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ADIS DRUG EVALUATION

Eftrenonacog Alfa: A Review in Haemophilia B

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Abstract

Eftrenonacog alfa (Alprolix®) is an extended half-life recombinant factor IX (rFIX)-Fc fusion protein (hereafter referred to as rFIXFc). Administered as an intravenous bolus, it is approved for prophylactic use and the treatment of bleeding in patients with haemophilia B in various countries worldwide, including those of the EU, as well as the USA. In multinational, phase III trials, rFIXFc was effective for the prophylaxis, perioperative management or on-demand treatment of bleeding in male patients with severe haemophilia B regardless of age and irrespective of whether or not they had been previously treated with FIX replacement products. Prophylactic efficacy was maintained over the longer term (up to 5 years) in previously treated patients. rFIXFc effectiveness in the real-world setting is supported by results of prospective studies, as well as the outcomes of several retrospective trials. rFIXFc was well tolerated in clinical trials in previously treated and untreated children, adolescents and/or adults with severe haemophilia B. Thus, rFIXFc continues to represent a useful treatment option among the haemophilia B patient population.

Plain Language Summary

Haemophilia B is a rare inherited bleeding disorder caused by a deficiency in coagulation factor IX (FIX). Its management involves rectifying the deficiency in FIX by administering an FIX replacement product, thereby increasing FIX activity and reducing bleeding. FIX replacement therapy can be administered at the time of bleeding (i.e. as on-demand treatment) or prophylactically (as scheduled injections), as well as before surgery. Eftrenonacog alfa (also known as rFIXFc; Alprolix®) is a replacement FIX therapy comprising FIX linked to a region of human immunoglobulin G to prolong the half-life of the product. It has been approved for the prevention and treatment of bleeding in patients with haemophilia B in various countries worldwide. Designed to require less frequent injections, rFIXFc was effective and well tolerated when used to prevent or treat bleeding, including before surgery, in individuals with haemophilia B regardless of age or whether they have been treated previously with an FIX replacement product. Thus, rFIXFc continues to represent a useful treatment option for individuals with haemophilia B.

Digital Features for this Adis Drug Evaluation can be found at https://doi.org/10.6084/m9.figshare.22266553.

Eftrenonacog alfa: clinical considerations in haemophilia B

Fusion protein linking human FIX to the Fc domain of human IgG1
Provides effective prophylaxis, control of acute bleeding episodes and perioperative management in patients of all ages regardless of whether or not they had been previously treated with an FIX replacement
Maintains prophylactic efficacy over the longer term (up to 5 years) in clinical trials
Well tolerated in children, adolescents and/or adults; the nature and frequency of AEs were consistent with those expected in the haemophilia B population

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1 Introduction

Haemophilia B is a rare X chromosome-linked bleeding disorder characterized by a genetic deficiency of coagulation factor IX (FIX) [1, 2]. Disease severity is classified based on residual plasma FIX levels [2, 3]. The primary strategy in haemophilia B management is to rectify the factor deficiency by administering exogenous FIX replacement therapy, thereby increasing FIX activity and reducing bleeding [1, 2]. FIX replacement therapy can be administered at the time of bleeding (i.e. as on-demand treatment), prophylactically (as scheduled injections) or perioperatively [1, 2]. Prophylactic FIX therapy, which aims to prevent bleeding through maintaining FIX levels above a trough level of 1 IU/dL, is the standard of care for severe haemophilia B [2]. However, prophylaxis with conventional FIX replacement concentrates is associated with a considerable treatment burden; the relatively short half-lives (t½) of these products generally necessitate ≥ 2 injections per week [2–4]. FIX products with improved pharmacokinetic profiles that require less frequent administration have the potential to be of greater convenience and to improve compliance [3, 4]. One approach for prolonging the terminal plasma t½ of exogenous FIX is to fuse FIX to another protein with a longer t½, such as human albumin or the fragment crystallizable (Fc) region of human immunoglobulin G (IgG) [3–5].

Eftrenonacog alfa (Alprolix®), a recombinant fusion protein comprising human FIX covalently linked to the Fc domain of human IgG1 (i.e. rFIXFc) [6, 7], is approved for prophylactic use and the treatment of bleeding in patients with haemophilia B in various countries worldwide (Sect. 4). While the use of eftrenonacog alfa (hereafter referred to as rFIXFc) in this indication has been previously reviewed in *Drugs* [8], additional data from clinical trials and real-world experience are now available. This article provides an update of the therapeutic efficacy and tolerability of rFIXFc in the treatment of haemophilia B. A brief overview of the pharmacological properties of rFIXFc is presented in Table 1.

2 Therapeutic Efficacy of rFIXFc

The therapeutic efficacy of intravenous rFIXFc for the prophylaxis and acute treatment of bleeding episodes associated with severe haemophilia B was evaluated in a series of nonrandomized, open-label, multinational phase III trials in previously treated male patients aged ≥ 12 years (B-LONG [9]; Sect. 2.1) or < 12 years (Kids B-LONG [10]; Sect. 2.2) [both reviewed previously [8]] and in previously untreated male patients aged < 18 years (PUPs B-LONG [11]; Sect. 2.3). Longer-term data from the open-label extension of B-LONG and Kids B-LONG (B-YOND [12]; Sects. 2.1.1.1 and 2.2.1.1), which was primarily a safety study, are also available. Clinical trial data are supported by real-world experience with rFIXFc in various prospective and retrospective studies (Sect. 2.4).

B-LONG, Kids B-LONG and PUPs B-LONG enrolled patients with severe haemophilia B, defined as ≤ 2 IU/dL (≤ 2%) of endogenous FIX activity (or a documented genotype known to cause severe haemophilia B [9, 10]) [9–11]. Patients eligible for B-LONG had received prophylaxis, or treatment for ≥ 8 bleeding events in the year prior to enrolment with an FIX replacement product and accrued ≥ 100 exposure days (EDs), while those eligible for Kids B-LONG had been previously treated for ≥ 50 EDs [9, 10]. Patients in PUPs B-LONG had no prior exposure to FIX concentrates other than ≥ 3 rFIXFc injections before eligibility confirmation and < 28 days prior to screening [11]. Patients with a history of detectable inhibitors (i.e. neutralizing antibodies) or of anaphylaxis associated with FIX therapy were excluded [9–11].

In B-LONG, patients received rFIXFc as weekly prophylaxis (initially 50 IU/kg every 7 days, with the dose adjusted to maintain a target trough level), individualized interval prophylaxis (initially 100 IU/kg every 10 days, with the interval adjusted to maintain a target trough level), on-demand treatment (20–100 IU/kg, based on bleeding severity) or treatment as part of perioperative care [9]. Patients who had received prophylaxis prior to B-LONG were eligible for enrolment in the prophylaxis groups, while those who had previously received on-demand treatment were eligible for enrolment in any group. The perioperative care group included patients who required major surgery and received rFIXFc 40–100 IU/kg based on the type of surgery; those who switched to the perioperative care group from another treatment group returned to their original group following surgical rehabilitation [9]. In Kids B-LONG, patients initially received a weekly prophylactic injection of rFIXFc 50–60 IU/kg, with subsequent adjustments to dose (≤ 100 IU/kg per injection) or dose frequency (within the range of once to twice weekly) made based on individual patient characteristics [10]. In PUPs B-LONG, patients initially received a weekly prophylactic rFIXFc injection of 50 IU/kg, with the dose and dosing interval adjusted based on bleeding episodes, pharmacokinetic data and physical activity [11]. Before prophylaxis initiation, investigators could treat patients with on-demand rFIXFc at their discretion [11]. The studies were considered completed when ≥ 20 patients [10, 11] or ≥ 53 patients [9] reached ≥ 50 rFIXFc EDs (in conjunction with other criteria [9, 10]).

The primary efficacy endpoint of B-LONG was per-patient annualized bleeding rate (ABR), with the weekly and individualized interval prophylaxis groups in turn

Table 1 Pharmacological properties of rFIXFc

Manufacturing process	
Produced via recombinant DNA technology in a well-characterized human embryonic kidney cell line (HEK293H), without use of any exogenous human- or animal-derived raw materials (thus minimizing pathogenic contamination risks) [6, 7, 38]	
Manufacturing process involves multiple purification and viral clearance steps (including chromatography and nanofiltration) [6, 7, 38]	
High purity and consistent product quality confirmed in manufacturing process validation studies; robust and reproducible removal of adventitious viruses and process-related impurities demonstrated [38]	
Manufacturing process readily scalable and transferable (important for maintaining a consistent and continuous supply) [38]	
Pharmacodynamic properties	
Increases the plasma level of FIX to temporarily correct FIX deficiency and related bleeding tendencies; activated FIX and FVIII together activate FX, which converts prothrombin into thrombin, with thrombin in turn converting fibrinogen into fibrin to form clots [6]	
Fc domain of IgG1 (linked to rFIX) binds to FcRn [6, 7], which protects IgG proteins from lysosomal degradation and re-releases them into circulation (thus prolonging their plasma t½) [6, 7, 39]; animal studies confirm that extended $t_{½}$ values with rFIXFc vs rFIX result from the interaction between the Fc domain and FcRn, with $t_{½}$ values not differing between rFIXFc and rFIX in FcRn knock-out mice [40]	
Prolongs clotting activity (correlating with prolonged survival benefit) relative to rFIX in animal models of haemophilia B [13]	
Pharmacokinetic properties	
Age-dependent pharmacokinetics in pts with severe haemophilia B; as pt age increases, CL values decrease while exposure, t½ and IR values increase [9, 10] and, as such, higher or more frequent doses may be necessary in younger pts (aged < 12 years) [6, 7]	
In pts aged < 6 years ($n = 11$)[a] [10]	IR 0.6 IU/dL per IU/kg, dose-normalized AUC 22.7 IU·h/dL per IU/kg, V_{ss} 365.1 mL/kg, median residence time 83.7 h, CL 4.4 mL/h/kg and terminal t½ 66.5 h (based on blood sampling over up until 168 h after infusion)
In pts aged 6 to < 12 years ($n = 13$)[a] [10]	IR 0.7 IU/dL per IU/kg, dose-normalized AUC 28.5 IU·h/dL per IU/kg, V_{ss} 289.0 mL/kg, median residence time 82.5 h, CL 3.5 mL/h/kg and terminal t½ 70.3 h (based on blood sampling over up until 168 h after infusion)
In pts aged ≥ 12 years ($n = 22$)[a] [9]	IR 0.9 IU/dL per IU/kg, dose-normalized AUC 31.3 IU·h/dL per IU/kg, V_{ss} 314.8 mL/kg, mean residence time 98.6 h, CL 3.2 mL/h/kg, terminal t½ 82.1 h (based on blood sampling duration of 240 h), time to 3 IU/dL above BL 5.8 days and time to 1 IU/dL above BL 11.2 days
The pharmacokinetics of rFIXFc are best described by a three-compartment model [41] and are stable over repeated dosing (pharmacokinetic data may thus be used to individualize dosing; Sect. 4) [7, 9, 41]	
Pharmacokinetic parameters support an extended dose interval relative to rFIX; in pts aged ≥ 12 years [9] and < 12 years [10], CL was significantly ($p < 0.001$) lower, t½ was significantly ($p < 0.001$) longer (by ≥ 2.4-fold[b]), and dose-normalized AUC and V_{ss} were significantly ($p \leq 0.025$) higher with rFIXFc vs rFIX after a single 50 IU/kg IV dose	
Simulations based on population pharmacokinetic modelling predict that dosages of 50 IU/kg once weekly, 100 IU/kg once every 10 days and 100 IU/kg once every 14 days result in target range trough/peak (trough ≥ 1% to peak < 150%) in > 95, > 85 and > 50% of the population, respectively [13]; in pts aged ≥ 12 years administered a single IV dose of rFIXFc 50 or 100 IU/kg, mean FIX activity of > 2 IU/dL was maintained for 10 days and 12 days, respectively [6]	
Real-world pharmacokinetic data in pts switched from FIX to rFIXFc ($n = 15$) are consistent with clinical trial data [42]	

AUC area under the curve, *BL* baseline, *CL* clearance, *Fc* fragment crystallizable constant region, *FcRn* neonatal Fc receptor, *F(VIII/IX/X)* coagulation factor (VIII/IX/X), *IR* incremental recovery, *IU* international unit(s), *IV* intravenous, *pt(s)* patient(s), *rFIX* recombinant coagulation factor IX, *rFIXFc* recombinant coagulation factor IX fragment crystallizable fusion protein, *t½* half-life, *Vss* volume of distribution at steady state

[a]Pharmacokinetic parameters following a single IV dose of 50 IU/kg in B-LONG (Sect. 2.1) or Kids B-LONG (Sect. 2.2)

[b]In B-LONG [9] and Kids B-LONG [10], respectively, the t½ of rFIX was calculated using a 96-h and 48-h sampling schedule, with rFIXFc shown to have a 2.4-fold and 3.7-fold longer t½ than rFIX.When a (traditional) 48-h sampling schedule was used in B-LONG [9], the t½ of rFIX was 17.04 h, resulting in a 4.8-fold longer t½ with rFIXFc than rFIX

being compared with the on-demand treatment group [9, 13]. Inhibitor development (assessed by Nijmegen-modified Bethesda assays) was a primary safety endpoint in B-LONG [9] and the sole primary endpoint in Kids B-LONG [10] and PUPs B-LONG [11].

Patients who completed B-LONG or Kids B-LONG were eligible to enter B-YOND [12], in which they received rFIXFc as weekly prophylaxis (20–100 IU/kg every 7 days), individualized interval prophylaxis (100 IU/kg every 8–16 days or twice monthly), modified prophylaxis (doses further personalized to the individual patient) or on-demand treatment (only offered to patients aged ≥ 12 years). Patients were permitted to change treatment groups at any time during the study [12].

2.1 In Previously Treated Patients Aged ≥ 12 Years

At baseline in B-LONG, patients had a median age of 28–36 years [9]. Across the groups, 3–8% and 52–60% of patients were positive for HIV and hepatitis C virus (HCV), respectively. More than 75% of patients in each group had an FIX level of < 1 IU/dL. In patients previously receiving prophylaxis, the median estimated number of bleeding episodes in the prior 12 months was 2.0–2.5. The median duration of rFIXFc treatment in B-LONG was 51.6 weeks, 58.3 weeks and 40.9 weeks in the weekly prophylaxis, individualized interval prophylaxis and on-demand treatment groups, respectively (median 55.0, 38.0 and 16.0 EDs). Most (> 95%) patients in each of the prophylaxis groups were considered to be adherent to their regimen, taking ≥ 80% of

doses at their prescribed dose and ≥ 80% at the prescribed interval [9].

2.1.1 Prophylaxis

rFIXFc provided effective prophylaxis in B-LONG [9]. Weekly prophylaxis and individualized interval prophylaxis both significantly ($p < 0.001$) reduced the ABR relative to that seen with on-demand rFIXFc treatment (by 83% and 87%, respectively, based on estimates from a negative binomial regression model) and were associated with low median overall, spontaneous and traumatic ABRs (Table 2). In prespecified subgroup analyses of the primary endpoint, ABR reductions with weekly prophylaxis versus on-demand treatment were consistent across all subgroups, including those based on pre-study regimen (prophylaxis or on-demand treatment), number of bleeding events in the prior 12 months, age (12–17 years or 18–65 years) and number of target joints (defined as a major joint with ≥ 3 bleeding episodes in a 3-month period). Patients in the weekly prophylaxis, individualized interval prophylaxis and on-demand treatment groups with very high rates of bleeding prior to study entry (≥ 36 bleeding episodes) had median ABRs of 2.05, 2.76 and 29.43, respectively. During B-LONG, 23% of patients in the weekly prophylaxis group and 42% in the individualized interval prophylaxis group experienced no bleeding episodes [9].

In terms of joint and muscle bleeds, median overall, spontaneous and traumatic joint ABRs, respectively, were low in the weekly prophylaxis (1.1, 1.0 and 0.0) and individualized interval prophylaxis (0.4, 0.0 and 0.0) groups relative to those in the on-demand treatment group (13.6, 5.1 and 1.3) [9]. Median overall, spontaneous and traumatic muscle ABRs were all 0.0 in each of the prophylaxis groups versus 4.0, 1.0 and 1.1, respectively, in the on-demand treatment group [9].

Overall and during the last 6 and 3 months of B-LONG, respectively, the median weekly rFIXFc dose in the weekly prophylaxis group was 45.2, 40.7 and 40.5 IU/kg, and the median rFIXFc dosing interval in the individualized interval prophylaxis group was 12.5, 13.8 and 14.0 days [9]. Fourteen of 26 patients in the individualized interval prophylaxis group who remained in the study for ≥ 6 months had a dosing interval of ≥ 14 days during the final 3 months [9].

rFIXFc prophylaxis resulted in meaningful improvements in health-related quality of life (HR-QOL) as assessed by the Haemophilia-specific Quality of Life (Haem-A-QoL) questionnaire in patients aged ≥ 18 years, based on post hoc analyses of B-LONG data [14]. At week 26, mean changes from baseline in the Haem-A-QoL Total Score and both key domains (Physical Health; Sports and Leisure) were statistically significant ($p < 0.05$) in patients who received weekly rFIXFc prophylaxis ($n = 30$–38); only the change in the Physical Health domain reached significance in patients who received individualized interval prophylaxis ($n = 9$–13). In the weekly and individualized interval groups, 44% and 42% of patients were classified as HR-QOL responders (achieving a ≥ 7-point reduction from baseline in Haem-A-QoL Total Score) [14].

Prophylaxis with rFIXFc also improved pain and physical activity as measured by individual items of the Haem-A-QoL questionnaire or Haemophilia-specific Quality of Life for adolescents (Haem-QoL) questionnaire [15]. At the end of B-LONG, significantly ($p < 0.05$ vs baseline) greater proportions of prophylaxis recipients were free from painful swellings (64% vs 44%), painful joints (44% vs 28%) or pain when moving (54% vs 41%) [$n = 73$–78]. In addition, significantly ($p < 0.05$ vs baseline) greater proportions of recipients reported playing sports as much as the general population (52% vs 37%) and being unlikely to avoid participation in sports they enjoyed due to their haemophilia (47% vs 27%), to avoid participation in sports like football (30% vs 8%) or to have difficulty walking as far as desired (63% vs 43%) [$n = 50$–76] [15].

2.1.1.1 Longer-Term Prophylactic Efficacy The prophylactic efficacy of rFIXFc was maintained over up to 5 years in B-YOND (cumulative treatment duration up to 6.5 years) [12]. Prophylaxis recipients experienced low median overall, spontaneous and traumatic ABRs (Table 2), as well as low median joint ABRs (0.7, 1.6, 1.5 and 8.5 with weekly prophylaxis, individualized interval prophylaxis, modified prophylaxis and on-demand treatment, respectively) and median spontaneous joint ABRs (0.4, 0.4, 0.3 and 2.2). Median overall ABRs were also low in prophylaxis recipients with ≥ 1 target joint at entry into B-LONG (3.3, 3.7, 3.2 and 20.0 with weekly prophylaxis, individualized interval prophylaxis, modified prophylaxis and on-demand treatment, respectively; $n = 24$, 11, 13 and 6). In the weekly prophylaxis, individualized interval prophylaxis and modified prophylaxis groups, respectively, the median weekly rFIXFc dose was 48.5, 50.8 and 68.2 IU/kg, and the median rFIXFc dosing interval was 7.0, 13.6 and 6.6 days. From the end of B-LONG through to the end of B-YOND, median weekly factor consumption did not change and 79% of patients maintained the dosing interval achieved in B-LONG [12]. rFIXFc prophylaxis also displayed sustained clinical benefits in a post hoc analysis of pooled longitudinal data from B-LONG and B-YOND (cumulative treatment duration up to 6.5 years; median 165 EDs) [16]. At year 1, 2, 3, 4 and 5, respectively, in patients receiving weekly prophylaxis ($n = 67$, 39, 37, 26 and 22) or individualized interval prophylaxis ($n = 34$, 28, 25, 22 and 19), median

Table 2 Prophylactic efficacy of rFIXFc in patients with severe haemophilia B: results of phase III clinical trials

Trial	No. of pts	Median ABR			Study time adjusted ABR (95% CI)[a]
		Overall	Spontaneous	Traumatic	
B-LONG (previously treated male pts aged ≥ 12 years) [9]					
Weekly prophylaxis	61	3.0	1.0	1.0	3.12 (2.46–3.95)*
Individualized interval prophylaxis	26	1.4	0.9	0.0	2.40 (1.67–3.47)*
On-demand	27	17.7	11.8	2.2	18.67 (14.01–24.89)
B-YOND (B-LONG OLE) [12]					
Weekly prophylaxis	51	2.3	0.9	0.5	
Individualized interval prophylaxis	31	1.9	0.7	0.5	
Modified prophylaxis	16	2.9	0.4	1.1	
On-demand	15	11.6	3.4	1.1	
Kids B-LONG (previously treated male pts aged < 12 years) [10]					
Weekly prophylaxis (all pts)	30	2.0	0.0	0.5	
Weekly prophylaxis (pts aged < 6 years)	15	1.1	0.0	0.0	
Weekly prophylaxis (pts aged 6 to < 12 years)	15	2.1	0.0	1.1	
B-YOND (Kids B-LONG OLE) [12]					
Weekly prophylaxis (pts aged < 6 years)	13	1.0	0	0.5	
Weekly prophylaxis (pts aged 6 to < 12 years)	10	1.1	0.1	0.5	
Individualized interval prophylaxis (pts aged 6 to < 12 years)	5	3.7	0.7	2.4	
PUPs B-LONG (previously untreated male pts aged < 18 years) [11]					
Prophylaxis	28	1.2	0.0	0.9	
On-demand	22	0.2	0.0	0.0	

ABR annualized bleeding rate, *pt(s)* patient(s), *OLE* open-label extension

*$p < 0.001$ vs on-demand rFIXFc treatment

[a]Primary endpoint in B-LONG; calculated using negative binomial regression model to control for pt time in study

overall ABRs remained low (weekly prophylaxis: 2.1, 1.0, 2.2, 2.0 and 1.5; individualized interval prophylaxis: 2.1, 2.0, 2.1, 1.0 and 1.0) and median spontaneous, traumatic and joint ABRs were all ≤ 1.1 [apart from the median joint ABR for patients receiving individualized interval prophylaxis in year 1 (ABR 2.1)]. Moreover, median annualized factor consumption remained stable (2390–2635 IU/kg) and dose and interval adherence was high (99.3% and 97.7%) from year 1 to year 5 in patients receiving weekly and individualized interval prophylaxis [16].

2.1.2 Treatment of Bleeding Episodes

rFIXFc was effective in treating bleeding episodes in B-LONG [9]. In this study, 636 bleeding episodes (mostly spontaneous bleeding) occurred in 114 patients across the weekly prophylaxis, individualized interval prophylaxis and on-demand treatment groups [7, 9]. Most (90.4%) were resolved with 1 rFIXFc injection and 97.3% with ≤ 2 injections. For cases in which ≥ 1 injection was required for resolution, there was a median interval of 45 h between the first and second injection [9]. The median dose per injection required to resolve bleeding was 47.1 IU/kg in the weekly prophylaxis group, 44.8 IU/kg in the individualized interval prophylaxis group and 46.0 IU/kg in the on-demand group [13]; median total doses per bleeding episode were 51.5 IU/kg, 49.6 IU/kg and 46.6 IU/kg, respectively [13].

During B-YOND, the injection counts and doses of rFIXFc required to control acute bleeding episodes were comparable to those during B-LONG and generally similar between treatment regimens [12]. Most bleeding episodes were resolved with only 1 injection (88% overall; 84.6%, 85.9%, 88.0% and 94.9% in the weekly prophylaxis, individualized interval prophylaxis, mixed prophylaxis and on-demand treatment groups, respectively) or ≤ 2 injections (97% overall; 96.9%, 96.5%, 97.3% and 98.9%, respectively). The median total dose required to resolve an acute bleed was 51.8 IU/kg in the weekly prophylaxis group, 36.6 IU/kg in the individualized interval prophylaxis group, 54.9 IU/kg in the mixed prophylaxis group and 40.5 IU/kg in the on-demand treatment group [12].

2.1.3 Perioperative Management

Perioperative bleeding was effectively controlled by rFIXFc in B-LONG and B-YOND [12, 17, 18]. Collated surgical experience data from these studies [including limited data from Kids B-LONG (Sect. 2.2)] are available [17]. Overall, 35 major surgeries were performed in 22 patients aged 9–62 years (14 surgeries during B-LONG and 21 during B-YOND, including 1 in a participant who entered B-YOND from Kids B-LONG). Most (69%) of these surgeries were orthopaedic, with unilateral knee replacement or revision being the most common procedure (23% of major surgeries). For most (83%) major surgeries, only one rFIXFc injection was required to maintain haemostasis through to the end of the surgery. For orthopaedic and non-orthopaedic procedures, respectively, the median dose per injection was 96 and 80 IU/kg on the day of surgery (with a median of two and one injections required) and 48–68 and 49–64 IU/kg on postoperative days 1–14. Most surgeries required no more than one injection per day from days 1 to 14. For all major surgeries with a haemostatic assessment (33/35 surgeries), the haemostatic response to rFIXFc was rated by the investigators or surgeons as excellent (88%) or good (12%); a rating of excellent denotes blood loss (intraoperative and post-operative) comparable to that expected in patients without haemophilia [17].

In the collated dataset, 62 minor surgeries were performed in 37 patients (15 surgeries during B-LONG, 3 during Kids B-LONG and 44 during B-YOND, including 2 participants who entered B-YOND from Kids B-LONG) [17]. Tooth extraction was the most common type of minor surgery (39%). Most (74%) minor surgeries only required a single pre-operative dose of rFIXFc; for 13% of minor surgeries, no rFIXFc injections were reported. In patients aged ≥ 12 years, the median rFIXFc consumption on the day of the surgery was 84 IU/kg. For minor surgeries with a haemostatic assessment (38/62 surgeries), haemostatic responses were rated by investigators or surgeons as excellent (84%), good (11%) or fair (5%; both of these surgeries were dental procedures) [17].

2.2 In Previously Treated Patients Aged < 12 Years

At baseline in Kids B-LONG, patients had a median age of 5.0 years and reported experiencing a median of 2.5 total bleeds during the previous 12 months (3.0 in patients aged < 6 years and 2.0 in patients aged 6 to < 12 years) [10]. All patients were treated prophylactically before the study, 70% (21/30) with an FIX product administered twice per week. Median study time was 49.4 weeks (48.0 weeks for patients aged < 6 years and 50.0 for those aged 6 to < 12 years); 90% of 30 patients completed the study [10].

2.2.1 Prophylaxis

Weekly rFIXFc prophylaxis was effective in preventing bleeding events in Kids B-LONG [10]. Median overall, spontaneous and traumatic ABRs were low in the overall population, as well as in subgroups of patients aged < 6 years and 6 years to < 12 years (Table 2). Median joint ABRs (total, spontaneous and traumatic), muscle ABRs (total and traumatic), and skin or mucosa ABRs (total and traumatic) were all 0.0 in the overall population and both subgroups, except for the median total joint ABR in patients aged 6 to < 12 years (ABR 1.1). Overall, 33% of patients reported no bleeding events and 63% reported no joint bleeding events [10].

Median average weekly prophylactic rFIXFc doses were 58.6, 59.4 and 57.8 IU/kg in the overall population, the < 6 years subgroup and the 6 to < 12 years subgroup, respectively [10]. In 63% of patients (19/30), the prescribed starting dose remained unchanged throughout the study. The median average actual dosing interval was 7.0 days; 80% (22/27) of patients experienced a reduction in dosing frequency with on-study rFIXFc versus pre-study FIX [10].

2.2.1.1 Longer-Term Prophylactic Efficacy The prophylactic efficacy of rFIXFc in patients aged < 12 years was maintained over up to ≈4 years of treatment in B-YOND (cumulative treatment duration up to 4.8 years) [12]. Low median ABRs (overall, spontaneous and traumatic) were maintained over long-term weekly prophylaxis or individualized interval prophylaxis with rFIXFc (Table 2). ABRs were comparable between age-based subgroups (< 6 years and 6 years to < 12 years) in patients who received weekly prophylaxis. With respect to joint bleeds, median overall joint ABRs remained low during B-YOND (0.0, 0.8 and 0.9 in patients aged < 6 years receiving weekly prophylaxis, those aged 6 to < 12 years receiving weekly prophylaxis and those aged 6 to < 12 years receiving individualized interval prophylaxis, respectively), as did median spontaneous joint ABRs (0.0 for all patient groups) [12].

Most (77%) of the 27 patients who entered B-YOND from Kids B-LONG received weekly prophylaxis [12]. Patients aged < 6 years in the weekly prophylaxis group, those aged 6 to < 12 years in the weekly prophylaxis group and those aged 6 to < 12 years in the individualized interval prophylaxis group, respectively, received a median weekly rFIXFc dose of 64.6, 60.0 and 67.7 IU/kg and had a median rFIXFc dosing interval of 7.0, 7.0 and 10.2 days. From the end of Kids B-LONG through to the end of B-YOND, median weekly factor consumption was unchanged and 78% of patients maintained the dosing interval achieved in Kids B-LONG. Most (85%) Kids B-LONG patients who entered B-YOND finished the trial [12].

The durability of weekly rFIXFc prophylaxis efficacy was also confirmed in a post hoc analysis of pooled longitudinal data from Kids B-LONG and B-YOND (cumulative treatment duration up to 4.8 years; median 165 EDs) [16]. At year 1, 2, 3 and 4, respectively, median overall ABRs remained low (2.0, 2.0, 0.5 and 0.0), median spontaneous ABRs were all 0.0 and median traumatic and joint ABRs were all ≤1.0 ($n=29$, 21, 12 and 10). Median annualized factor consumption remained stable (2998–3374 IU/kg) and dose and interval adherence was high (99.1% and 97.4%) from year 1 to year 4 [16].

2.2.2 Treatment of Bleeding Episodes

rFIXFc was effective in treating bleeding episodes in Kids B-LONG and B-YOND [10, 12]. During Kids B-LONG, 60 bleeding episodes occurred in 20 patients (22 in 9 patients aged <6 years and 38 in 11 patients aged 6 to <12 years) [10]. Most (75%) episodes were resolved with 1 rFIXFc injection and 92% of episodes with ≤2 injections. For episodes requiring two injections, there was a median interval of 26.8 h between the first and second injection. The median average rFIXFc dose per injection required to resolve a bleeding episode was 63.5 IU/kg in the overall population (63.7 and 62.9 IU/kg in the younger and older subgroups), while the total dose administered per bleeding episode was 68.2 IU/kg (65.4 and 89.8 IU/kg) [10]. During B-YOND, 93% and 87% of bleeding episodes in patients aged <6 years and 6 years to <12 years, respectively, were resolved with only one rFIXFc injection [12]. With ≤2 injections, 99% and 97% of bleeding episodes in the respective age groups were resolved. The median total dose required was 58.8 IU/kg in patients aged <6 years and 91.6 IU/kg in those aged 6 to <12 years [12].

2.2.3 Perioperative Management

No patients underwent major surgeries during Kids B-LONG, although two patients underwent three minor surgeries [10]. For all three minor surgeries, the haemostatic response was assessed by the investigator to be excellent [10, 13]. During B-YOND, three patients from Kids B-LONG underwent surgeries (one major and two minor) [17]. The major surgery was a tonsillectomy, which only required one 99 IU/kg rFIXFc injection on the day of the surgery and a total hospital stay of 6 days [17]. Along with the three minor surgeries during Kids B-LONG, these surgeries were included in a pooled analysis of perioperative outcomes during B-LONG, Kids B-LONG and B-YOND (Sect. 2.1.3) [17].

2.3 In Previously Untreated Patients Aged <18 Years

At enrolment in PUPs B-LONG, patients had a median age of 7.2 months [11]. Spontaneous bleeding episodes (one of which was a spontaneous joint bleed) occurred in 15% of 33 patients during the 3 months prior to screening; 88% of patients had an FIX activity of <1 IU/dL at screening. The median rFIXFc duration was 77.5 weeks for prophylaxis and 22.9 weeks for on-demand treatment. Of the 22 patients who initially received on-demand treatment with rFIXFc, 77% switched to rFIXFc prophylaxis over the course of the study. For prophylactic rFIXFc, rates of dose compliance, dosing interval compliance and dose plus interval compliance were ≥80% in 82%, 68% and 57% of patients, respectively. Most (82%) patients enrolled and treated in PUPs B-LONG completed the study [11].

2.3.1 Prophylaxis

rFIXFc showed effective prophylaxis during the efficacy period of PUPs B-LONG and was associated with low median overall, spontaneous and traumatic ABRs (Table 2) [11]. In patients with ≥50 EDs with a prophylactic rFIXFc regimen ($n=20$), overall median ABR (1.32) was comparable to that in the overall prophylaxis group. Most patients (82%) who received prophylactic rFIXFc experienced no episodes of spontaneous bleeding. With respect to joint bleeds, median ABRs for both spontaneous and traumatic joint bleeding episodes were 0.0 in both the prophylactic and on-demand rFIXFc groups. In patients who received rFIXFc prophylaxis during PUPs B-LONG, median annualized rFIXFc consumption was 3175 IU/kg. Median average weekly dose and dosing interval were 58.0 IU/kg and 7 days. Most (79%) patients who received prophylaxis maintained their dosing schedule throughout the study. For cases in which the dosing interval was changed, it was more frequently extended ($n=4$) than reduced ($n=1$) [11].

2.3.2 Treatment of Bleeding Episodes

rFIXFc was effective in resolving bleeding episodes during PUPs B-LONG; 85% (23/27) and 88% (51/58) of bleeding episodes in patients receiving on-demand and prophylactic rFIXFc were resolved by 1 rFIXFc injection, while 89% (24/27) and 97% (56/58) of episodes in the respective groups were resolved with ≤2 injections [11]. In the prophylactic and on-demand groups, respectively, the median average dose per rFIXFc injection was 71.9 and 88.5 IU/kg and the median total rFIXFc dose required to resolve a bleeding episode was 78.7 and 91.7 IU/kg. For most rFIXFc injections with available data, the patients' response to the injection was assessed as excellent or good (88% of 57 injections and 100% of 22 injections for bleeding episodes in the prophylactic and on-demand groups, respectively) [11].

2.4 Real-World Experience

The effectiveness of prophylactic and on-demand rFIXFc in the real-world setting is supported by results of three non-interventional, multicentre, prospective studies ($n > 20$) conducted in Europe and the Middle East (B-MORE [19]), France (B-SURE [20, 21]) and Germany (PREVENT [22]), as well as the outcomes of several retrospective trials [23–26].

Based on interim results (data cutoff October 2021) from B-MORE (median age 16 years; 79.5% of patients had severe haemophilia B), rFIXFc prophylaxis was associated with a low median ABR and low factor consumption [19]. Patients in this study received a median of one prophylactic rFIXFc injection per week ($n = 106$) and had a median factor consumption of 47.6 IU/kg/week ($n = 104$). At the time of the analysis (mean overall rFIXFc duration 824 and 457 days in 106 and 11 patients receiving prophylactic or on-demand rFIXFc), prophylactic rFIXFc led to an ABR of 0.0 and 1.2 in patients who had previously received a prophylactic or on-demand FIX regimen ($n = 72$ and 5) [19]. In B-SURE, rFIXFc showed effectiveness when used in both the prophylactic [20] and perioperative [21] setting. Results of a final (24-month) analysis of data from patients who switched from FIX prophylaxis to rFIXFc prophylaxis (median observation period 637 days) showed a median annualized injection frequency of 52.1 and median annualized factor consumption of 2837 IU/kg/year during the prospective rFIXFc treatment period ($n = 65$) [20]. The median change in annualized injection frequency and annualized factor consumption since rFIXFc initiation was − 45 and − 482 ($n = 56$) and median ABRs improved from 2.0 to 1.0 ($n = 61$) [20]. In 9 patients (median age 44 years; 100% with severe disease) who underwent 10 major surgeries (90% being orthopaedic) and 26 patients (median age 37 years; 85% with severe haemophilia B) who underwent 39 minor surgeries, a median of 1 rFIXFc injection per day was required (interim analysis; data cutoff September 2020) [21]. Prophylactic efficacy was also seen in the final analysis (median follow-up 21.0 months) of PREVENT data [22]. Of the 47 patients (median age of 26.0 years) with haemophilia B in this study, 42 had severe disease, 35 had previously received rFIXFc and 9 were aged < 12 years. rFIXFc prophylaxis resulted in a median ABR of 1.7 ($n = 47$), a mean weekly injection frequency of 1.2 ($n = 45$) and a mean weekly factor consumption of 56.2 IU/kg/week ($n = 45$). The average proportion of patients experiencing zero bleeds during 6-month intervals of follow-up increased from 45.7% to 60.0% [22].

Results of prospective trials are supported by those from large ($n > 50$) retrospective studies [23–26]. In the largest ($n = 64$) of these (a multicentre study conducted in the USA), improvements in ABRs and reductions in overall factor consumption and injection frequency were seen in patients with haemophilia B (age 2–78 years; 59% with severe disease) who switched from an on-demand or prophylactic factor regimen (i.e. pre-rFIXFc) [$n = 29$ and 34; 1 further patient had an unknown prior treatment regimen] to on-demand or prophylactic rFIXFc ($n = 10$ and 54; median follow-up duration 2.7 years) [23]. Overall ABRs were 1.2, 3.2 and 1.5 for patients with severe, moderate and mild disease ($n = 34$, 10 and 5, respectively) who were receiving rFIXFc prophylaxis, and 3.7 and 1.8 for patients with moderate and mild disease ($n = 7$ and 3) who were receiving on-demand rFIXFc. An ≈ 50% reduction in weekly factor consumption was seen in patients receiving rFIXFc prophylaxis ($n = 54$) versus those receiving pre-rFIXFc prophylaxis ($n = 32$). The initial dosing interval was maintained or lengthened in 91% of 53 patients who switched from a pre-rFIXFc on-demand or prophylactic regimen to rFIXFc prophylaxis [23].

3 Tolerability of rFIXFc

3.1 In Previously Treated Patients

Intravenous rFIXFc was well tolerated in clinical [9, 10, 12] and real-world [21, 24, 26] trials in previously treated children, adolescents and adults with severe haemophilia B. Results of an integrated analysis ($n = 153$) [27] of data from patients who had received ≥ 1 dose of rFIXFc in B-LONG [9], Kids B-LONG [10] and B-YOND [12] [patients received rFIXFc for a median 188.31 weeks (median 165.0 EDs)] showed rFIXFc to have an acceptable safety profile, with no unusual findings or new safety signals, over > 5 years. Various demographic characteristics, including age, ethnicity, body mass index and comorbidities (e.g. HCV, HIV), were found to have no impact on the safety profile of rFIXFc [27].

The nature and frequency of AEs seen with rFIXFc were consistent with those expected in the haemophilia B population [27]. Most (90.2%) patients experienced ≥ 1 treatment-emergent AE (TEAE), with the most frequently reported (incidence ≥ 10%) TEAEs (excluding those that emerged during the perioperative management period for a major surgery) being nasopharyngitis (24.2% of patients), fall (15.0%), headache (15.0%), arthralgia (13.1%) and influenza (11.1%). Most TEAEs were mild or moderate in severity and unrelated to rFIXFc. Indeed, 17.6% of patients experienced ≥ 1 severe TEAE and 9.8% experienced treatment-related AEs (TRAEs). Of the 19 TRAEs described in 15 patients, oral paresthesia, headache and obstructive uropathy were the only TRAEs to be reported more than once (with each seen in 2 patients); no TRAEs emerged during the perioperative management period for a major surgery. At least one treatment-emergent serious

AE (TESAE; excluding those that emerged during the perioperative management period for a major surgery) were seen in 33.3% of patients. All but two of the TESAEs were considered to be unrelated to rFIXFc treatment; both cases (obstructive uropathy; renal colic) resolved and did not result in study discontinuation. Three patients (2.0%) discontinued treatment with rFIXFc or withdrew from B-LONG or B-YOND ($n = 2$ and 1) due to a TEAE (none of which were deemed to be treatment related). No patients died during B-LONG, Kids B-LONG and B-YOND [27].

AEs associated with haemophilia B or its treatment, and considered of special interest include the development of FIX inhibitors (which affect efficacy and quality of life, and are one of the most serious complications of haemophilia), grade ≥ 2 allergic reactions (hypersensitivity) and vascular thrombotic events [27]. In the integrated analysis, none of the 153 patients (including 109 patients with ≥ 100 rFIXFc EDs) developed an inhibitor, and no TESAEs of allergic reaction (defined as a grade ≥ 2 allergic reaction), hypersensitivity or anaphylaxis were reported. One TESAE (device occlusion) and one TEAE (coronary artery stenosis) were seen in a patient with prior angina pectoris events; a vascular thrombotic event was not reported in either case, with both cases assessed as being unrelated to rFIXFc therapy [27].

3.2 In Previously Untreated Patients

rFIXFc was well tolerated in previously untreated children and adolescents with severe haemophilia B participating in PUPs B-LONG [11]. There were no unanticipated safety findings, with the nature and frequency of TEAEs and TESAEs seen with rFIXFc consistent with those expected in this patient population [11].

Most (91%) of the 33 patients who received ≥ 1 dose of rFIXFc (57.5 patient–years of follow-up; 2233 EDs) experienced ≥ 1 TEAE, with the most frequently reported TEAE being infection [79% of patients; nasopharyngitis (33%) and upper respiratory tract infection (21%) were the most common infectious TEAEs] [11]. TESAEs occurred in 70% of patients, with central venous catheterization (27% of patients), fall (15%), poor venous access (9%) and head injury (9%) the most frequently reported (incidence ≥ 6%) TESAEs. Two patients experienced five treatment-related TEAEs: three injection-site erythema events (each assessed as nonserious) occurred in one patient, while another patient had a hypersensitivity reaction and tested positive for (low titre) inhibitor development (both assessed as serious). Life-threatening events (spontaneous subdural hematoma and spontaneous spinal cord haematoma) occurred in two patients, who were both receiving on-demand rFIXFc. There were no central venous access device thrombosis or anaphylaxis TEAEs, and no deaths reported [11].

Patients are most at risk of inhibitor development during the first 50 EDs of factor replacement [11]. In PUPs B-LONG, 3% of the 33 patients (1/33) exposed to rFIXFc developed a low titre inhibitor (i.e. ≥ 0.6 to < 5.0 BU/mL) after 11 EDs, which was considered serious. This patient, who had an FIX genotype classified as high risk for the development of inhibitors (nonsense mutation) and who also experienced a TESAE of hypersensitivity during the 11th injection of rFIXFc (that resolved with treatment), discontinued treatment and withdrew from the study. No high titre inhibitors (i.e. ≥ 5.0 BU/mL) were detected. The incidence of inhibitor formation was 4.6% in the 22 patients reaching ≥ 50 EDs to rFIXFc or an inhibitor, which is consistent with historical rates of inhibitor development in haemophilia B [11].

4 Dosage and Administration of rFIXFc

rFIXFc is approved for the prophylaxis and treatment of bleeding in patients with haemophilia B in various countries worldwide, including those of the EU [6], as well as the USA [7]. It is administered as an intravenous bolus infusion over several minutes, at a rate of up to 10 mL/min (dependent upon patient comfort) [6, 7]. The dose and duration of rFIXFc for prophylaxis, on-demand treatment of bleeding or use in the perioperative management of bleeding varies based on FIX deficiency severity, the location and extent of bleeding (or type of surgery), and characteristics of the individual patient (e.g. clinical condition, age and pharmacokinetic profile). Patients receiving rFIXFc should be monitored for FIX levels and, where appropriate, the development of neutralizing antibodies to FIX (Sect. 3) [6, 7]. Local prescribing information should be consulted for details regarding regimen recommendations, reconstitution and administration procedures, contraindications, warnings and precautions, patient monitoring and use in specific patient populations.

5 Place of rFIXFc in the Management of Haemophilia B

In patients with haemophilia B, the dosing frequency required for prophylaxis with standard t½ clotting factor concentrates (CFCs) is associated with an increased treatment burden (which can result in poor adherence); extended t½ CFCs were developed to reduce this burden [2, 4, 28]. rFIXFc was the first such product to be approved for patients with haemophilia B in the EU [6] and the USA [7], followed by albutrepenonacog alfa (a recombinant fusion protein linking human FIX with human albumin; hereafter referred to as rFIX-FP) [29, 30] and nonacog beta pegol [rFIX with a 40 kDa

polyethylene-glycol (PEG) conjugated to the protein; hereafter referred to as PEGylated rFIX] [31, 32]. Both rFIXFc [6, 7] and rIX-FP [29, 30] are approved in the EU and the USA for the prophylaxis and treatment of bleeding in patients of all ages with haemophilia B, while PEGylated rFIX is approved for the prophylaxis and treatment of bleeding in patients with haemophilia B aged ≥ 12 years in the EU [31] and of all ages in the USA [32]. In the EU, the safety and efficacy of rFIXFc [6], but not rIX-FP [29] and PEGylated rFIX [31], have been established in previously untreated patients.

Factor levels are affected by several variables, with the most important being the dosing frequency and t½/clearance of the product [28]. As prophylaxis, rFIXFc, rIX-FP and PEGylated rFIX can each be administered less frequently than conventional FIX products: once every 7 days (rFIXFc [6, 7], rIX-FP [29, 30] and PEGylated rFIX [31, 32]), once every 10 days (rFIXFc [6, 7] and rIX-FP [29]) and once every ≥ 14 days (rFIXFc [6] and rIX-FP [29, 30]). Where reported, the routine monitoring of FIX activity is not necessary for PEGylated rFIX [31], but is advised for rIX-FP [29] and rFIXFc [6]. Extravascular FIX distribution is another variable for consideration when tailoring patient therapy [33]. Most FIX resides in the extravascular space (where it is believed to play a role in haemostasis), with a dynamic equilibrium maintained between extravascular FIX and plasma FIX [33, 34]. The lower recovery of FIX seen with standard t½ rFIX CFCs is not displayed by extended t½ rFIX CFCs [28]. Indeed, several extended t½ rFIX CFCs demonstrate far higher factor recovery, suggesting that a lower proportion of the product is distributed to the extravascular space. In such cases, lower prophylactic doses than standard t½ rFIX CFCs may be effective. While further research is required, measuring plasma pharmacokinetic properties should be supplemented by a clinical assessment of efficacy when using such products [28].

In clinical trials in previously treated male patients with severe haemophilia B, rFIXFc effectively prevented bleeding episodes in individuals aged ≥ 12 years (Sect. 2.1.1) and those aged < 12 years (Sect. 2.2.1). In patients aged ≥ 12 years, the benefits of rFIXFc prophylaxis went beyond low median overall, spontaneous and traumatic ABRs, with improvements seen in HR-QOL, pain and physical activity (Sect. 2.1.1). Prophylactic efficacy was maintained over up to 5 years in patients aged ≥ 12 years (Sect. 2.1.1.1) and over up to ≈ 4 years in those aged < 12 years (Sect. 2.2.1.1) in this setting. rFIXFc also effectively controlled acute bleeding episodes (Sects. 2.1.2 and 2.2.2) and perioperative haemostasis (Sects. 2.1.3 and 2.2.3) in the respective populations. In a trial in previously untreated male patients aged < 18 years with severe haemophilia B, rFIXFc was effective in preventing (Sect. 2.3.1) and treating (Sect. 2.3.2) bleeding episodes. rFIXFc effectiveness is supported by results of prospective real-world studies, as well as the outcomes of several retrospective trials (Sect. 2.4).

rFIXFc was well tolerated in clinical trials in children, adolescents and/or adults with severe haemophilia B, regardless of whether the patients were previously treated (Sect. 3.1) or untreated (Sect. 3.2). There were no unexpected safety findings, with the nature and frequency of AEs seen with rFIXFc consistent with those expected in the haemophilia B population (Sects. 3.1 and 3.2). Over the longer term (> 5 years), rFIXFc had an acceptable safety profile in previously treated patients in clinical trials (Sect. 3.1). Inhibitor development did not occur in previously treated patients (Sect. 3.1) and was low in previously untreated patients with ≥ 50 EDs (Sect. 3.2).

To date, there is no evidence of any clinical safety issues arising from the various mechanisms of action (e.g. Fc-fusion, albumin-fusion, PEGylation) used to extend the t½ of CFCs [28]. In the absence of head-to-head trials between extended t½ CFCs, a matching-adjusted indirect treatment comparison in male patients aged ≥ 12 years with haemophilia B suggests that the estimated ABRs for patients receiving rFIXFc in B-LONG did not significantly differ from those seen in patients receiving rIX-FP in a multinational phase III trial (PROLONG-9FP) [35].

As the cost of prophylaxis in patients with haemophilia is very sensitive to the costs of the CFC itself and prophylaxis intensity (i.e. dose and frequency) [28], data on rFIXFc cost effectiveness are desirable. In recent cost-effectiveness analyses using Markov models with lifetime horizons, weekly [36, 37] and individualized interval [36] rFIXFc prophylaxis was dominant [i.e. associated with fewer bleeds (and thus a greater number of quality-adjusted life-years) and lower costs] relative to on-demand rFIX in patients (aged 2–12 years [37] and ≥ 12 years [36, 37]) with haemophilia B without inhibitors from an Italian National Health Service [36] and a Chinese healthcare system [37] perspective.

In conclusion, rFIXFc for the prophylaxis, perioperative management or on-demand treatment of bleeding is effective and well tolerated in patients with haemophilia B regardless of age and irrespective of whether they had been previously treated with FIX replacement products. Thus, rFIXFc continues to represent a useful treatment option among the haemophilia B patient population.

Data Selection Eftrenonacog Alfa: 136 records identified	
Duplicates removed	0
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	55
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	39
Cited efficacy/tolerability articles	18
Cited articles not efficacy/tolerability	24
Search Strategy: MEDLINE and PubMed from 2017 to present. Previous Adis Drug Evaluation published in 2017 was hand-searched for relevant data. Clinical trial registries/databases and websites were also searched for relevant data. Key words were eftrenonacog, Alprolix, factor IX Fc fusion protein, recombinant factor IX Fc, rFIXFc, FIX Fc, BIIB-029, hemophilia, haemophilia. Records were limited to those in English language. Searches last updated 3 April 2023	

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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