ORIGINAL ARTICLE

Clinical haemophilia

Real-world data demonstrate improved bleed control and extended dosing intervals for patients with haemophilia B after switching to recombinant factor IX Fc fusion protein (rFIXFc) for up to 5 years

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Abstract

Introduction: In clinical trials, recombinant factor IX fusion protein (rFIXFc) has demonstrated safety, efficacy and prolonged activity with extended dosing intervals for treatment of haemophilia B.

Aim: To assess the real-world clinical utility of rFIXFc in a variable patient population and routine clinical practice.

Methods: A multicentre, retrospective chart review was conducted of patients with haemophilia B who had received rFIXFc prophylaxis or on-demand treatment for ≥6 months across six sites in the United States.

Results: Sixty-four eligible patients were identified who had a median (range) duration on rFIXFc of 2.7 (0.5-5.0) years. Of 32 patients on rFIXFc prophylaxis who switched from prophylaxis with another factor treatment (ie pre-rFIXFc) and had a known pre-rFIXFc dosing interval, the initial dosing interval was lengthened for 26 (81%) patients and maintained for the remaining 6 (19%) patients. Most (n = 48 [91%]) patients who received rFIXFc prophylaxis from the beginning to the end of the chart review period (n = 53) maintained or lengthened the dosing interval from first through last dose of rFIXFc. For patients receiving rFIXFc prophylaxis, there was an approximate 50% reduction in weekly factor consumption compared with pre-rFIXFc prophylaxis. Overall annualized bleed rates, annualized spontaneous bleed rates and annualized joint bleed rates decreased after switching to rFIXFc prophylaxis (n = 24 with bleed data). Compliance to recommended treatment improved or remained stable in most patients with available data (30/31).

Conclusion: Recombinant factor IX fusion protein prophylaxis improved bleed control, reduced overall consumption, reduced frequency of infusion and improved compliance for patients with haemophilia B in a real-world setting.

1 | INTRODUCTION

Prophylactic treatment with replacement factor IX (FIX) is the standard of care for severe haemophilia B in countries with sufficient health resources.[1,2] Prophylaxis aims to maintain plasma FIX activity at levels that prevent or suppress bleeding episodes, with long-term prophylaxis preserving joint health and maintaining quality of life.[3,4] These are increasingly important outcomes for people with haemophilia because median life expectancy (63 and 75 years for patients with severe and mild-to-moderate haemophilia, respectively[5]) is getting closer to that of the general population.

Ideally, factors such as clinical phenotype, pharmacokinetic profile, physical activity level, joint status and treatment preferences are considered when tailoring prophylaxis regimens to an individual.[6-8] Adherence to prophylaxis using standard half-life (SHL) FIX concentrates is challenging because their half-life necessitates frequent infusions (often at least twice-weekly dosing).[9,10] Extended half-life (EHL) products have been developed that are designed to decrease FIX clearance and improve bleed protection by allowing individuals to achieve higher trough levels with a decreased treatment burden (reduced frequency of infusion of up to once every 2 weeks).[9,10]

Recombinant FIX Fc fusion protein (rFIXFc) was the first approved EHL FIX therapy.[11] rFIXFc is indicated for on-demand treatment and control of bleeding episodes, perioperative management and routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with haemophilia B.[12] The safety and efficacy of individualized rFIXFc prophylaxis regimens for subjects with haemophilia B were demonstrated in two pivotal Phase 3 studies (B-LONG for adults and adolescents ≥12 years of age [NCT01027364]; Kids B-LONG for children <12 years of age [NCT01440946]) and an extension trial (B-YOND [NCT01425723]).[13-15] The combined results from these trials confirmed the long-term (up to 6.5 years) safety and efficacy of rFIXFc prophylaxis in previously treated subjects of all ages with severe haemophilia B. rFIXFc provided dosing flexibility that allowed treatment to be tailored to the individual subject, which is important for its potential to reduce the treatment burden, improve adherence to prophylaxis and provide greater levels of protection, leading to improved clinical outcomes. Median (interquartile range [IQR]) dosing interval for the individualized interval prophylaxis arm in B-YOND was 14 (10-14) days for adults/adolescents (n = 31) and 10 (10-11) days for paediatric subjects (n = 5). For these subjects, the median (IQR) overall annualized bleed rate (ABR) and spontaneous ABR were 1.9 (0.8-4.0) and 0.7 (0.2-1.9), respectively, for adults/adolescents, and 3.7 (3.5-5.2) and 0.7 (0.6-1.1), respectively, for paediatric subjects. Dosing interval compliance in B-YOND was 98% in subjects receiving prophylaxis regimens (individualized interval, weekly and modified).[14]

Although the Phase 3 data are robust and aspects of the B-YOND clinical trial approximated real-world clinical practice (eg individualized dosing and the option to switch treatment regimens), selection of subjects and controlled trial conditions limit the applicability of these findings to a wider population. Real-world data are required to assess the clinical utility of rFIXFc in a more comprehensive patient population and routine clinical practice. However, reports describing the real-world clinical application of rFIXFc are limited.[16,17] Therefore, a retrospective chart review was performed to further understand the clinical experience and outcomes associated with real-world treatment of haemophilia B with rFIXFc.

2 | MATERIALS AND METHODS

2.1 | Study design and patient population

This was a multicentre, retrospective chart review conducted at six haemophilia treatment centres across the United States. All patients with haemophilia B who had received rFIXFc for ≥6 months at the date of site initiation either for prophylaxis or on-demand treatment were identified from the date of rFIXFc approval by the United States Food and Drug Administration (FDA; 28 March 2014) to 6 months prior to the date of site initiation. At sites with fewer than 15 patients, all patients were screened for eligibility. At sites with more than 15 patients, selection priority was based on the duration of follow-up on rFIXFc. For outcomes to be attributable to rFIXFc, no more than 1 month of non-rFIXFc use out of 12 months must have occurred. Patients with other coagulation disorders or a positive FIX inhibitor titre at the time of rFIXFc initiation (or any time after initiation), or a patient who was deceased, were excluded. The study period for retrospective data abstraction was 12 months prior to rFIXFc initiation and until the date of site initiation. De-identified patient level data were transcribed onto anonymous electronic case report forms. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and all applicable local regulations. Investigators obtained ethics committee approval for the study protocol.

2.2 | Objective and endpoints

The primary objective was to understand the clinical characteristics and outcomes resulting from the real-world management of patients with haemophilia B being treated with rFIXFc. Endpoints included changes in the FIX therapy dosing interval, factor consumption, ABR (including overall, spontaneous and joint), patient adherence before and after rFIXFc initiation, reason for switching to rFIXFc and target joint outcomes.

TABLE 1 Patient characteristics[a]

	Aged <12 y (n = 13)	Aged 12-18 y (n = 12)	Aged >18 y (n = 39)	Total (N = 64)
Median (range) age, years[b]	6 (2-11)	16 (12-18)	42 (19-78)	22 (2-78)
Disease severity, n (%)				
Mild	3 (23)	1 (8)	5 (13)	9 (14)
Moderate	3 (23)	5 (42)	9 (23)	17 (27)
Severe	7 (54)	6 (50)	25 (64)	38 (59)
Race, n (%)				
White	13 (100)	10 (83)	27 (69)	50 (78)
Black	0 (0)	1 (8)	5 (13)	6 (9)
Asian	0 (0)	1 (8)	2 (5)	3 (5)
Other	0 (0)	0 (0)	1 (3)	1 (2)
Unknown	0 (0)	0 (0)	4 (10)	4 (6)
Genotype, n (%)				
Missense	10 (77)	7 (58)	14 (36)	31 (48)
Nonsense	2 (15)	2 (17)	4 (10)	8 (13)
Frameshift	0 (0)	1 (8)	0 (0)	1 (2)
Splice mutation	0 (0)	1 (8)	3 (8)	4 (6)
Small deletion	0 (0)	0 (0)	2 (5)	2 (3)
Partial gene deletion	0 (0)	0 (0)	1 (3)	1 (2)
Unknown	1 (8)	1 (8)	8 (21)	10 (16)
Other	0 (0)	1 (8)	10 (26)	11 (17)
Comorbidities, n (%)				
Haemophilic arthropathy	0 (0)	0 (0)	20 (51)	20 (31)
Hepatitis C	0 (0)	0 (0)	17 (44)	17 (27)
Pre-rFIXFc treatment regimen, n (%)				
On demand	6 (46)	6 (50)	17 (44)	29 (45)
Prophylaxis	6 (46)	6 (50)	22 (56)	34 (53)
Missing	1 (8)	0 (0)	0 (0)	1 (2)
End of chart review treatment regimen, n (%)				
On demand	4 (31)	3 (25)	3 (8)	10 (16)
Prophylaxis	9 (69)	9 (75)	36 (92)	54 (84)

Abbreviation: rFIXFc, recombinant factor IX Fc fusion protein.

[a]Percentages may not add up to 100 because of rounding.

[b]Age at rFIXFc initiation.

Adherence, including mention of non-compliance and percent infused vs expected, was collected from the patient's chart, pharmacy records or patient diary (if captured as part of routine clinical practice), and percent compliance (ie ≥90%, ≥80%, <80%) was based on pharmacy records or patient diaries. It was expected that target joint and target joint resolution were defined as per the Scientific and Standardization Committee (Appendix S1),[18] but application of these definitions ultimately was at the discretion of the individual healthcare provider. The availability of clinical endpoints of interest varied between sites.

Specific adverse events that were collected and recorded during rFIXFc therapy included hypersensitivity (including anaphylaxis), nephrotic syndrome and thrombosis/thromboembolism. Other adverse events were not collected in this chart review. Sites were instructed to follow their standard spontaneous postmarketing reporting procedures for all adverse events.

2.3 | ABRs

ABRs were estimated by using the number of bleeds reported at a visit adjusted by the duration of time elapsed from the prior visit in years. Because it is possible that the number of bleeds reported in the first visit after rFIXFc initiation could include bleeds prior to switching, the calculation of the number of bleeds on rFIXFc only included bleed

data from the first visit after rFIXFc initiation if the time from the previous visit to the date of switching or initiation was 1 month or less.

2.4 | Target joints

Target joints were estimated using the same method as for ABRs. Target joint data from the first visit after rFIXFc initiation were included only if the duration from the previous visit to the initiation of rFIXFc was 1 month or less.

2.5 | Statistical analysis

Descriptive statistics were used to summarize the results. Subgroup analysis was performed based on age, haemophilia B severity and treatment regimen (prophylaxis vs on demand). Changes in factor consumption and ABR were assessed using paired t tests or Wilcoxon's signed-rank tests.

3 | RESULTS

3.1 | Study population

A total of 64 eligible patients were included in this chart review (Table 1). Eligible patients had a median (range) age of 22 (2-78) years at rFIXFc initiation, of which 61% (39/64) were >18 years of age, 19% (12/64) were 12-18 years of age and 20% (13/64) were <12 years of age. Most patients (59% [38/64]) had severe haemophilia; 27% (17/64) and 14% (9/64) had moderate and mild haemophilia, respectively. Of the patients >18 years of age, 51% (20/39) had haemophilic arthropathy and 44% (17/39) had hepatitis C infection; these morbidities were absent in younger patients.

3.2 | Duration of treatment

The median (range) duration of follow-up for all patients receiving rFIXFc was 2.7 (0.5-5.0) years. To capture as much real-world data as possible, 7 patients were included in this analysis who received rFIXFc prior to market approval, given their participation in Kids B-LONG (n = 2)[13] or B-LONG (n = 5).[15] Some data included in the chart review were collected during the B-LONG, Kids B-LONG or B-YOND extension trial; however, most data collected for these patients were from after Phase 3 study termination.

3.3 | Treatment flow

Twenty-nine (45%) patients were receiving an on-demand factor replacement regimen prior to initiating rFIXFc (Table 1). At the end of the chart review period, 66% (19/29) of these patients had switched
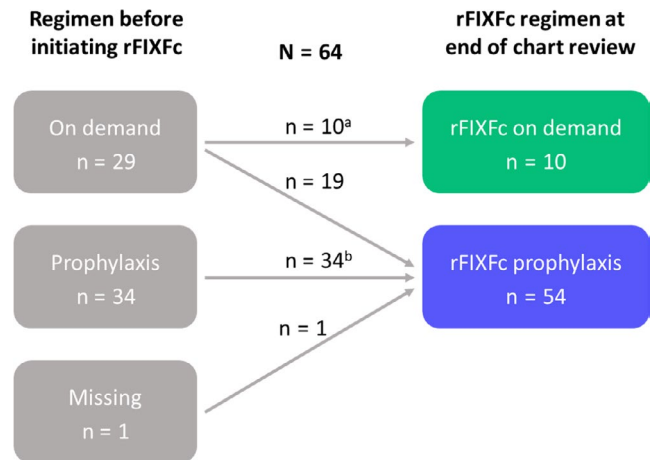

FIGURE 1 Patient treatment flow. rFIXFc, recombinant factor IX Fc fusion protein. [a]One patient who received on-demand treatment prior to initiation of rFIXFc and then continued to on-demand rFIXFc was missing detailed pre-rFIXFc therapy information. [b]One patient who received prophylaxis prior to initiation of rFIXFc and then continued to rFIXFc prophylaxis was missing pre-rFIXFc prophylaxis interval information [Colour figure can be viewed at wileyonlinelibrary.com]

to rFIXFc prophylaxis and the remaining 34% (10/29) continued receiving on-demand rFIXFc (Figure 1). Thirty-four (53%) patients were on prophylaxis prior to starting rFIXFc. At the end of the chart review period, all 34 patients continued rFIXFc prophylaxis. One additional patient with an unknown treatment regimen prior to starting rFIXFc was receiving prophylaxis at the end of the chart review period.

3.4 | Dosing interval on rFIXFc prophylaxis

Nineteen (of 29) patients switched from a pre-rFIXFc on-demand regimen to rFIXFc prophylaxis. rFIXFc prophylaxis was personalized to meet the needs of individual patients. At the start of rFIXFc prophylaxis, 14/19 (74%) patients were dosed once weekly, 2/19 (11%) patients were dosed every 10 days and 3/19 (16%) patients were dosed every 14 days (Appendix S1). Most patients (89%) maintained (14/19) or lengthened (3/19) their initial dosing interval on rFIXFc prophylaxis, while 11% (2/19) shortened it, through the end of the chart review period.

Most patients who were receiving prestudy FIX prophylaxis and switched to rFIXFc prophylaxis extended their dosing interval (Figure 2; Appendix S1). Thirty-two patients had a specified dosing interval prior to receiving rFIXFc prophylaxis. From the pre-rFIXFc regimen to the initial rFIXFc regimen, 26/32 (81%) patients lengthened their dosing interval (range, twice weekly to every 14 days) and 6/32 (19%) patients continued with the same dosing interval (range, once weekly to twice weekly) (Figure 3A). Fifty-three prophylaxis patients had a specified dosing interval at both the start of rFIXFc prophylaxis and at the end of the chart review period (Figure 3B). From the initial

FIGURE 2 Dosing intervals for patients receiving prophylaxis prior to and at the end of the chart review period. For patients who received prophylaxis prior to receiving rFIXFc (n = 32) and after starting rFIXFc (n = 53), and whose dosing interval was known. Two patients are not included in the pre-rFIXFc group, as pre-rFIXFc dosing interval was 'activity-based' for 1 patient and 'unknown' for 1 patient. One patient was not included in the rFIXFc (last dose) group as their last rFIXFc dosing interval was 'every 7 d during increased activity'. rFIXFc, recombinant factor IX Fc fusion protein [Colour figure can be viewed at wileyonlinelibrary.com]
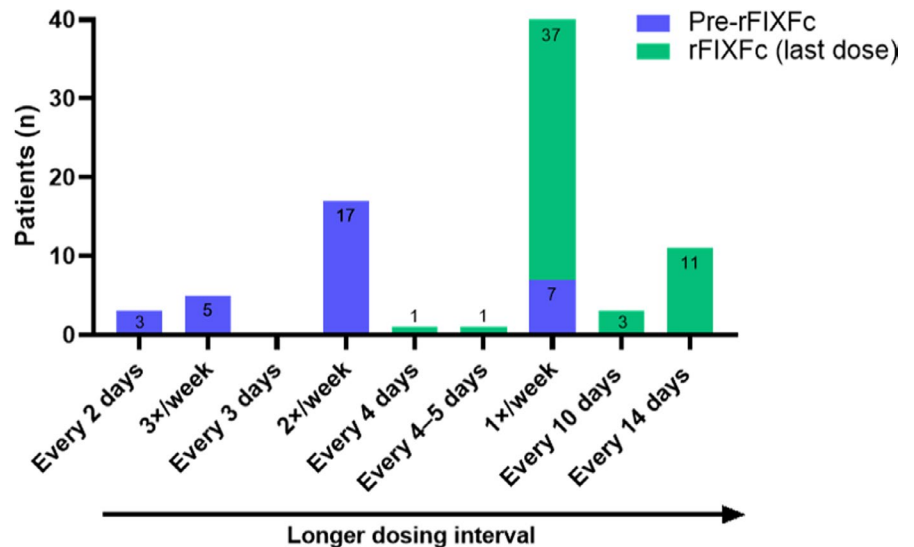
FIGURE 3 Relative dosing frequency for patients receiving rFIXFc prophylaxis during the chart review period. A, Relative change in dosing interval for patients receiving prophylaxis prior to the start of the chart review to the first dose of rFIXFc, by age and disease severity. B, Relative change in dosing interval from the first dose of rFIXFc to the last dose of rFIXFc in all patients receiving rFIXFc prophylaxis, by age and disease severity. Included patients received prophylaxis prior to receiving rFIXFc and after starting rFIXFc, and had a known dosing interval. rFIXFc, recombinant factor IX Fc fusion protein. [a]Two patients are not included, as pre-rFIXFc dosing interval was 'activity-based' for 1 patient and 'unknown' for 1 patient. [b]One patient was not included as their pre-rFIXFc dosing interval was 'unknown'. [c]One patient was not included as their last dosing interval was 'every 7 d during increased activity' [Colour figure can be viewed at wileyonlinelibrary.com]
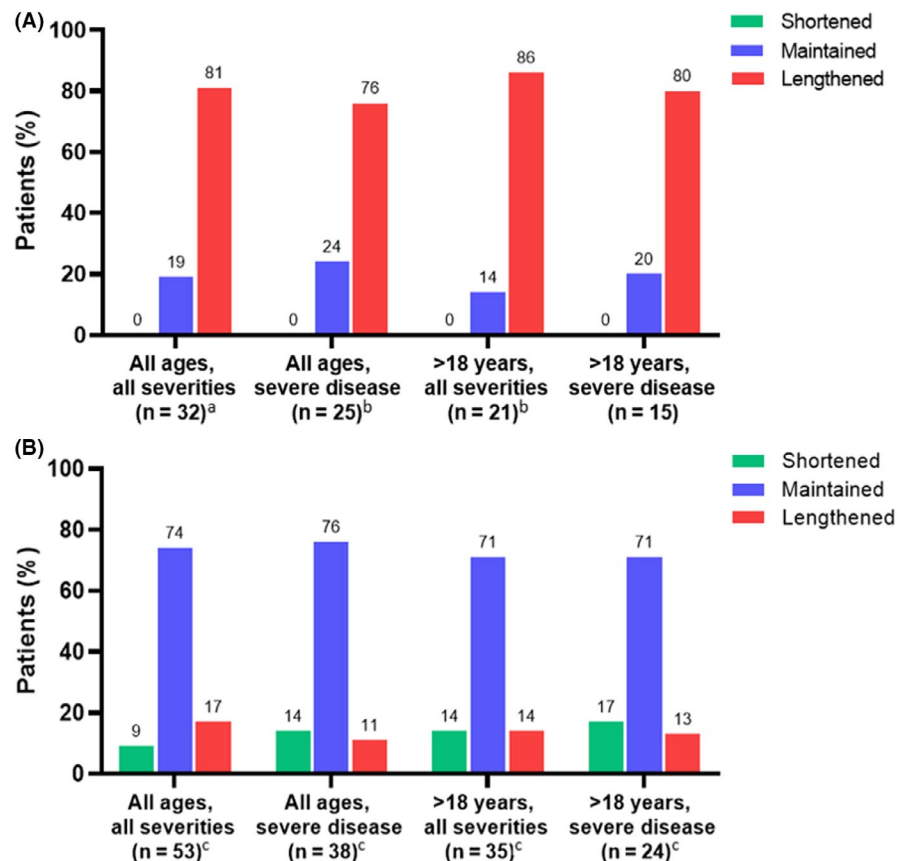
rFIXFc regimen, 9/53 (17%) patients lengthened their dosing interval (range, once weekly to every 14 days), 39/53 (74%) patients continued with the same dosing interval (range, once weekly to every 14 days), and 5/53 (9%) shortened the dosing interval (all once weekly).

3.5 | Factor consumption on rFIXFc prophylaxis

For patients receiving rFIXFc prophylaxis (n = 54), there was an approximately 50% lower weekly factor consumption across haemophilia phenotypes (severe, moderate and mild) compared with pre-rFIXFc prophylaxis regimens (n = 32) (Table 2). For patients receiving rFIXFc with available consumption data pre- and postswitch to rFIXFc, the median (IQR) change in weekly factor consumption was −44.0 (−114.0 to −22.0) IU/kg for patients with severe disease (n = 25) and −68.50 (−170.5 to −50.0) IU/kg for patients with moderate disease (n = 4).

For patients of all disease severities with consumption data at first and last dose on rFIXFc (n = 53), there was no change in the median total weekly factor consumption. At the end of the chart review

TABLE 2 Weekly factor consumption of patients on rFIXFc prophylaxis (N = 54)[a]

Median (IQR) weekly consumption, IU/kg	Haemophilia phenotype			
	Overall	Severe	Moderate	Mild
Pre-rFIXFc	116.0 (90.0, 189.0) n = 32	100.0 (80.0, 198.0) n = 25	116.0 (111.0, 242.0) n = 4	136.0 (105.0, 150.0) n = 3
At first rFIXFc infusion	50.0 (50.0, 70.0) n = 53	53.5 (50.0, 70.0) n = 38	55.0 (40.0, 100.0) n = 10	50.0 (45.0, 50.0) n = 5
At last rFIXFc infusion	52.0 (50.0, 76.0) n = 54	55.0 (50.0, 87.0) n = 38	57.0 (35.0, 60.0) n = 11	47.0 (40.0, 50.0) n = 5
Change from pre-rFIXFc to first rFIXFc infusion	−56.0 (−112.0, −27.5) n = 32 P < .0001	−44.0 (−114.0, −22.0) n = 25 P = .003	−68.5 (−170.5, −50.0) n = 4 P = .123	−86.0 (−100.0, −60.0) n = 3 P = .02
Change from first rFIXFc infusion to last rFIXFc infusion	0.0 (−7.0, 8.0) n = 53 P = .611	0.0 (−7.0, 8.0) n = 38 P = .956	0.0 (−40.0, 10.0) n = 10 P = .436	0.0 (−3.0, 0.0) n = 5 P = .800

Abbreviations: IQR, interquartile range; rFIXFc, recombinant factor IX Fc fusion protein.

[a]Number of patients with available consumption data pre- and postswitch to rFIXFc prophylaxis.

period, the median (IQR) total weekly factor consumption was 55 (50-87) IU/kg for patients with severe disease (n = 38) and 58.5 (35-60) IU/kg for patients with moderate disease (n = 10). The pattern of results was similar for all age groups.

3.6 | ABRs on rFIXFc prophylaxis

Overall ABRs numerically decreased for patients after switching to rFIXFc prophylaxis (Figure 4). For patients receiving rFIXFc prophylaxis with available bleed data pre-rFIXFc and overall while on rFIXFc, overall ABR decreased for both patients with severe (4.5-1.1 [n = 16]) and moderate disease (6.9-3.3 [n = 6]). From pre- to postswitch to rFIXFc, ABRs numerically decreased for patients receiving pre-rFIXFc on-demand treatment (n = 10) and for those receiving pre-rFIXFc prophylaxis (n = 13) (Figure 5). Overall ABRs while on rFIXFc prophylaxis were 1.2 for patients with severe disease (n = 34), 3.2 for patients with moderate disease (n = 10) and 1.5 for patients with mild disease (n = 5). For patients receiving on-demand rFIXFc, corresponding ABRs were 3.7 and 1.8 for moderate (n = 7) and mild (n = 3) disease, respectively.

3.7 | Joint health on rFIXFc prophylaxis

Prior to starting rFIXFc, 19 patients had a total of 53 target joints. One patient with severe haemophilia in the 12-18 years age group had one target joint, and 18 patients >18 years of age had 52 target joints. Of patients >18 years of age, 13 patients with severe haemophilia had a total of 40 target joints.

At the end of the chart review period, 17/53 (32%) target joints had resolved and 9/19 (47%) patients did not report a target joint. The target joint reported by the 1 patient in the 12-18 years age group was resolved. For the 18 patients >18 years of age, 16/52 (31%) of the target joints had resolved and 8/18 (44%) patients no longer had target joints, including 7/13 (54%) patients with severe haemophilia.

3.8 | Compliance and adherence

For patients with pre- and post-rFIXFc compliance data, compliance improved in 10/31 (32%) patients by the end of the chart review period. Treatment compliance remained stable in 20 (65%) patients and worsened in 1 patient. The compliance rate was 90%–100% for 93% and 91% of patients in the first and last year after initiation of rFIXFc, respectively. None of the 53 patients with adherence data had adherence issues after initiating rFIXFc prophylaxis.

3.9 | Reason for switching

The most common reason for switching to rFIXFc was to reduce the burden associated with therapy (44% selected this reason). Additional reasons included lack of efficacy with previous therapy, difficulty with venous access and adherence issues (Figure 6).

3.10 | Adverse events

One patient experienced an adverse event of hypersensitivity, which was not associated with inhibitor development.

4 | DISCUSSION

The results of this real-world study in patients with haemophilia B demonstrated that regardless of disease severity, following initiation of rFIXFc there were marked improvements in bleed control, reduced factor consumption, reduced frequency of infusions and maintained or improved adherence. Similar to the Phase 3 trials of rFIXFc, the results demonstrated that rFIXFc is efficacious across patients of all ages.

Standard half-life FIX therapies require frequent infusions by patients with severe haemophilia B, and sometimes, there is
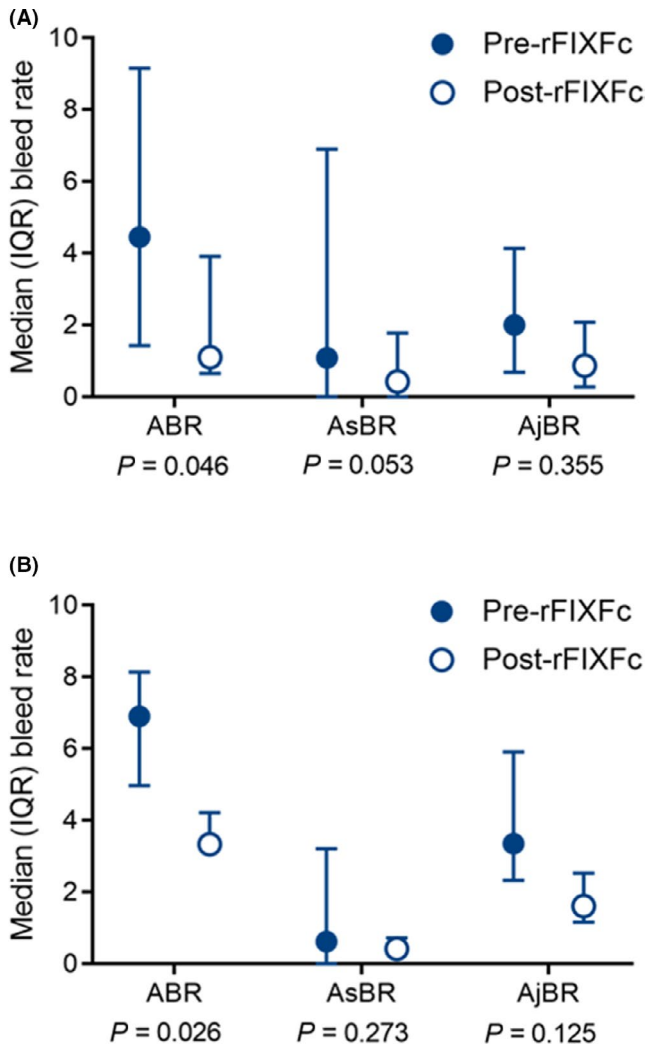
(A)

(B)

FIGURE 4 Median (IQR) bleed rates pre- and postswitch to rFIXFc prophylaxis, by disease severity. A, Patients with severe haemophilia (n = 16). B, Patients with moderate haemophilia (n = 6). Included patients had available ABR data pre- and postswitch to rFIXFc prophylaxis. Two patients with mild haemophilia are not included in the figure; the overall ABR of 1 patient decreased from 15.2 to 8.3, and the second patient decreased from 6.0 to 1.8. ABR, annualized bleed rate; AjBR, annualized joint bleed rate; AsBR, annualized spontaneous bleed rate; IQR, interquartile range; rFIXFc, recombinant factor IX Fc fusion protein [Colour figure can be viewed at wileyonlinelibrary.com]

uncertainty about the initial dosing interval when switching to an EHL. In this chart review, most patients lengthened the dosing interval when they started rFIXFc prophylaxis and then maintained their lengthened dosing interval through to the end of the chart review period. Importantly, rFIXFc can provide individualized dosing for patients by administering it with longer dosing intervals compared with SHL FIX products or with a similar dosing frequency to achieve higher trough levels, depending on patient preference.[11,15]

A retrospective analysis of aggregate Specialty Pharmacy Provider records from shortly after FDA approval of rFIXFc (May 2014 through March 2015) analysed real-world patient characteristics and treatment interval patterns in patients of all ages with
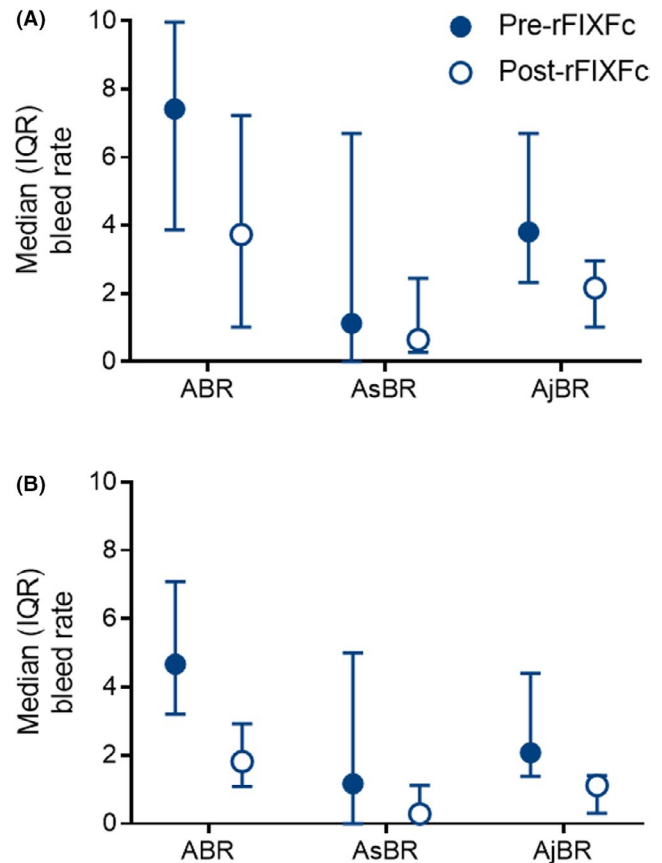
(A)

(B)

FIGURE 5 Median (IQR) bleed rates pre- and postswitch to rFIXFc prophylaxis, by preswitch regimen. A, On-demand to rFIXFc prophylaxis (n = 10). B, Prophylaxis to rFIXFc prophylaxis (n = 13). Included patients had available ABR data pre- and postswitch to rFIXFc prophylaxis. One patient is not included in this figure as they did not have data on the pre-rFIXFc treatment regimen. ABR, annualized bleed rate; AjBR, annualized joint bleed rate; AsBR, annualized spontaneous bleed rate; IQR, interquartile range; rFIXFc, recombinant factor IX Fc fusion protein [Colour figure can be viewed at wileyonlinelibrary.com]
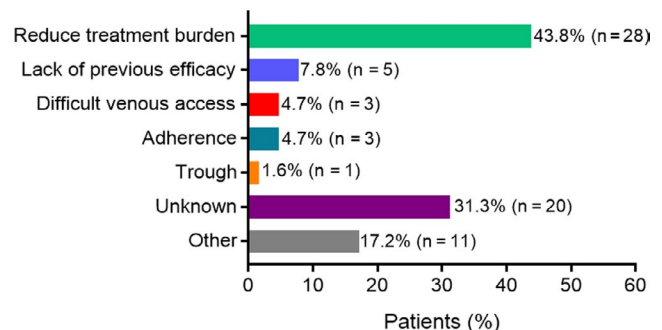
FIGURE 6 Reasons for switching to rFIXFc. Patients could select more than one reason for switch. rFIXFc, recombinant factor IX Fc fusion protein [Colour figure can be viewed at wileyonlinelibrary.com]

haemophilia B (n = 313) who received at least one shipment of rFIXFc for a prophylactic treatment.[17] After switching to rFIXFc, 93% of patients had a dosing frequency of once weekly or longer. Of

the patients that had previous recombinant FIX dispensing records, the most common recombinant FIX dosing frequency was twice weekly. These patients had fewer prophylactic infusions per week on rFIXFc; infusion frequency was reduced to once weekly in 78% of patients, and to every 10 days in 11% of patients.

The results from the current retrospective analysis are consistent with those of other studies. In patients with haemophilia B, Furlan et al[19] found that the relative importance of frequency of administration was 48%, while in the current analysis 44% of patients selected reduction of treatment burden. Patients with haemophilia B in the United States may experience reductions in FIX infusion frequency when they switch to rFIXFc, with conversion to a once-weekly infusion frequency as the most common treatment regimen.[19]

Data from the current study expand on the findings by Buckley et al[17] Weekly factor consumption was reduced by almost 50% for patients with severe haemophilia and previously on FIX prophylaxis, and bleed control improved after switching to rFIXFc prophylaxis for patients with all disease severities previously receiving FIX on-demand or prophylaxis treatment. Switching to rFIXFc improved compliance in approximately one-third of patients (10/31) with compliance data prior to and after switching to rFIXFc, and the remaining two-thirds of patients (20/31) maintained their pre-rFIXFc compliance.

Additionally, results from this study are consistent with observations for subjects receiving rFIXFc prophylactic regimens in the Phase 3 B-LONG[15,20] and Kids B-LONG[13] studies of rFIXFc, which also demonstrated low ABRs with rFIXFc dosed approximately once weekly in the majority of subjects. Furthermore, rFIXFc was being used in a broad patient population based on age range, for both the clinical trials and this real-world chart review.

As an EHL agent, rFIXFc offers opportunities for enhanced protection by administering with longer dosing intervals compared with conventional FIX products or administering with a similar dosing frequency to achieve higher trough levels. Less frequent dosing increases the cost effectiveness of EHL agents and may result in long-term cost savings through preserving joint health and reducing the need for joint replacement.[21] In developing countries where budget restraints can lead to suboptimal treatment,[22] EHL agents may be a feasible cost-effective treatment option.

4.1 | Limitations

These data are limited by the retrospective nature of the chart review and small sample sizes. Further, data abstraction may have been compromised by the availability, completeness and accuracy of medical charts, as well as the variability of the information collected by different observers (e.g. variation in the diagnosis of bleeding episodes between sites). In addition, data are presented using descriptive statistics; therefore, extrapolation of results to patients outside the study population may be limited.

During this study, we compared patients who received rFIXFc prophylaxis and on-demand treatment, the former of whom are generally considered to achieve better outcomes.[23] Furthermore, our analysis included patients with mild and moderate haemophilia B in addition to patients with severe disease; patients with mild disease do not usually require prophylactic treatment,[24] and inclusion may have introduced bias into the study. Finally, this study did not assess quality of life through a validated measure, such as the EuroQol-5D score.[25]

5 | CONCLUSION

This real-world study of rFIXFc demonstrates improved bleed control, reduced overall consumption and reduced frequency of infusions for patients with haemophilia B receiving prophylaxis treatment. rFIXFc use yielded longer dosing intervals and improved or maintained compliance, which may facilitate better management of disease. These results support the findings of the pivotal trials and add to the pool of evidence supporting rFIXFc for the treatment of haemophilia B.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and data set specifications. Patient level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com/.

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REFERENCES

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19:e1-e47.
2. National Hemophilia Foundation. MASAC document 241: MASAC recommendations concerning prophylaxis. https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/MASAC-Recommendation-Concerning-Prophylaxis. Accessed August 27, 2019.
3. Oladapo AO, Epstein JD, Williams E, Ito D, Gringeri A, Valentino LA. Health-related quality of life assessment in haemophilia patients on prophylaxis therapy: a systematic review of results from prospective clinical trials. *Haemophilia*. 2015;21:e344-e358.
4. Kulkarni R, Pasi J, Liesner R, et al. *Post hoc* analysis to evaluate the effect of recombinant factor IX Fc fusion protein (rFIXFc) prophylaxis in adults and adolescents with target joints and hemophilia B. *Haemophilia*. 2016;22:44.
5. Darby SC, Kan SW, Spooner RJ, et al. Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. *Blood*. 2007;110:815-825.
6. Oldenburg J. Optimal treatment strategies for hemophilia: Achievements and limitations of current prophylactic regimens. *Blood*. 2015;125:2038-2044.
7. Sørensen B, Auerswald G, Benson G, et al. Rationale for individualizing haemophilia care. *Blood Coagul Fibrinolysis*. 2015;26:849-857.
8. Carcao MD, Iorio A. Individualizing factor replacement therapy in severe hemophilia. *Semin Thromb Hemost*. 2015;41:864-871.
9. Castaman G. The benefits of prophylaxis in patients with hemophilia B. *Expert Rev Hematol*. 2018;11:673-683.
10. Mannucci PM. Miracle of haemophilia drugs: personal views about a few main players. *Haemophilia*. 2018;24:557-562.
11. Miguelino MG, Powell JS. Clinical utility and patient perspectives on the use of extended half-life rFIXFc in the management of hemophilia B. *Patient Prefer Adherence*. 2014;8:1073-1083.
12. Alprolix [prescribing information]. Waltham, MA: Bioverativ Therapeutics Inc.; 2019. https://www.alprolix.com/_assets/pdf/alprolix_prescribing-information.pdf. Accessed August 27, 2019.
13. Fischer K, Kulkarni R, Nolan B, et al. Recombinant factor IX Fc fusion protein in children with haemophilia B (Kids B-LONG): results from a multicentre, non-randomised phase 3 study. *Lancet Haematol*. 2017;4:e75-e82.
14. Pasi K, Fischer K, Ragni M, et al. Long-term safety and sustained efficacy for up to 5 years of treatment with recombinant factor IX Fc fusion protein in subjects with haemophilia B: results from the B-YOND extension study. *Haemophilia*. 2020. https://doi.org/10.1111/hae.14036
15. Powell JS, Pasi KJ, Ragni MV, et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. *N Engl J Med*. 2013;369:2313-2323.
16. Wang C, Young G. Clinical use of recombinant factor VII Fc and recombinant factor IX Fc in patients with haemophilia A and B. *Haemophilia*. 2018;24:414-419.
17. Buckley B, Hall E, Kendter J, Hagberg B. Real-world dosing and patient characteristics of rFIXFc in hemophilia B patients. *J Manag Care Spec Pharm*. 2015;21:S24.
18. Blanchette VS, Key NS, Ljung LR, et al. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12:1935-1939.
19. Furlan R, Krishnan S, Vietri J. Patient and parent preferences for characteristics of prophylactic treatment in hemophilia. *Patient Prefer Adherence*. 2015;9:1687-1694.
20. Powell J, Shapiro A, Ragni M, et al. Switching to recombinant factor IX Fc fusion protein prophylaxis results in fewer infusions, decreased factor IX consumption and lower bleeding rates. *Br J Haematol*. 2015;168:113-123.
21. Lambert T, Benson G, Dolan G, et al. Practical aspects of extended half-life products for the treatment of haemophilia. *Ther Adv Hematol*. 2018;9:295-308.
22. Poon MC, Lee A. Individualized prophylaxis for optimizing hemophilia care: can we apply this to both developed and developing nations? *Thromb J*. 2016;14:32.
23. Oak B, Nambiar S, Springs S, Eguale T. A comparison of prophylactic versus on-demand treatment regimens of coagulation factor VIII for bleeding and joint outcomes in hemophilia A patients without inhibitors: a systematic review and meta-analysis. *Value Health*. 2018;21:S247.
24. Benson G, Auerswald G, Dolan G, et al. Diagnosis and care of patients with mild haemophilia: practical recommendations for clinical management. *Blood Transfus*. 2018;16:535-544.
25. Carroll L, Benson G, Lambert J, Benmedjahed K, Zak M, Lee XY. Real-world utilities and health-related quality-of-life data in hemophilia patients in France and the United Kingdom. *Patient Prefer Adherence*. 2019;13:941-957.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.