend for reported TEAEs across all 3 studies was for a lower incidence of TEAE onset with increased numbers of EDs when assessed by 50-ED intervals. Over all 3 studies, the percentage of subjects with at least 1 TEAE decreased from 79.7% with onset in the <50 ED interval to 48.1% in the 300 to <350 ED interval. Only 3 subjects had TEAEs reported from intervals >350 EDs.

Possible factors contributing to the overall trend of lower TEAE incidence with higher number of EDs by interval may include reporting bias by Investigators and subjects in the early treatment phase of the clinical studies and differences in protocol-specified frequency of telephone contacts and visit schedule in the parent studies compared with the extension study.

The MAH concluded, that there was no apparent pattern in the type or frequency of AEs reported to suggest a safety concern with longer exposure as measured by greater cumulative ED intervals.

Adverse Events by Severity

Overall, the majority of the TEAEs were judged by the Investigator to be mild to moderate in severity. Of the 153 subjects treated with rFIXFc, 27 subjects (17.6%) had at least 1 TEAE classified as severe, 77 subjects (50.3%) had none classified as severe but at least 1 classified as moderate, and 33 subjects (21.6%) had no TEAEs classified as severe or moderate, but at least 1 classified as mild. No TEAEs had a missing severity assessment.

While the majority of TEAEs were mild to moderate in subjects from both parent studies, the severity profiles differed between subjects from Study 998HB102 and subjects from Study 9HB02PED in that there was a higher percentage of subjects with at least 1 TEAE classified as severe in Study 998HB102 compared with Study 9HB02PED. The maximum severities of TEAEs for subjects presented by the 2 parent studies were as follows:

- Study 998HB102: mild in 21 subjects (17.1%), moderate in 62 subjects (50.4%), and severe in 25 subjects (20.3%)
- Study 9HB02PED: mild in 12 subjects (40.0%), moderate in 15 subjects (50.0%), and severe in 2 subjects (6.7%)

A summary of severe TEAEs is presented by PT in descending order of incidence for subjects from each parent study and the 153 subjects in the integrated data set in Table 15. The majority of severe TEAEs were reported in 1 subject each, with the exceptions of fall, hemophilic arthropathy, headache, obstructive uropathy, and tooth abscess (2 subjects each [1.3%]).

Other than severe AEs that would be expected for subjects with hemophilia (e.g., hemophilic arthropathy and arthralgia), the pattern of severe AE reporting is typical of events that are common in the adult and pediatric populations studied.

Table 15: Cumulative summary of severe rFIXFc treatment-emergent adverse events by preferred term in descending order of incidence for all subjects enrolled in studies 998HB102, 9HB02PED and 9HB01EXT by parent study

Preferred term	Parent study: Study 9HB02PED (N=30)	Parent study: Study 998HB102 (N=123)	Total (N=153)
Total number of severe TEAEs	3	39	42
Number of subjects with at least one severe TEAE	2 (6.7%)	25 (20.3%)	27 (17.6%)
FALL	0	2 (1.6%)	2 (1.3%)
HAEMOPHILIC ARTHROPATHY	0	2 (1.6%)	2 (1.3%)
HEADACHE	0	2 (1.6%)	2 (1.3%)
OBSTRUCTIVE UROPATHY	0	2 (1.6%)	2 (1.3%)
TOOTH ABSCESS	0	2 (1.6%)	2 (1.3%)
ANAL ABSCESS	0	1 (0.8%)	1 (0.7%)
ARTHRALGIA	0	1 (0.8%)	1 (0.7%)
CONTUSION	0	1 (0.8%)	1 (0.7%)
EAR INFECTION	1 (3.3%)	0	1 (0.7%)
EPISTAXIS	0	1 (0.8%)	1 (0.7%)
EXTRADURAL HAEMATOMA	0	1 (0.8%)	1 (0.7%)
GASTRITIS	0	1 (0.8%)	1 (0.7%)
GASTROINTESTINAL HAEMORRHAGE	0	1 (0.8%)	1 (0.7%)
GOUT	0	1 (0.8%)	1 (0.7%)
HEAD INJURY	1 (3.3%)	0	1 (0.7%)
HEPATIC NEOPLASM MALIGNANT	0	1 (0.8%)	1 (0.7%)
HEPATITIS C	0	1 (0.8%)	1 (0.7%)
HYPERTENSION	0	1 (0.8%)	1 (0.7%)
INTERVERTEBRAL DISC PROTRUSION	0	1 (0.8%)	1 (0.7%)
LIGAMENT SPRAIN	0	1 (0.8%)	1 (0.7%)
LIMB CRUSHING INJURY	0	1 (0.8%)	1 (0.7%)
MUSCLE HAEMORRHAGE	0	1 (0.8%)	1 (0.7%)
NECROTISING RETINITIS	0	1 (0.8%)	1 (0.7%)
ORCHITIS	0	1 (0.8%)	1 (0.7%)
OTITIS MEDIA BACTERIAL	1 (3.3%)	0	1 (0.7%)
PERITONSILLAR ABSCESS	0	1 (0.8%)	1 (0.7%)
PHANTOM PAIN	0	1 (0.8%)	1 (0.7%)
RENAL COLIC	0	1 (0.8%)	1 (0.7%)
RENAL FAILURE ACUTE	0	1 (0.8%)	1 (0.7%)
ROAD TRAFFIC ACCIDENT	0	1 (0.8%)	1 (0.7%)
SPINAL COLUMN STENOSIS	0	1 (0.8%)	1 (0.7%)
TONSILLAR HAEMORRHAGE	0	1 (0.8%)	1 (0.7%)
TONSILLITIS	0	1 (0.8%)	1 (0.7%)
TRAUMATIC HAEMATOMA	0	1 (0.8%)	1 (0.7%)
TRAUMATIC INTRACRANIAL HAEMORRHAGE	0	1 (0.8%)	1 (0.7%)
UPPER GASTROINTESTINAL HAEMORRHAGE	0	1 (0.8%)	1 (0.7%)

NOTE 1: Percentages are based on the number of subjects dosed with rFIXFc in each parent study or overall.
2: Using the MedDRA Version 15.0 dictionary.
3: Subjects are counted once if they report multiple severe events in the same preferred term.
4: Does not include AEs emergent during major surgical/rehabilitation periods.
5: AEs without an assessment of severity are included in this table as 'severe' events.

Source: Table 9 – Summary of Clinical Safety

Adverse Events by Relationship to Study Treatment

The incidence of TEAEs by relationship to study treatment is presented by the 2 parent studies and for the 153 subjects in the integrated set by SOC and PT.

Overall, the majority of the TEAEs were judged by the Investigator as unrelated to rFIXFc treatment. Of the 153 subjects who were treated with rFIXFc, related TEAEs were reported in 15 subjects (9.8%) with 19 related TEAEs. With the exceptions of paresthesia oral, headache, and obstructive uropathy (each in 2 subjects [1.3%]), the TEAEs considered related to rFIXFc treatment were reported in 1 subject each (0.7%). No subject experienced a related AE that emerged during the perioperative management period for a major surgery.

The TEAEs assessed as related to rFIXFc treatment by the Investigator are listed below by study and all were included in the previous submission (i.e., occurred before the data cut-off date of 17 October 2014).

The following subject experienced a TEAE during Study **9HB02PED** that was assessed by the Investigator as related to rFIXFc: **decreased appetite**

The following subjects experienced a TEAE during Study **998HB102** that was assessed by the Investigator as related to rFIXFc:

- **dysgeusia**
- **infusion site pain**
- **paresthesia oral**
- **palpitations**
- **hypotension**
- **breath odor**
- **headache**
- **dizziness (2 events), paresthesia oral, obstructive uropathy (2 events)**. The second event of obstructive uropathy was reported as a TESAE.
- **fatigue**
- **headache**

The following subjects experienced a TEAE during **Study 9HB01EXT** that was assessed by the Investigator as related to rFIXFc:

- **obstructive uropathy; hematuria**
- **non-cardiac chest pain; renal colic:** The event was reported as a TESAE.

Adverse Drug Reactions (ADRs)

No new ADRs have been reported following the previous submission (i.e., occurring after the data cut-off date of 17 October 2014).

ADRs were initially identified based on the Investigator's assessment of the AE relationship to rFIXFc, followed by medical assessment of the available data for each event. The Phase 3 study in adults and adolescents ≥12 years of age (998HB102), the Phase 3 study in children <12 years of age (9HB02PED), and the extension study (9HB01EXT) were considered the best sources for identifying ADRs to rFIXFc.

Of the 153 subjects treated with rFIXFc, 15 subjects experienced an AE assessed by the Investigator as related to rFIXFc treatment. A total of 19 related TEAEs were reported in these 15 subjects, where 14 AEs were unique PTs. Upon medical review of the 19 AEs assessed as related by the Investigator, 18 were considered ADRs in 14 subjects (9.2%) and included: breath odor, decreased appetite, dizziness, dysgeusia, fatigue, headache, hematuria, hypotension, infusion site pain, obstructive uropathy, palpitations, paresthesia oral, and renal colic. For 1 of the 19 events assessed by the Investigator as related (non-cardiac chest pain [Investigator term: Non-Cardiac Chest Pain], a medical review of available data does not support the inclusion of the event as an ADR. Non-cardiac chest pain had an onset on an unknown study day in December 2012, without an apparent temporal association with any injection of rFIXFc. Upon follow-up with the Investigator, all cardiovascular investigations were normal, and the event resolved and did not recur despite continued treatment with rFIXFc.

Of the 18 AEs defined as ADRs, 3 were assessed by the Investigator as severe (obstructive uropathy in 2 subjects and renal colic in one subject, and the remaining were assessed by the Investigator as mild to moderate in severity. Two of the ADRs were reported as SAEs (obstructive uropathy and renal colic); the

remaining ADRs were reported as non-serious. 16 of the 18 ADRs resolved; decreased appetite and breath odor were ongoing at the time of reporting. No action was taken with study treatment as a consequence of these 18 ADRs.

Deaths

No subjects died during the conduct of Studies 998HB102, 9HB02PED or 9HB01EXT.

Serious Adverse Events

Overall, of the total 153 subjects treated with rFIXFc, 51 subjects (33.3%) experienced a total of 96 TESAEs (i.e., SAEs emergent with rFIXFc treatment but not emergent during the perioperative management period for a major surgery). The SOCs with 2 or more subjects (i.e., at >1% incidence) experiencing a TESAE were: injury, poisoning, and procedural complications in 16 subjects (10.5%); infections and infestations in 15 subjects (9.8%); musculoskeletal and connective tissue disorders in 9 subjects (5.9%); gastrointestinal disorders in 7 subjects (4.6%); renal and urinary disorders in 7 subjects (4.6%); nervous system disorders in 3 subjects (2.0%); general disorders and administration site conditions in 2 subjects (1.3%); neoplasms benign, malignant and unspecified in 2 subjects (1.3%); respiratory, thoracic and mediastinal disorders in 2 subjects (1.3%); and surgical and medical procedures in 2 subjects (1.3%).

Individual TESAE PTs reported in 2 or more subjects (i.e., at >1% incidence) were fall (8 subjects [5.2%]), cellulitis (4 subjects [2.6%]), hemophilic arthropathy (4 subjects [2.6%]), tooth abscess (2 subjects [1.3%]), head injury (2 subjects [1.3%]), rib fracture (2 subjects [1.3%]), road traffic accident (2 subjects [1.3%]), arthropathy (2 subjects [1.3%]), hepatic neoplasm malignant (2 subjects [1.3%]), calculus ureteric (2 subjects [1.3%]), and hematuria (2 subjects [1.3%]). Obstructive uropathy in one subject and renal colic in another subject were assessed by the Investigator as related to rFIXFc treatment; the remaining TESAEs were considered unrelated to rFIXFc. All except 6 TESAEs resolved: hepatitis C, hepatic neoplasm malignant, calculus ureteric, hemophilic arthropathy and angina pectoris in different subjects were ongoing as of the end of the relevant clinical studies. Two of the TESAEs (road traffic accident and device related infection resulted in discontinuation of rFIXFc treatment and withdrawal from the study; neither event was considered related to rFIXFc. In both subjects, rFIXFc treatment was permanently discontinued because they were hospitalized in countries where the study treatment could not be imported.

In addition to the 96 TESAEs, 3 subjects experienced 6 SAEs that did not meet the definition of TESAEs: one subject experienced an SAE (Pseudomonas infection) that occurred prior to receiving his first dose of rFIXFc, and 2 subjects experienced SAEs that emerged during the perioperative management period following major surgeries. All of these SAEs were assessed by the Investigator as unrelated to rFIXFc and resolved. None of these SAEs led to discontinuation from the study.

According to the MAH, the SAEs observed in the 2 parent studies and the extension study were consistent with those expected in the hemophilia population and applicable age group. Two of the SAEs (obstructive uropathy and renal colic) were assessed by the Investigator as related to rFIXFc treatment and are considered ADRs.

Other Significant Adverse Events

Of the 153 subjects treated with rFIXFc and included in the integrated data set, 3 (2.0%) were reported to have experienced at least 1 TEAE that led to withdrawal of rFIXFc treatment and/or premature discontinuation from the study. All 3 subjects were originally enrolled into Study 998HB102, and the TEAEs leading to discontinuation/withdrawal occurred in the parent study for 2 and the extension study for 1. There were no TEAEs leading to discontinuation/ withdrawal from Study 9HB02PED.

All TEAEs leading to premature discontinuation of rFIXFc treatment and/or withdrawal from the study are presented below. Narratives of the TEAEs are presented in the respective Clinical Study Reports. .

- **Individual Subjects**

New TEAEs Leading to Discontinuation / Withdrawal (since 17 October 2014)

- **Road traffic accident and hemorrhage intracranial; Study 9HB01EXT**

TEAEs Leading to Discontinuation / Withdrawal Previously Reported (before 17 October 2014)

- **Road traffic accident (Study 998HB102)**
- **Device related infection (Study 998HB102)**

These TEAEs were assessed by the Investigator as unrelated to treatment with rFIXc.

In addition to the 3 subjects described above, it was noted upon medical review of data listings that 1 subject was reported to have discontinued the study due to withdrawal of consent (Study 998HB102) in the context of a mild headache that was assessed by the Investigator as related to rFIXFc. It is unknown whether this event contributed to the subject's decision to withdraw consent.

Analysis of Adverse Events by Organ System or Syndrome

- Protocol-Specified Adverse Events of Special Interest Relevant to Hemophilia B or Treatment

AEs of special interest chosen for their relevance to hemophilia B or its treatment (AEs considered medically important) were pre-specified in the study protocols and were required to be reported as SAEs. These AEs included development of inhibitors, Grade 2 or higher allergic reactions (hypersensitivity), and vascular thrombotic events.

Development of Inhibitor

Development of an inhibitor (neutralizing antibodies directed against FIX) is considered one of the most serious complications of hemophilia therapy today because it affects treatment efficacy and significantly impacts quality of life, morbidity, and mortality. In the studies included in the integrated analysis, development of an inhibitor was defined as a neutralizing antibody value ≥0.6 BU/mL (as measured by Nijmegen-modified Bethesda assay by the central laboratory) confirmed on retesting of a second, independent sample obtained within 2 to 4 weeks.

No subjects developed an inhibitor in the parent or extension studies.

Allergic Reaction

Allergic-type hypersensitivity reactions are a well-recognized risk of FIX replacement products and can prevent the use of FIX concentrate as treatment, thereby limiting optimal care and increasing morbidity risk and mortality. Per the protocol for these studies, an allergic reaction associated with the administration of rFIXFc that was ≥Grade 2 (based on the Recommendations for Grading of Acute and Subacute Toxic Effects on the WHO scale) was required to be reported as an SAE.

In the total of 153 subjects who received at least 1 dose of rFIXFc, no SAEs of allergic reaction, hypersensitivity, or anaphylaxis were reported.

A comprehensive review of the data was performed to identify nonserious AEs that may represent possible allergic reactions to rFIXFc (no etiology reported). 18 TEAEs of possible allergic reactions in 16 subjects were identified.

All of them were assessed by the Investigator as unrelated to rFIXFc and mild to moderate in severity.

To summarize, according to the MAH, there were no SAEs of allergic reaction, hypersensitivity, or anaphylaxis reported. 18 TEAEs in 16 subjects were identified that may represent possible allergic reactions to rFIXFc. All of these events were assessed by the Investigator as unrelated to rFIXFc and none resulted in discontinuation of rFIXFc treatment or withdrawal of the subject from the study. Allergic-type hypersensitivity reactions are a well-recognized risk of factor replacement products.

Vascular Thrombotic Events

Serious vascular thrombotic events may occur with factor replacement therapies. According to the study protocols, development of a thrombotic event (with the exception of IV injection site thrombophlebitis) in association with the administration of rFIXFc was required to be reported as an SAE. A comprehensive review of the data was performed to identify AEs and SAEs that may represent vascular thrombotic events. Of the total of 153 subjects treated with rFIXFc, there was 1 TESAE (PT Device occlusion, Investigator term “Occlusion of port catheter”) and 1 TEAE (PT Coronary artery stenosis) of a potential vascular thrombotic event. Both events were assessed by the Investigator as unrelated to rFIXFc. The event of device occlusion was assessed as moderate in severity, had no associated vascular thrombotic event, and no action was taken with rFIXFc. A full narrative is provided in the 9HB02PED Clinical Study Report. The event of coronary artery stenosis was assessed as mild in severity, had no associated vascular thrombotic event, and no action was taken with rFIXFc.

In conclusion, there was 1 SAE of device occlusion and 1 AE of coronary artery stenosis in a subject with prior events of angina pectoris; an associated vascular thrombotic event was not reported in either case. Both events were assessed by the Investigator as unrelated to rFIXFc and no action was taken with rFIXFc as a result of either event. According to the MAH, the data do not indicate an increased risk of vascular thrombotic events related to rFIXFc treatment.

Other Adverse Events

In addition to protocol-specified AEs of special interest, a review of the data was performed to identify AEs related to bleeding, infection events including possible suspected transmission of an infectious agent, and hepatobiliary events. Medical review assessed both TESAEs and nonserious TEAEs.

Adverse Events Related to Bleeding

Serious bleeding events were reported for 17 TESAEs in 14 subjects. 16 of the 17 TESAEs were assessed by the Investigator as unrelated to rFIXFc and 1 TESAE (PT Renal colic, Investigator term hemorrhage urinary tract [hematuria with clot colic]) was assessed as related to rFIXFc. 9 events were assessed as mild to moderate in severity and 8 events were assessed as severe (see below for additional details; full narratives are provided in the Clinical Study Reports).

New Severe Bleeding Events (since 17 October 2014)

- Traumatic intracranial hemorrhage
- Tonsillar hemorrhage
- Upper gastrointestinal hemorrhage

Severe Bleeding Events Previously Reported (before 17 October 2014)

- Epistaxis

- Extradural hematoma
- Traumatic hematoma
- Gastrointestinal hemorrhage
- Renal colic

According to the MAH, the data do not indicate an increased risk of serious bleeding events related to rFIXFc treatment.

Infection

Suspected Transmission of an Infectious Agent

rFIXFc is a fully recombinant protein manufactured in a human cell line with no added human- or animal-derived components used in the manufacturing process. Although the risk of transmission of an infectious agent is low for recombinant proteins, data were carefully evaluated for any potential suspected transmission of an infectious agent. rFIXFc is a recombinant protein manufactured in a human cell line (HEK-293) that has been extensively tested to ensure safety regarding stability, sterility, and viral contamination. No human- or animal-derived materials are added to cell banks (master cell bank or working cell bank) or used in the manufacturing process.

Manufacturing controls are included to reduce the risk of introducing contamination. rFIXFc is purified by a combination of multistep chromatography and filtration techniques and a viral clearance process for purity and safety. Given these precautions, the risk of transmission of an infectious agent is negligible for rFIXFc. Nonetheless, data were carefully evaluated for any potential suspected transmission of an infectious agent. Of the total 153 subjects treated with rFIXFc, no suspected transmission of an infectious agent via rFIXFc treatment was reported.

Infection

While there may have been a theoretical concern that saturation of neonatal FC receptor (FcRn) with rFIXFc might result in increased catabolism and reduced half-life of immunoglobulin G (IgG) (thereby increasing a subject's risk of infection), this concern was not supported by human physiology or results from the nonclinical toxicology studies or clinical studies. Nonetheless, a comprehensive medical review of event terms relevant to infection was performed. Of the 153 subjects treated with rFIXFc, 103 subjects (67.3%) experienced at least 1 TEAE in the infections and infestations SOC. The TEAEs reported in 8 or more subjects (≥5%) were nasopharyngitis in 37 subjects (24.2%), influenza in 17 subjects (11.1%), upper respiratory tract infection in 14 subjects (9.2%), sinusitis in 12 subjects (7.8%), and viral infection in 9 subjects (5.9%). All of the TEAEs in the infections and infestations SOC were assessed by the Investigator as unrelated to rFIXFc treatment; TEAEs in 96 subjects were assessed as mild to moderate in severity and in 7 subjects were assessed as severe.

Of the 153 subjects treated with rFIXFc, 15 subjects (9.8%) experienced 19 TESAEs in the infections and infestations SOC. The TESAEs reported in 2 or more subjects were cellulitis in 4 subjects (2.6%) and tooth abscess in 2 subjects (1.3%). All 19 TESAEs were assessed by the Investigator as unrelated to rFIXFc; 14 of the events were assessed as mild to moderate in severity and 5 of the events were assessed as severe (see below for additional details).

In addition to the 19 TESAEs described above, 1 subject experienced 2 SAEs of bacterial sepsis during two separate major surgical/rehabilitation periods. Both of these SAEs were assessed by the Investigator as severe and unrelated to rFIXFc.

New Severe TESAEs in Infections and Infestations SOC (since 17 October 2014)

- Anal abscess

Severe TESAEs in Infections and Infestations SOC Previously Reported (before 17 October 2014)

- Orchitis
- Peritonsillar abscess
- Tooth abscess
- Bacterial sepsis (2 events)

According to the MAH, data from Studies 998HB102, 9HB02PED, and 9HB01EXT do not indicate an increased risk of transmission of an infectious agent via rFIXFc or an increased risk of infection with rFIXFc treatment. There is no evidence for transmission of an infectious agent via rFIXFc treatment. The pattern of infectious events is consistent with that in the general hemophilia population or is typical of events that are common in the adult and pediatric patients studied.

Hepatobiliary Events

HCV remains a significant cause of morbidity and mortality within the hemophilia population. Chronic liver inflammation may lead to slowly progressive hepatic fibrosis and clinically significant liver disease over time. In recent years, HCV has become one of the most common causes of death among hemophilia patients.

Of the total of 153 subjects treated with rFIXFc, 4 TESAEs of hepatobiliary events were reported: hepatitis C in 1 subject and hepatic neoplasm malignant in another subject (2 events). All 4 serious hepatobiliary events were assessed by the Investigator as unrelated to rFIXFc; 3 of the events were assessed as moderate in severity and 1 of the events was assessed as severe (hepatic neoplasm malignant). Full narratives are provided in the Study 9HB01EXT Clinical Study Report.

A comprehensive review of the data was performed to identify nonserious AEs that may represent hepatobiliary events with a focus on events in the hepatobiliary disorders SOC and relevant events in the infections and infestations SOC and the investigations SOC. 24 nonserious hepatobiliary TEAEs were identified in 16 subjects and are listed below.

New Nonserious Hepatobiliary Events (since 17 October 2014)

- Hepatitis C (2 subjects)
- Hepatic enzyme increased (1 subject)
- Alanine aminotransferase increased (1 subject)
- Aspartate aminotransferase increased (1 subject)
- Blood bilirubin increased (1 subject)
- Transaminases increased (1 subject [2 events])
- Cholecystitis (1 subject)

Previously Reported Nonserious Hepatobiliary Events (before 17 October 2014)

- Hepatitis C (5 subjects)

- Hepatitis C positive (1 subject)
- Liver function test abnormal (1 subject)
- Hepatic function abnormal (1 subject)
- Bile duct stone (1 subject)
- Hepatic steatosis (1 subject)
- Alanine aminotransferase increased (1 subject)
- Aspartate aminotransferase increased (1 subject)
- Jaundice (1 subject)
- Hepatic enzyme increased (2 subjects)

Of the 24 nonserious hepatobiliary events, all were assessed by the Investigator as unrelated to rFIXFc; 23 were assessed as mild to moderate in severity and 1 was assessed as severe (Hepatitis C in 1 subject). Of the 16 subjects reported to have experience hepatobiliary events, 9 had a medical history of hepatitis C, 5 had a medical history of hepatitis B, and 1 had a medical history of HIV.

In conclusion, 4 serious hepatobiliary events were reported in 3 subjects, and 24 nonserious hepatobiliary events were reported in 16 subjects. All events were assessed by the Investigator as unrelated to rFIXFc treatment. The majority of subjects with reported hepatobiliary events had a medical history of hepatitis C, which was likely contributory. According to the MAH, the data do not support an increased risk of hepatobiliary events with rFIXFc treatment.

Clinical laboratory evaluations

Clinical laboratory evaluations available from the Phase 3 study in adults and adolescents ≥12 years of age (Study 998HB102), Phase 3 study in children <12 years of age (Study 9HB02PED), and extension study (Study 9HB01EXT) for hematology (including red blood cell and white blood cell parameters and platelet count) and blood chemistry (including liver function, renal function, electrolytes, and other parameters) are presented in the respective Clinical Study Reports.

No clinically meaningful changes were observed in the mean actual values or mean changes from baseline in hematology or blood chemistry parameters in any of the 3 studies.

Anti-rFIXFc Binding Antibody

Overall, 4 subjects had ADA first detected prior to treatment with rFIXFc (3 subjects) from Study 998HB102 and 1 subject from Study 9HB02PED). In all 4 subjects who had ADA detected prior to rFIXFc treatment, ADA titers declined during the course of the parent studies and were no longer detectable by the final study visit of the parent studies. None of the 4 subjects who had positive ADA prior to rFIXFc treatment experienced allergic reaction events or serious bleeding events during the parent or the extension study.

Of the 153 subjects in the integrated data set, 148 subjects were evaluated for ADA (defined as those subjects negative at baseline with 1 or more post-baseline screening antibody result in either parent or extension study). Of the 148 subjects evaluated for ADA, 145 (98.0%) had no positive post-baseline ADA result and 3 (2.0%) had at least 1 positive post-baseline ADA result. All 3 subjects with at least 1 positive post-baseline ADA result were from Study 998HB102.

For the 3 subjects with a negative ADA prior to receiving rFIXFc and a positive ADA result observed on study, 1 had their first positive result at between >39 and ≤52 weeks after start of treatment and 2 had their first positive result at >65 weeks after start of treatment. None of these 3 subjects experienced an SAE of hypersensitivity. All 3 subjects had a negative result at final evaluation.

- Subject had a single positive anti-rFIXFc assessment at Month 6 of Study 9HB01EXT followed by 5 negative anti-rFIXFc assessments including his Final Study Visit. This positive result was included in the previous submission.
- Subject had a total of 5 positive results, with 3 positive antibody titers (1 in the parent study and 2 in the extension study) followed by 2 negative ADA results, and subsequently had another 2 positive ADA results followed by a negative ADA result at the last study visit in the extension study. Four of the positive results were included in the previous submission.
- Subject had a single positive anti-rFIXFc assessment at Month 42 of Study 9HB01EXT followed by 4 negative anti-rFIXFc assessments including his Final Study Visit. This positive result was not included in the previous submission.

All 3 subjects completed Study 998HB102, enrolled into, and completed the extension study. None of the 3 subjects experienced allergic reaction events. One experienced a TESAE of epistaxis not temporally associated with the ADA positive determination (see full narrative of this event in Study 9HB01EXT Clinical Study Report). Two subjects did not report any serious bleeding AEs during the study.

Overall, according to the MAH, the presence of an ADA-positive test result did not have an observed clinical impact on the safety of subjects in the parent studies or the extension study.

Vital Signs, Physical Findings, and other observations related to safety

There was no clinically meaningful pattern or consistent trend in AEs associated with vital sign abnormalities observed in any of the 3 studies.

Post-marketing data

rFIXFc was first approved in Canada on 20 March 2014. As of 19 March 2018 (the DLP of the last PSUR), rFIXFc was approved for marketing in 46 countries globally for the treatment of hemophilia B. Postmarketing data from patients on rFIXFc treatment are summarised below.

Patient exposure from post-marketing experience

As of 19 March 2018, patient exposure to rFIXFc in the postmarketing setting has occurred in multiple countries from commercial sales and the Humanitarian Aid Program run by the World Federation of Hemophilia (WFH). Commercial sales have taken place in the US, Canada, Japan, European Union/European Economic Area (EU/EEA), Australia, Saudi Arabia, Colombia, and Switzerland.

The cumulative estimated patient exposure in the postmarketing setting for commercial sales (including named patient use) is presented in Table 16.

The number of units of rFIXFc in the reporting interval of the current PSUR (20 September 2017 to 19 March 2018) is determined from reports of wholesale units within the country/region. The estimated number of patients exposed to rFIXFc from commercial marketing experience in the PSUR interval is then calculated for each of these locations using an assumed mean number of IUs per patient per month. This mean number of IUs per patient was estimated using data from patients receiving prophylactic treatment

in two Phase 3 trials (Studies 998HB102 and 9HB02PED) conducted by Biogen and was weighted by age (assumed 22.9% of patients to be less than age 12 years based on the age distribution in a subset of US specialty pharmacy providers and the US Marketing Authorization Holder's [MAH's] free drug program). This calculation assumes usage and weight of patients in the postmarketing setting are the same as those in Biogen's Phase 3 trials and that the proportion of children under 12 years is the same in all geographic locations. Additionally, it only takes into account prophylactic usage and assumes that all distributed IUs are utilized as of 19 March 2018. The number of months the IUs were available for use was made constant at 6 months (i.e., number of months in the current PSUR interval). These assumptions result in estimates for the number of patients that may differ from the actual patient count and person-time.

The cumulative number of patients was calculated by summing the interval number of patients with the number of patients that have discontinued commercial rFIXFc since launch. The discontinuation rate used to determine the number of patients that have discontinued commercial rFIXFc is derived from longitudinal patient dispensing records from specialty pharmacies representing 40% to 45% of commercial IU volume in the US. This calculation assumes that the discontinuation rate is the same in the entirety of the US and in all geographic locations. These assumptions result in estimates for the cumulative number of patients that may differ from the actual patient count. Cumulative patient-years are calculated as the sum of interval patient-years in all PSUR periods using the interval PSUR methodology described above.

Approximately 1,782 patients have received rFIXFc in the postmarketing setting, based on commercial sales. The estimated patient exposure to rFIXFc is 3,459 person-years cumulatively since launch, based on commercial sales (Table 16).

Table 16. Estimated cumulative patients exposure from postmarketing experience as of 19 March 2018

Source	Number of Patients	Patient-Years
United States	1099	2507
Japan	256	516
Canada	103	139
Switzerland	7	6
EU/EEA[a]	307	284
Australia	4	2
Brazil	0	0
Taiwan	0	0
Saudi Arabia	3	2
Colombia	0	0
ROW[b]	3	3
Total Exposed	**1782**	**3459**

EEA=European Economic Area; EU=European Union; IBD=International Birth Date; ROW=Rest of World
[a] EU/EEA represents sales in Austria, Belgium, Cayman Islands, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Norway, Poland, Slovakia, Slovenia, Sweden, and the United Kingdom.
[b] ROW Market Setting reflects patient exposure from commercial sales (Doctor Specific Patient Request) in Arab Emirates, Oman, and Qatar.
Source: Alprolix PSUR 8, 18 May 2018, Table 8.

Regulatory Actions Taken Related to Marketed rFIXFc

No actions have been taken related to the safety of marketed rFIXFc.

Post-marketing adverse events of special interest

Inhibitor Development to FIX

A search of the rFIXFc Global Safety Database was performed, using the following MedDRA PTs: Factor IX inhibition, Anti factor IX antibody positive, Anti factor IX antibody increased, Anti factor IX antibody, Inhibiting antibodies, Inhibiting antibodies positive, Neutralising antibodies and Neutralising antibodies positive.

As of 19 March 2018, there were 6 cumulative case reports of inhibitor development in the postmarketing setting (5 SAEs of factor IX inhibition and 1 SAE of factor IX antibody increased). Additional details are presented in rFIXFc PSUR #8, Table 12. Inhibitors are an established potential complication of factor replacement therapy in hemophilia B. Review of the postmarketing SAEs of inhibitor development does not change the current benefit-risk profile of rFIXFc, and routine pharmacovigilance will continue.

Serious Hypersensitivity, Serious Allergic Reaction, and/or Anaphylaxis

A search of the rFIXFc Global Safety Database was performed using the MedDRA Standardized MedDRA Queries (SMQs) Anaphylactic reaction and Hypersensitivity (limiting search result to SAEs).

As of 19 March 2018, 12 case reports (13 SAEs) of serious hypersensitivity, serious allergic reaction, and/or anaphylaxis were identified in the postmarketing setting including 4 SAEs of hypersensitivity, 8 SAEs of anaphylactic reaction, and 1 SAE of erythema. Hypersensitivity and anaphylaxis are established potential complications of factor replacement therapy. Review of the postmarketing SAEs of potential hypersensitivity reactions does not change the current benefit-risk profile of rFIXFc, and routine pharmacovigilance will continue.

Vascular Thromboembolic Events

A search of the rFIXFc Global Safety Database was performed, using the MedDRA SMQ Embolic and thrombotic events. Catheter-related events (e.g. MedDRA PTs Central venous catheterization and Device occlusion) without a concurrent report of associated vascular thrombosis were excluded from further analysis.

As of 19 March 2018, 3 case reports of serious possible vascular thromboembolic events have been identified; 1 SAE of retinal vein thrombosis in a patient with a history of ophthalmologic disease who continued rFIXFc treatment, 1 non-medically confirmed SAE of thrombosis, and one SAE of catheter site thrombosis. There is a potential risk of thromboembolic episodes following the administration of factor IX products. Review of the postmarketing AEs of possible vascular thromboembolic events does not change the current benefit-risk profile of rFIXFc, and according to the MAH routine pharmacovigilance will continue.

Use in special populations

Post-marketing Reports in the Elderly Population

A search of the rFIXFc Global Safety Database was performed for events that included rFIXFc as a suspect or interacting drug in patients ≥65 years of age or age group "Elderly."

As of 19 March 2018, 65 AEs in 25 postmarketing reports in patients ≥65 years of age have been received including 23 SAEs in 13 reports. There were no patterns identified from these data which remain limited. According to the MAH, routine pharmacovigilance will continue.

Pregnancy and Lactation Exposure

A search of the rFIXFc Global Safety Database was performed to identify use of rFIXFc in female patients.

As of 19 March 2018, there were 10 case reports (including 15 AEs and 3 SAEs) involving female patients. All reports originate from the US. No report is medically confirmed. There is 1 case of exposure to rFIXFc during pregnancy (maternal or paternal exposure) and no reports of lactation in the rFIXFc Global Safety Database. Information regarding the safety profile of rFIXFc in female patients, including during pregnancy and lactation, remains limited and according to the MAH routine pharmacovigilance will continue.

Lack of efficacy

As of 19 March 2018, there were no reports of lack of efficacy in the ongoing or completed clinical studies with rFIXFc. Similarly, data from the postmarketing setting do not suggest a lack of efficacy for rFIXFc.

Overdose

As of 19 March 2018, there were no reports of overdose in the postmarketing setting.

Medication errors

A search of the rFIXFc Global Safety Database was performed using the MedDRA SMQ Medication Errors.

As of 19 March 2018, a cumulative total of 21 case reports have been received from all sources (clinical trial and postmarketing). Of these 21 case reports, 19 nonserious reports of medication errors were received from the postmarketing setting. The most commonly reported event, by MedDRA PT is Drug dose omission (n = 7). In some instances, it is not clear if the dose omission was an unintentional event (i.e. medication error) or if there were other reasons for interruption in treatment. Additional details are presented in rFIXFc PSUR #8. According to the MAH, no pattern of medication errors was identified and routine pharmacovigilance will continue.

Conclusions from the post-marketing experience

Analysis of the available safety data reported as of 19 March 2018 revealed no new safety concerns. FIX inhibitor development and serious hypersensitivity, serious allergic reaction, and/or anaphylaxis have been observed and are included as Important Identified Risks in the Core Risk Management Plan. Important risks will continue to be managed and minimized; according to the MAH no additional risk minimization activity is considered necessary. The MAH will continue to monitor safety and efficacy data through routine pharmacovigilance to evaluate the benefit-risk for rFIXFc.

7.2 Discussion

An integrated analysis of data pooled from the completed extension study 9HB01EXT and its two parent studies (998HB102 and 9HB02PED) has been submitted via the current Type II application. A total of 120 subjects dosed with rFIXFc were included in the extension study; 27 subjects (90.0 %) enrolled from study 9HB02PED and 93 subjects (75.6 %) enrolled from study 998HB102, respectively. 33 subjects who completed either study 998HB102 or study 9HB02PED but did not participate in study 9HB01EXT were also included in the analysis. Thus, the integrated safety data set comprised a total of 153 subjects with a median total duration on rFIXFc treatment of 188.31 weeks, including 126 subjects treated for ≥1 year, 107 subjects treated for ≥2 years, 96 subjects treated for ≥3 years, 67 subjects treated for ≥4 years, and 53 subjects treated for ≥5 years.

The median total EDs was 165.0 with 128 of the 153 subjects achieving ≥50 EDs of cumulative exposure, 109 subjects achieving ≥100 EDs, and a total exposure of 26,106 EDs for the integrated data set. The 153 subjects represented a broad, diverse population, with age at entry to the parent studies ranging from 1 to 71 years.

The primary endpoint of the extension trial, Study 9HB01EXT, was development of FIX inhibitors. None of the 153 subjects in the integrated data set developed an inhibitor, including the 109 subjects with ≥100 EDs to rFIXFc. Also none of the 128 subjects who exhibited a valid inhibitor test following ≥50 EDs to rFIXFc developed an inhibitor (95% CI: 0%, 2.86%).

Adverse events (AEs) were monitored for a total of 560.64 subject-years (20,106 EDs). 138 out of the 153 subjects (90.2%) treated with rFIXFc experienced at least 1 TEAE. A total of 1151 TEAEs (including the surgery subgroup) occurred in the 153 subjects of which at least 51 TEAEs (33.3%) were reported to be serious. 2 TESAEs were assessed by the Investigators as related to rFIXFc treatment. However, both events resolved and did not lead to discontinuation from the study. 3 out of the 153 subjects (2.0%) have discontinued rFIXFc treatment or withdrawn from the study due to an AE. All 3 subjects were originally enrolled into Study 998HB102, and the TEAEs leading to discontinuation/withdrawal occurred in the parent study for 2 and the extension study for 1. However, none of these TEAEs were assessed by the Investigators as related to study treatment.

There were no identified tolerability issues and no reports of anaphylaxis or serious hypersensitivity events. No deaths, no vascular thrombotic events and no suspected transmission of infectious agents via rFIXFc treatment occurred.

Type and incidence of AEs observed in the extension and the two parent studies were found to be consistent with what is expected for the general hemophilia B population. The most common AEs that emerged after rFIXFc treatment (incidence ≥10% of the total) were nasopharyngitis, fall, headache, arthralgia, and influenza. The majority of the AEs were reported to be unrelated to rFIXFc treatment.

Age, body mass index, ethnic, geographic, or other demographic characteristics, including comorbidities such as HCV or HIV were not found to impact the safety profile of rFIXFc. No pattern in the type or frequency of events could be observed that would suggest a safety concern with longer exposure as measured by greater cumulative ED intervals.

No new ADRs emerged. In line with the previously reported data, ADRs occurred in 14 subjects (9.2%) and included paresthesia oral, headache, and obstructive uropathy (1.3% each); and palpitations, breath odor, fatigue, infusion site pain, decreased appetite, dizziness, dysgeusia, hematuria, renal colic, and hypotension(0.7% each).

The pattern of infections reported during the 3 studies was typical of the population studied and was not suggestive of an increased risk of infection with rFIXFc treatment or immune compromise.

No safety issues were observed in children <6 years of age or 6 to <12 years of age or in adolescents 12 to <18 years of age.

No patterns or trends were observed during the 3 studies in abnormalities of clinical chemistry or hematology. No trends in vital sign abnormalities or physical examination findings were found.

Post-marketing data as of 19 March 2018 revealed no new safety concerns.

To summarize, the integrated safety analysis did not reveal unusual findings or new safety signals for Alprolix. Long-term treatment for more than 5 years has demonstrated that Alprolix exhibits an acceptable safety profile and is well-tolerated in children, adolescents and adults with hemophilia B. Some minor updates are proposed in Section 4.8 of the SmPC due to new safety data available from the extension study and its integrated analysis with the two parent studies. In principle, this is endorsed.

However, according to the SmPC guideline statements should be brief and precise and only limited information relevant to the prescriber should be presented. Therefore, the MAH is requested to revise the proposed updates in Section 4.8 of the SmPC (see Attachment 1 for further details).

8. Risk management plan

The MAH submitted an updated RMP version with this application. The main proposed RMP changes were the following:

- Update per current template (Rev.2 accompanying GVP Module V Rev.2)
- Module SIII; additional data from the completed clinical trial 9HB01EXT and the integrated safety data analysis in Previously Treated Patients (PTPs).
- Part III; Pharmacovigilance plan updated to reflect 9HB01EXT being completed

The updated RMP version 1.4 covered in this assessment has a new format. Therefore, there is no track-change version of the currently approved RMP version 1.3 available. Annex 8 "Summary of changes to the risk management plan over time" has not been completed.

Part II: Module SIII - Clinical trial exposure

From 27 April 2010 (the Developmental International Birth Date) through 19 March 2018, 182 subjects have been enrolled and dosed with rFIXFc in the Biogen/Bioverativ sponsored clinical studies. The cumulative subject exposure, which includes subjects from completed and ongoing clinical studies, is shown by age range in Table 1 and by race in Table 2.

Table 1: Proportion of Subjects Exposed in rFIXFc Clinical Studies by Age as of 19 March 2018

	Completed Studies (in PTPs)			Ongoing Studies (in PUPs)	
Age (years)[a]	998HB102 (N = 123)	9HB02PED (N = 30)	9HB01EXT (N = 120)	998HB303 (N = 29)[b]	Total (N = 182)
<6	0	15 (50.0%)	13 (10.8%)	29 (100.0%)	44 (24.2%)
6-11	0	15 (50.0%)	14 (11.7%)	0	15 (8.2%)
12-17	11 (8.9%)	0	11 (9.2%)	0	11 (6.0%)
≥18	112 (91.1%)	0	82 (68.3%)	0	112 (61.5%)

N = number of subjects; PTP = previously treated patient; PUP = previously untreated patient; rFIXFc = recombinant coagulation factor IX Fc fusion protein.
Source: FACTOR9HB/PSUR/PSUR2018/T-DEM-CHARACTERISTICS.SAS (23Mar2018)
Notes: Percentages are based on the number of subjects with non-missing data in each study or overall. Subjects participating in more than one study are counted in both study columns. Each subject is counted only once in the total column. Fourteen subjects from the Phase 1/2a study (SYN-FIXFc-07-001) are excluded from this table as they received a single dose of rFIXFc.
[a] For Study 9HB01EXT, the age used in classifying the subjects into different age categories was the age at entry to the parent study.
[b] One patient received commercial rFIXFc during the screening period (which was allowed per protocol) but was not enrolled due to screen failure. This explains why 29 patients have been exposed to rFIXFc in Study 998HB303, but only 28 are enrolled.

Table 2: Proportion of Subjects Exposed in rFIXFc Clinical Studies by Race as of 19 March 2018

	Completed Studies (in PTPs)	Ongoing Studies (in PUPs)	

Racial Group	998HB102 (N = 123)	9HB02PED (N = 30)	9HB01EXT (N = 120)	998HB303 (N = 29)	Total (N = 182)
White	73 (59.3%)	22 (73.3%)	66 (55.0%)	21 (72.4%)	116 (63.7%)
Black	10 (8.1%)	2 (6.7%)	11 (9.2%)	1 (3.4%)	13 (7.1%)
Asian	29 (23.6%)	5 (16.7%)	32 (26.7%)	0	34 (18.7%)
American Indian or Alaska native	1 (0.8%)	0	0	0	1 (0.5%)
Other	10 (8.1%)	1 (3.3%)	11 (9.2%)	4 (13.8%)	15 (8.2%)
Not reported due to confidentiality regulations	0	0	0	3 (10.3%)	3 (1.6%)

N = number of subjects; PTP = previously treated patient; PUP = previously untreated patient; rFIXFc = recombinant coagulation factor IX Fc fusion protein.
Source: FACTOR9HB/PSUR/PSUR2018/T-DEM-CHARACTERISTICS.SAS (23Mar2018)
Notes: Percentages are based on the number of subjects with non-missing data in each study or overall. Subjects participating in more than one study are counted in both study columns. Each subject is counted only once in the total column. Fourteen subjects from the Phase 1/2a study (SYN-FIXFc-07-001) are excluded from this table as they received a single dose of rFIXFc.

For the integrated safety analysis of previously treated patients (PTPs), exposure to rFIXFc (duration of dosing, total exposure days (EDs), and total number of injections per subject) was summarized cumulatively from the parent study (998HB102 and 9HB02PED) to the extension study (9HB01EXT).
Of the 153 subjects dosed with rFIXFc in the integrated safety analysis of PTPs, the median total duration on rFIXFc treatment was 188.31 weeks (range: <1 to 337.7 weeks). Of these 153 subjects, 126 subjects (82.4% were on rFIXFc treatment for at least 1 year, 107 subjects (69.9%) for at least 2 years, 96 subjects (62.7%) for at least 3 years, 67 subjects (43.8%) for at least 4 years, and 53 subjects (34.6%) for at least 5 years.
Of the 153 subjects dosed with rFIXFc in the integrated safety analysis of PTPs, the median total EDs was 165 (range: 1 to 528). A total of 128 subjects (83.7%) had >50 EDs of cumulative exposure in the parent and extension studies. A total of 109 subjects (71.2%) had >100 EDs of cumulative exposure, and the total exposure for the integrated data set was 26,106 EDs.

Part II, Module SVII: Identified and potential risks

Important Identified Risk: Inhibitor development to FIX (text from RMP abbreviated)

Study 9HB01EXT was designed to assess the long-term safety of rFIXFc in PTPs with hemophilia B. Safety data from this study were integrated with safety data from the 2 parent studies in PTPs: 99HB02PED and 998HB102. None of the 153 subjects in the integrated data set developed an inhibitor, including the 109 subjects with ≥100 EDs to rFIXFc.

Part II, Module SVIII: Summary of the safety concerns

Table 3: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Inhibitor development to FIX Serious hypersensitivity, serious allergic reaction, and/or anaphylaxis
Important potential risks	Serious vascular thromboembolic events Medication errors

Summary of safety concerns	
Missing information	Safety profile in patients ≥65 years old Safety profile in PUPs Use of rFIXFc for ITI Safety profile in women (including pregnant and breast-feeding women)

Assessor's comment:

Safety concerns haven't changed compared to the previous RMP version 1.3.

The missing information "Safety profile in patients ≥65 years old" had been addressed in long-term study 9HB01EXT, but only subjects not more than 63 years old were enrolled. Therefore, this safety concern is preserved.

Part III: Pharmacovigilance Plan

Table 4: On-going and planned studies in the post-authorisation pharmacovigilance development plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Study 998HB303 An Open-Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc; BIIB029) in the	The primary objective of the study is to evaluate the safety of rFIXFc in PUPs with severe hemophilia B.	• Safety profile in PUPs <18 years old • Inhibitor development to FIX • Use in ITI	Ongoing	Submission date dependent on study finish dates. Study last patient, last visit by June 2019 as per the agreed PIP (EMEA-C1-000914-PIP01-10-

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Prevention and Treatment of Bleeding in Previously Untreated Patients with Severe Hemophilia B (PUPs study), Category 3				M04).
Data collection from participation in the European Haemophilia Safety Surveillance System (**EUHASS**) registry. Category 3	To monitor the treatment safety of hemophilia B	• Inhibitor development to FIX • Serious hyper-sensitivity serious allergic reactions and/ or anaphylaxis • Serious vascular thromboembolic events	Ongoing	Data will be reviewed on an on-going basis as part of signal detection and reported within PSURs when available.
Data collection from participation in the European Pediatric Network (**PedNet**) registry. Category 3	To monitor the treatment safety of hemophilia B	• Inhibitor development to FIX	Ongoing	Data will be reviewed on an on-going basis as part of signal detection and reported within PSURs when available.

Table 5: Completed studies

Study / activity type, title, and category	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission

Study 9HB01EXT An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor IX Fusion Protein (rFIXFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects with Hemophilia B (safety extension study, Category 3) Category 3	The **primary objective** of the study is to evaluate the long-term safety of rFIXFc in subjects with hemophilia B. The **secondary objective** of this study is to evaluate the efficacy of rFIXFc in the prevention and treatment of bleeding episodes in subjects with hemophilia B.	• Long-term safety evaluation • Safety profile in patients ≥65 years old	27 April 2018

*Category 1 studies are imposed activities considered key to the benefit risk of the product.
Category 2 studies are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.
Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Assessor's comment:

The additional PhV activities proposed by the MAH are appropriate for characterising and identifying risks and providing missing information.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Summary of risk minimisation measures

Table 6: Summary table of Risk Minimisation activities by safety concern

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: Inhibitor development to FIX	*SmPC section 4.8.* *PL section 4* *Recommendation for monitoring development of inhibitors by appropriate clinical observation and laboratory tests are included in SmPC sections 4.4* *How to detect early signs and symptoms of inhibitor development in PL section 2*	*None*
Important identified risk: Serious hypersensitivity, serious allergic reaction, and/or anaphylaxis	*SmPC section 4.8.* *PL section 4* *Hypersensitivity to the active substance or excipients is a contraindication, SmPC section 4.3* *Recommendation to immediately discontinue use of product and contact their physician if symptoms of hypersensitivity occur are included in SmPC sections 4.4* *Instruction to not use product if allergic to active substance or any other ingredients in PL Section 2.* *How to detect and handle early signs and symptoms of anaphylaxis and allergic reactions in PL section 2.*	*None*
Important potential risk: Serious vascular thromboembolic events	*SmPC section 4.8.* *PL section 4* *Information about risk of thrombotic complications are included in SmPC section 4.4* *Information about risk of cardiovascular events in patient with existing cardiovascular risk factors is included in SmPC section 4.4* *Information about risk of catheter-related complications, including catheter site thrombosis is included in SmPC section 4.4* *Information about risk of risk of blood clots and catheter-related complications, including catheter site thrombosis is described in PL Section 2.*	*None*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Potential risk: Medication errors	*Instruction to always use medicine as prescribed. Instruction on how to handle accidental overdose or any missed dose is included in PL Section 3. Instruction to check the name and strength of the package, to make sure it contains the correct medicine is included in PL Section 7.* *Instructions for treatment monitoring (FIX activity) is included in SmPC section 4.2*	*None*
Missing information Safety profile in patients ≥65 years old	*SmPC section 4.2: There is limited experience in patients ≥65 years.*	
Missing information: Safety profile in PUPs	*SmPC Section 4.2: the safety and efficacy of rFIXFc in PUPs have not yet been established.*	
Missing information Use of rFIXFc for ITI therapy	*SmPC Section 4.8: Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reaction.*	
Missing information Safety profile in women (including pregnant and breastfeeding women)	*SmPC Section 4.6* *PL Section 2*	

Assessor's comment:

Routine risk minimization activities are sufficient to manage the safety concerns of the medicinal product.

8.1. Overall conclusion on the RMP

☒ The changes to the RMP are acceptable.

9. Changes to the Product Information

As a result of this variation, section(s) 4.8 and 5.1 of the SmPC are being updated to include new efficacy and safety data on long-term treatment with Alprolix.

Changes are also made to the PI to bring it in line with latest version of the "Excipients in the labelling and package leaflet of medicinal products for human use" guideline.

The Package Leaflet (PL) is updated accordingly. In addition, the list of local representatives in the PL is being revised and other minor editorial changes have been included.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

10. Request for supplementary information

10.1. Other concerns

Clinical aspects

1. The efficacy results for the 11 patients aged ≥12 to <18 years at entry to the pre-ceding study 998HB102 were not presented separately in the dossier and no information was provided what treatment arms these patients were assigned to. It is acknowledged that these efficacy analyses were not specifically required in the Alprolix PIP. However, the MAH is requested to provide these data as already outlined in the previous procedure (EMEA/H/C/004142/P46 005) to allow a final conclusion concerning efficacy also for this age cohort.
2. The Product Information needs to be revised (see Attachment 1) according to the comments made by the Rapporteur.
3. The variation application includes an integrated analysis and comparison of the extension study with the two pre-ceding phase 3 trials and resulting PI updates. The MAH is therefore requested to revise the EPAR of the previous Article 46 procedure (EMEA/H/C/004142/P46 005) accordingly.

11. Assessment of the responses to the request for supplementary information

11.1. Other concerns

Clinical aspects

Question 1:
The efficacy results for the 11 patients aged ≥12 to <18 years at entry to the pre-ceding study 998HB102 were not presented separately in the dossier and no information was provided what treatment arms these patients were assigned to. It is acknowledged that these efficacy analyses were not specifically required in the Alprolix PIP. However, the MAH is requested to provide these data as already outlined in the previous procedure (EMEA/H/C/004142/P46 005) to allow a final conclusion concerning efficacy also for this age cohort.

Summary of the MAH's response:
The MAH acknowledges the request for efficacy data in the 11 patients aged ≥12 to <18 years sub-population. Data on Annualized Bleeding Rate (ABR), Annualized Joint Bleeding Rate, and Annualized rFIXFc consumption in this sub-population is presented in Table 1, Table 2 and Table 3 below.

The annualized bleeding rates for the age group ≥12 to <18 years are consistent with the annualized bleeding rates for both children below the age of 12 and adults. The consumption in the age group 12-17 in the extension study (9HB01EXT) is lower than for children below the age of 12 years, which is as expected due to a lower clearance of factor IX with increasing age.

Safety analyses for this age group were presented in the Response to RSI in the Article 46 submission, EMEA/H/C/004142/P46 005 and in the Summary of Clinical Safety.

The number of patients is deemed too low to include data in the SmPC.

Assessment of the MAH's response:
The Applicant complied with the request and provided the main efficacy results for the patients aged 12 to 17 years in the extension study. The results of this age cohort (a total of 9 patients in the end) seem largely similar those obtained for the other age subgroups. Hence, these results do not alter the positive benefit/risk profile of Alprolix. It is agreed that the number of patients is deemed too low to include data in the SmPC. However, the results should be presented in the EPAR.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

Question 2:
The Product Information needs to be revised (see Attachment 1) according to the comments made by the Rapporteur.

Summary of the MAH's response:
The MAH acknowledges the comments to the proposed SmPC and has updated accordingly, i.e. condenced the data from the extension study (BYOND).

Section 4.8. The MAH agree to remove the duration of the extension study from this section, however we would like to emphasize the importance for having information on total number subject-years where adverse events have been monitored to provide context to prescribing physicians. Therefore we propose to include this information in SmPC section 5.1. Also, this information has presidence from other FIX products, for example Refixia.

Section 5.1. It is recognized that the information in the SmPC should be brief and the MAH has acknowledged this request and condenced the information on the extension study in section 5.1.

We have also made the text updates more fluent and easy to read.

The MAH considers it´s essential to present efficacy outcome as annualized bleeding rate with separate numbers for the pre-authorisation study and the extension study.

ABR is an important efficacy parameter, as patients and their treating physicians aim for as few bleeds as possible when starting a prophylactic treatment. Repeated bleeds into a joint result in gradual destruction of joint tissue resulting in pain and decreased mobility that may eventually be chronic. As recognized by the EMA, prevention of joint bleeds is of significant importance to the individual patients.

In the interest of presenting brief information in the SmPC, and due to the low number of subjects on personalized prophylaxis regimen, we have chosen to present individualized prophylaxis and weekly prophylaxis in the SmPC. ABR in on-demand-treatment reflects severity and bleeding-profile of the respective patients but not treatment efficacy and is consequently not presented.

In the paediatric section of the SmPC text in 5.1 the applicant acknowledges the comments and we have condenced the text significantly. However, dosing and dosing intervals in children is specifically challenging and therefore we believe it´s important to inform the prescriber about the long-term data we

have for this sub-population. Therefore the duration of treatment and longterm efficacy data should be presented in this section, however in a brief and concise way.

Assessment of the MAH's response:
The MAH complied with the request to amend and shorten information proposed in sections 4.8 and 5.1 of the SmPC. The MAH further revised Section 5.1 to improve readability (see attached documents).

The new proposals made by the MAH are considered acceptable. Section 5.1 of the SmPC now includes the main efficacy results from the pivotal studies and the extension study. The statements presented are brief and precise and the whole Section 5.1 is now much easier to read.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

Question 3:
The variation application includes an integrated analysis and comparison of the extension study with the two pre-ceding phase 3 trials and resulting PI updates. The MAH is therefore requested to revise the EPAR of the previous Article 46 procedure (EMEA/H/C/004142/P46 005) accordingly.

Summary of the MAH's response:
MAH confirms that at time of approval of proposed PI the EPAR will be revised accordingly, including updates from the Article 46 submission.

Assessment of the MAH's response:
The MAH complies with the request and confirms to update the EPAR of the previous Article 46 procedure (EMEA/H/C/004142/P46 005) accordingly after approval of the proposed PI.

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall concl