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ORIGINAL ARTICLE

Real-world outcomes with recombinant factor IX Fc fusion protein (rFIXFc) prophylaxis: Longitudinal follow-up in a national adult cohort

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Abstract

Introduction: In 2017, all people with severe haemophilia B (PWSHB) in Ireland switched from standard half-life (SHL) recombinant FIX (rFIX) to rFIX Fc fusion protein (rFIXFc) prophylaxis.

Aims: To evaluate prophylaxis regimens, bleeding rates and factor usage for two years of rFIXFc prophylaxis in a real-world setting.

Methods: Data collected retrospectively from electronic diaries and medical records of PWSHB for a two-year period on rFIXFc prophylaxis were compared with paired baseline data on SHL rFIX treatment.

Results: 28 PWSHB (≥18 years) were enrolled, and at switchover 79% were receiving prophylaxis and 21% episodic treatment with SHL rFIX. At 24 months following switchover, all remained on rFIXFc prophylaxis with reduced infusion frequency; median dose per infusion once weekly (55 IU/kg, 20/28), every 10 days (63 IU/kg, 2/28) or every 14 days (98 IU/kg, 6/28). Median annualised bleed rate improved significantly on rFIXFc prophylaxis (2.0 versus 3.3 on SHL FIX) ($p = 0.01$). Median FIX trough level with once-weekly infusions was 0.09 IU/ml (0.06–0.14 IU/ml). Management of bleeding episodes was similar with rFIXFc and SHL rFIX; one infusion was sufficient to treat 74% and 77% of bleeds, respectively, with similar total median treatment per bleeding episode. Factor consumption reduced by 28% with rFIXFc prophylaxis (57 IU/kg/week, range 40–86 IU/kg/week) compared with SHL rFIX (79 IU/kg/week, range 44–210 IU/kg/week) ($p = 0.002$).

Conclusion: This study provides important insights into real-world experience of switching to rFIXFc prophylaxis in an adult population, demonstrating high rates of prophylaxis, with reduced infusion frequency, bleeding and FIX consumption.

KEYWORDS
extended half-life, Factor IX deficiency, haemophilia B, prophylaxis, rFIXFc

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1 | INTRODUCTION

Haemophilia B is a rare X-linked bleeding disorder resulting from a deficiency of clotting factor IX (FIX), with severe haemophilia B defined as FIX levels <1%.[1] Severe haemophilia is characterised by haemarthrosis, spontaneous and potentially life-threatening bleeds and in the longer term, progressive joint arthropathy resulting in mobility problems and chronic pain.[2] Haemophilia B has a reported prevalence of 3.8 per 100 000 males in a recent meta-analysis of national registries,[3] but the prevalence in Ireland is much higher at 8 per 100 000 males. The increased prevalence of haemophilia B in the Irish population is likely the result of founder effect rather than an increased incidence of de novo FIX mutations.[4]

The current standard of care for people with severe haemophilia B (PWSHB) is regular prophylaxis with recombinant factor IX (rFIX) to prevent bleeding, maintain joint health and optimise outcomes.[5-7] Prophylaxis is defined as regular treatment (intention to treat for 52 weeks of the year) with intravenous injection of factor concentrate to prevent bleeding.[1] Prophylaxis with standard half-life (SHL) clotting factor concentrates (CFC) requires frequent intravenous infusion, usually self-administered twice or three times weekly, resulting in a considerable treatment burden and therefore, may not be feasible for all patients. These barriers can result in some people with severe haemophilia being unable to access prophylaxis.[8] The development of extended half-life (EHL) products with longer terminal half-life and reduced clearance has permitted reduced frequency of administration and may improve rates of prophylaxis and adherence.[9-11]

In 2017, following a national tender process, all PWSHB in Ireland switched from SHL rFIX to rFIXFc prophylaxis. rFIXFc is a recombinant monomeric fusion protein composed of a single molecule of FIX covalently fused to the human IgG_1 Fc domain, which binds to the neonatal Fc receptor delaying lysosomal degradation and extending the $t_{1/2}$ of FIX.[12,13] Clinical trials have demonstrated safety and efficacy of rFIXFc in paediatric, adolescent and adult subjects,[9,13-15] but there is a need to evaluate if these outcomes can be replicated in the 'real-world' setting.

A survey of early experiences with EHL products in European haemophilia treatment centres reported increasing utilisation of EHL products, with reduced infusion frequency and varying trough levels of 1–10% with EHL-FIX.[16] Initial real-world data have been published on clinical experience of rFIXFc prophylaxis usage. Once-weekly rFIXFc prophylaxis (dose 50 IU/kg) was associated with an annualised bleeding rate (ABR) of 2, and 46% participants reported an ABR of 0.[17] The use of lower weekly doses of rFIXFc prophylaxis (30 IU/kg) in a small cohort of PWSHB has reported median trough levels of 0.04 IU/ml and ABR of 4.[18] Treatment with EHL-FIX products has also demonstrated nearly 50% reduction in factor consumption compared with SHL factors.[19,20]

This study evaluates the real-world experience of transitioning an unselected, complete cohort of PWSHB (≥18 years) from conventional SHL rFIX treatment to rFIXFc prophylaxis in an adult European haemophilia comprehensive care centre. We report prophylaxis regimens, bleeding rates, management of bleeding episodes and factor usage with rFIXFc in an Irish adult male cohort of PWSHB, who all received rFIXFc prophylaxis for a two-year period from 2017 to 2019.

2 | METHODS

This study was approved by the institutional ethics committee and the local research and innovation centre. Male patients with severe factor IX deficiency (FIX levels <0.01 IU/ml) ≥18 years who switched to prophylaxis with rFIXFc from SHL rFIX were identified from the National Haemophilia Electronic Health Record (EHR) (indici™, Valentia Technologies Limited, 9 Exchange Place, IFSC) and invited to participate. Following informed written consent, a retrospective review of EHR, paper medical records and patient electronic diaries was undertaken. An electronic database was designed with the following data fields: age, weight, height, haemophilia diagnosis, previous treatment and dosing regimen, current dosing regimen, factor usage, bleeding events and management of bleeding events. Data regarding CFC use and bleeding were collected primarily from patient electronic diaries (mpro5Hx™, Crimson Tide Ltd.,), where bleeding events and self-administered home treatment are patient-recorded using a haemophilia-specific smartphone application. Further data were collected from clinic letters, and hospital electronic and paper records, particularly useful in capturing data for patients who had been admitted to hospital for management of a bleed. Data were collected retrospectively for a four-year period for all patients, including the two-year period before switching from SHL rFIX treatment to determine the patients' baseline and the two-year period of rFIXFc prophylaxis post-switchover.

Bleeds were primarily patient-reported and patient managed. A bleed in the same location was recorded as a new bleed if it occurred >72 h after stopping treatment for the original bleed.[1] The ABR was calculated based on data for two years on SHL rFIX treatment prior to switchover to determine baseline ABR, and for year 1 and year 2 of rFIXFc prophylaxis. Where there were discrepancies between patient electronic diaries and clinic letters outlining the number of bleeds, the higher number was used to avoid under-reporting. The ABR for patients treated with episodic treatment was calculated for the period the patient was receiving that treatment. When a bleeding event resulted in an intervention (e.g., rectal bleeding investigated by endoscopy), the amount of CFC required to treat that bleed was calculated to the time of procedure, and not in the post-procedure period. FIX:C trough levels were measured immediately prior to administration of the next prophylaxis infusion the patient was due to receive. CFC usage figures for SHL rFIX and rFIXFc are based on IU dispensed to the patient for home self-administration in a one-year period for both SHL rFIX (2016) and rFIXFc (2018). Descriptive statistics are used to present the results. Changes in bleeding rates and factor consumption were assessed using the paired *t* test.

3 | RESULTS

3.1 | Study population

31 adult males (≥18 years) with severe haemophilia B were eligible for inclusion at time of study initiation. 29 participants were enrolled, with final analysis performed on 28 participants, representing 90% of the Irish adult population with severe haemophilia B. Participants had a median age of 44 years (range 18–70 years) and no active inhibitor (Table 1).

3.2 | Treatment regimens and dosing intervals

All participants had received long-term treatment with SHL rFIX. At time of switchover to rFIXFc, 21% (6/28) patients were receiving episodic treatment and 79% (22/28) were on prophylaxis with SHL rFIX (Figure 1). Of the 22 patients on prophylaxis, 19 (86%) received SHL rFIX infusions twice weekly (median dose per infusion 38 IU/kg, range 26–92 IU/kg), 2 (9%) infused treatment three times per week (dose per infusion 38 IU/kg and 65 IU/kg) and one patient (5%) administered prophylaxis once weekly (dose per infusion 62 IU/kg). In the two-year period prior to switching to rFIXFc prophylaxis, two patients received a combination of prophylaxis and episodic treatment, with one patient receiving episodic treatment for 16/24 months and the other for 12/24 months.

After switching to rFIXFc, all patients, including those with challenging venous access, were able to receive regular prophylaxis, representing a 21% increase in prophylaxis rates. Initially, prophylaxis dosing frequency was every seven days (22 patients, median dose per infusion 55 IU/kg), every ten days (one patient, dose per infusion 93 IU/kg) or every fourteen days (four patients, median dose per infusion 98 IU/kg), with one patient receiving prophylaxis twice weekly (Figure 1). Following three months of rFIXFc prophylaxis, median FIX:C trough levels were measured. Median FIX:C trough levels were 0.09 IU/ml (range 0.06–0.14 IU/ml, *n* = 14) with once-weekly rFIXFc infusions and 0.06 IU/ml (range 0.04–0.07 IU/ml, *n* = 4) with one infusion every fourteen days. Data were not available for the patient receiving prophylaxis every ten days. Median FIX:C trough with SHL rFIX, measured pre-switchover, representing a 72- or 96-h level, was 0.05 IU/ml (range 0.03–0.11 IU/ml, *n* = 20). Comparisons between individual FIX:C trough levels with rFIXFc and SHL rFIX demonstrate that most patients achieved a higher trough, with reduced infusions, with rFIXFc prophylaxis (Figure 2). After 24 months of treatment with rFIXFc, all patients remained on prophylaxis, with four (14%) patients increasing the prophylaxis interval (Table 2).

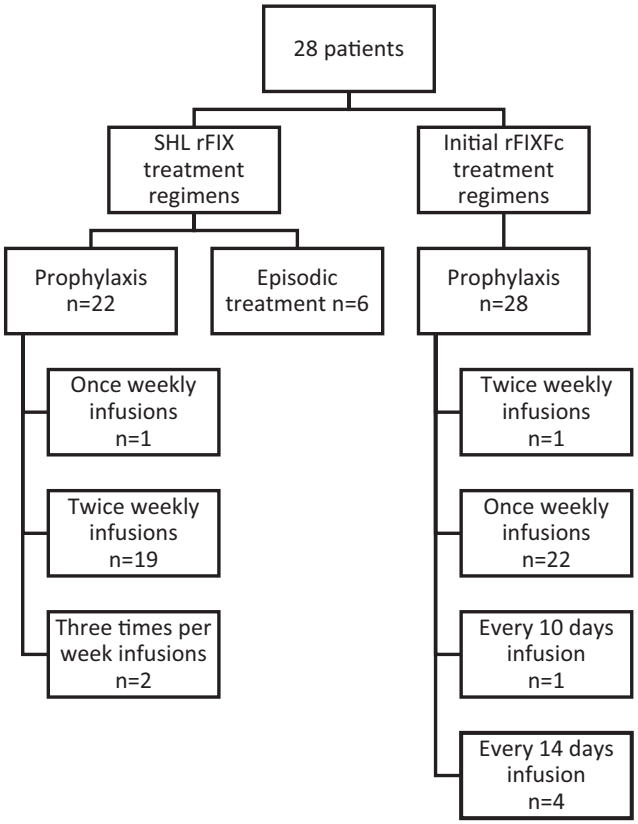

FIGURE 1 SHL rFIX treatment regimens at time of switchover and initial rFIXFc treatment regimens

TABLE 1 Baseline characteristics of study participants

	Median	Range	N=
Age (years)	44	18–70	28
Weight (kg)	83	56–120	28
Height (m)	1.75	1.63–1.84	25[a]
BMI (kg/m^2)	27	18–40	25[a]
Baseline factor IX level (IU/ml)	<0.01	<0.01	28
History of factor IX inhibitor			1
Baseline HJHS	25	0–53	28

Abbreviations: BMI, body mass index; HJHS, haemophilia joint health score.

[a]Data not available for three participants.

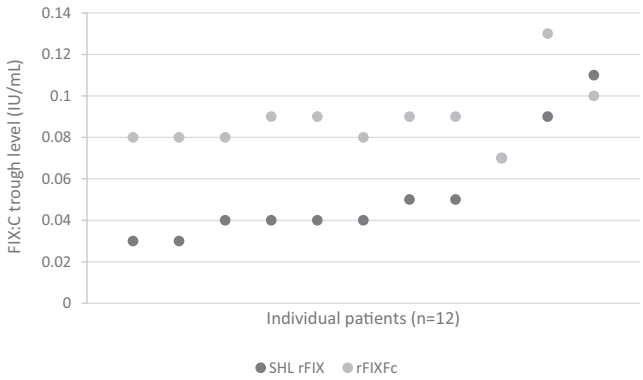

FIGURE 2 Individual FIX:C trough levels with SHL rFIX compared with paired FIX:C trough levels with rFIXFc prophylaxis (*n* = 12)

TABLE 2 Frequency and dose of rFIXFc prophylaxis at switchover and at 24 months post-switchover

	Initial rFIXFc prophylaxis regimen (*n*=)	Initial rFIXFc regimen dosing (IU/kg)	24-month rFIXFc regimen (*n*=)	24-month rFIXFc regimen dosing (IU/kg)
Prophylaxis every 7 days	22[a]	55 (range 49–63)	20	55 (range 49–88)
Prophylaxis every 10 days	1	93	2	63 (range 49–78)
Prophylaxis every 14 days	4	98 (range 92–100)	6	98 (range 92–108)

[a]At switchover, one patient received twice-weekly prophylaxis, 34 IU/kg on a Friday and 22 IU/kg on a Tuesday.

A personalised approach to prophylaxis frequency was adopted, with infusion frequency altered based on bleed control, venous access issues and patient preference. The majority of patients halved the number of infusions (52 vs 104 infusions) per annum with rFIXFc prophylaxis compared to prophylaxis with SHL rFIX.

3.3 | Efficacy

3.3.1 | Annualised Bleeding Rates

Bleed history was collected for two years on SHL rFIX prior to switching and for two years on rFIXFc prophylaxis (Table 3). The median ABR and annualised joint bleeding rate (AJBR) with SHL rFIX treatment were 3.3 (range 0–23) and 1.5 (range 0–20.5). There was a significant reduction in ABR with rFIXFc prophylaxis (p = 0.01) (Figure 3A). Following twelve months of rFIXFc prophylaxis, there was a 39% reduction in median ABR to 2.0 (range 0–11), and this improved ABR was maintained during the second year of prophylaxis (ABR 2.0, range 0–17). There was also a significant reduction in the mean AJBR (3.9 to 2.1, p = 0.05), with paired data available for 23 participants (Figure 3B). Those who received episodic treatment with SHL rFIX (ABR 6.5, range 1–39 and AJBR 6.3, range 0–34) showed a 69% reduction in bleeding rates after switching to prophylaxis with rFIXFc (ABR 2.0, range 0–7 and AJBR 1.5, range 0–2.5) (Figure 3C). With rFIXFc prophylaxis, 64% had an ABR ≤2 vs 36% during SHL rFIX treatment. There was also an increase in those who experienced no bleeding episodes on rFIXFc prophylaxis, 18% and 39% recording ABR and AJBR of zero, respectively, during the second year of rFIXFc prophylaxis, compared with 4% and 22% recording ABR and AJBR of zero with SHL rFIX treatment. Target joints (≥3 bleeds in a six-month period) were uncommon, with two patients reporting target joints prior to switchover and one patient with a target joint following two years of rFIXFc prophylaxis.

Intra-patient ABR analysis between year 1 and year 2 of rFIXFc prophylaxis, and SHL rFIX prophylaxis was performed (Figure 4). Two patients (patients 9 and 11) had a markedly higher ABR during the first year of rFIXFc prophylaxis but improved in the second year of rFIXFc prophylaxis, without a change in prophylaxis. Interestingly, most patients with ABRs in the upper quartile with SHL rFIX prophylaxis (patients 17–21) continued to have high reported ABRs during the first year of rFIXFc prophylaxis, despite FIX trough levels of 0.07–0.13 IU/ml. However, all but two (patients 19 and 20) demonstrated an improved ABR during the second year of rFIXFc prophylaxis compared with ABR with SHL rFIX.

TABLE 3 Annualised bleeding rate (ABR) and annualised joint bleeding rate (AJBR) with SHL rFIX and rFIXFc

	Median ABR (Range)	ABR=0	Median AJBR (Range)	AJBR=0
SHL rFIX treatment groups				
Prophylaxis	3.5 (0–17) *n* = 23[a]	1 (4%) *n* = 23	1.8 (0–13) *n* = 20	4 (20%) *n* = 20
Episodic treatment	6.5 (1–39) *n* = 7[a]	0 (0%) *n* = 7	6.3 (0–34) *n* = 4	1 (25%) *n* = 4
Combined prophylaxis and episodic treatment	3.3 (0–23) *n* = 28[a]	1 (4%) *n* = 28	1.5 (0–20.5) *n* = 23[b]	5 (22%) *n* = 23
rFIXFc prophylaxis				
0–12 months	2.0 (0–11 *n* = 28	4 (14%) *n* = 28	2.0 (0–8) *n* = 28	9 (32%) *n* = 28
12–24 months	2.0 (0–17) *n* = 28	5 (18%) *n* = 28	1.0 (0–11) *n* = 28	11 (39%) *n* = 28
Combined results of 24 months	1.8 (0–13.5) *n* = 28	1 (4%) *n* = 28	1.5 (0–7.5) *n* = 28	6 (21%) N = 28

[a]2 patients treated episodically and with prophylaxis for differing time periods in the two years prior to switchover.; [b]AJBR data with SHL rFIX not available for five participants.

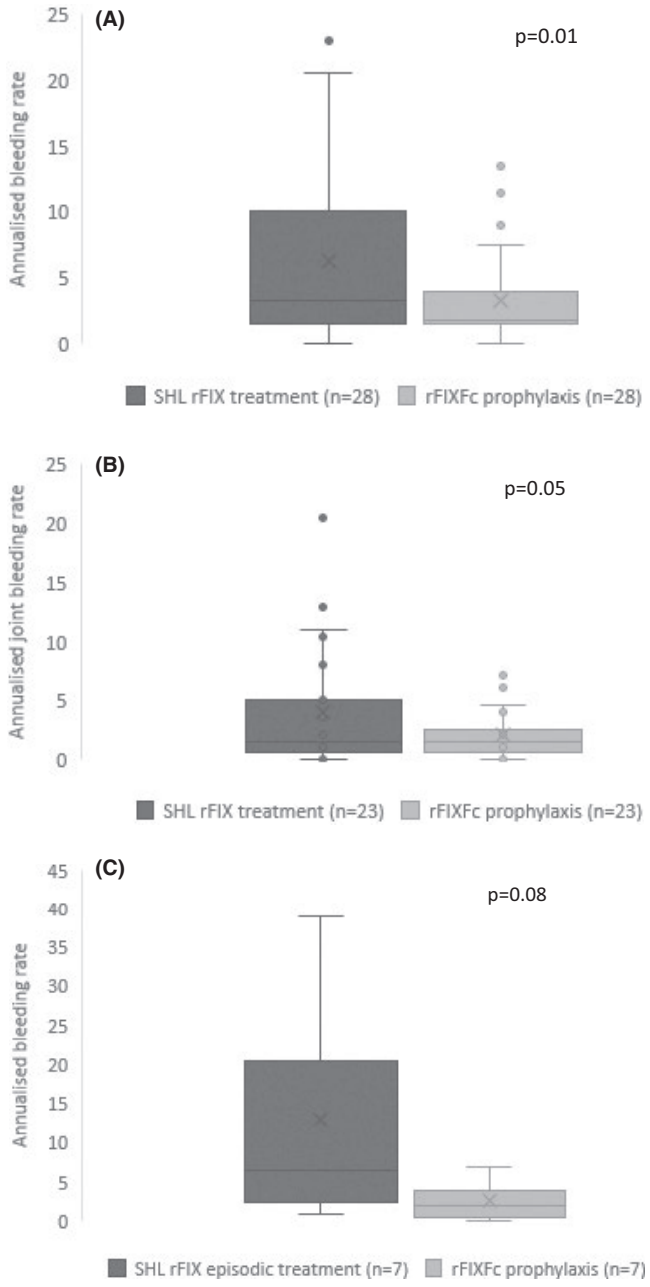

FIGURE 3 (A) Annualised bleeding rates with SHL rFIX (episodic treatment and prophylaxis) and two years of rFIXFc prophylaxis. (B) Annualised joint bleeding rates with SHL rFIX (episodic treatment and prophylaxis) and rFIXFc prophylaxis. (Paired data not available for five participants, n = 23). (c) Annualised bleeding rates with SHL rFIX episodic treatment and rFIXFc prophylaxis

3.3.2 | Management of bleeding episodes

A total of 185 bleeds were recorded for patients on rFIXFc prophylaxis and 348 bleeds recorded on treatment with SHL rFIX. The ankle and knee were the commonest sites of bleeding events. Data on management of bleeding episodes are available for 95% of bleeds on rFIXFc prophylaxis and 77% of bleeds on SHL rFIX. One infusion with rFIXFc was sufficient to treat 74% of bleeds and 90% resolved with one or two infusions, with similar findings for SHL rFIX; 77% and 89% of bleeding episodes required one, and one or two infusions for resolution, respectively. The median first dose administered to treat a bleeding episode with rFIXFc was 59 IU/kg (range 19–120 IU/kg) and with SHL rFIX was 66 IU/kg (range 25–139 IU/kg). The total median treatment per bleed was 74 IU/kg (range 19–909 IU/kg), median duration of 1 day (range 1–20 days) with rFIXFc and 72 IU/kg (range 25–1084 IU/kg) and median duration of 1 day (range 1–14 days) with SHL rFIX.

3.4 | Factor consumption

Annual SHL rFIX and rFIXFc factor usage were compared in patients who had received prophylaxis for the complete two-year period prior to switching to rFIXFc prophylaxis (Figure 5). The median rFIXFc consumption was 57 IU/kg/week (range 40–86 IU/kg/week), representing a 28% reduction compared with SHL rFIX prophylaxis of 79 IU/kg/week (range 44–210 IU/kg/week) (p = 0.002).

4 | DISCUSSION

This study demonstrates that rFIXFc prophylaxis in an unselected Irish cohort of PWSHB (≥ 18 years) resulted in higher rates of prophylaxis, reduced numbers of bleeding episodes with extended dosing intervals and reduced infusions, as well as lower factor consumption.

Our study reports a significant reduction in ABR with rFIXFc prophylaxis compared with SHL rFIX treatment (ABR 2.0 vs ABR 3.3) and is similar to that reported in the pivotal clinical trial, ABR 3.0 for the dose-adjusted prophylaxis group and ABR 1.4 for the interval-adjusted prophylaxis group.[9] Similar ABRs have been reported in other real-world studies.[17,18,20] This improvement is multifactorial, influenced by higher trough levels achieved with rFIXFc prophylaxis and more PWSHB able to achieve effective prophylaxis. The longer prophylaxis intervals possible with rFIXFc enabled patients to consider prophylaxis who were previously only able to access episodic treatment with SHL rFIX, primarily due to poor venous access, fulfilling one of the expectations of EHL products.[16,21] All participants were still on prophylaxis at the end of the study, with the majority of patients halving the number of required prophylaxis infusions. The introduction of rFIXFc also provided the impetus for patient re-engagement with the comprehensive care centre. This increased patient interaction and education at the time of changing treatment may also have contributed to the improved ABR reported in this study.

The ultimate goal of haemophilia care is debated, but most agree that functional cure and health equity should be the aim, including freedom from spontaneous bleeds, preservation of joint health and a lifestyle unrestricted by haemophilia.[22] In this study, 64% of participants had ABR ≤2 with rFIXFc prophylaxis, with 39% reporting no joint bleeds and 18% no bleeding events during the second year of rFIXFc prophylaxis. Given the FIX trough levels achieved in this study (median FIX:C 0.08 IU/ml, measured following three months

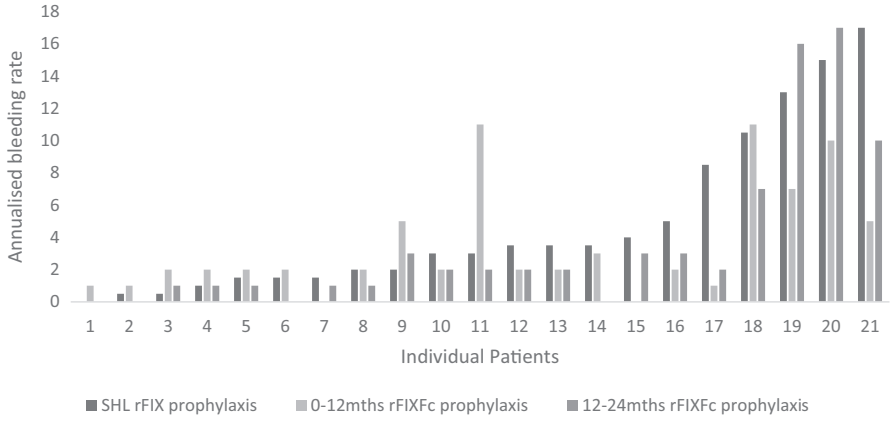

FIGURE 4 Intra-patient comparison of annualised bleeding rates with SHL rFIX compared with 0–12 months and 12–24 months of rFIXFc prophylaxis for patients treated with only prophylaxis

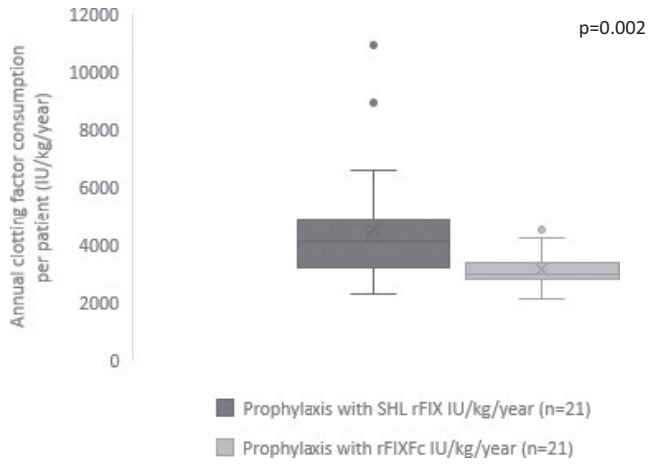

FIGURE 5 Comparison of annual SHL rFIX and rFIXFc prophylaxis factor usage

of prophylaxis), this may appear lower than anticipated. Early real-world studies have reported zero bleeds in 46% [17] and 63% (primarily paediatric population) [19] receiving rFIXFc prophylaxis. However, these studies had shorter follow-up times which may have resulted in a higher proportion of zero bleeds. Furthermore, bleeds in our study were not objectively confirmed and it is probable, given the recognised difficulty of differentiating between haemarthrosis and haemophilic arthropathy,[23] that some treated bleeds represented arthropathy rather than true bleeding. ABRs reported in this study are, however, comparable to rates reported in clinical trials with rFIX [24,25] and rFIXFc.[9,14]

Intra-patient comparisons of ABR on SHL rFIX prophylaxis and rFIXFc prophylaxis offer interesting insights into transitioning to a new haemophilia treatment. Many patients with high ABR on SHL rFIX prophylaxis demonstrated a similar pattern of high ABRs with rFIXFc prophylaxis. There are several reasons why PWSHB may have high rates of bleeding despite apparent adequate prophylaxis; poor adherence to prescribed prophylaxis, challenges in differentiating between haemarthrosis and haemophilic arthropathy and change in behaviour secondary to knowledge of higher trough levels (eg participating in higher risk activities). It has been reported that a subset of patients have demonstrated suboptimal responses with other extended half-life FIX concentrates,[26] but there has been no evidence to date to suggest this is a concern with rFIXFc. In this study, despite fluctuations in ABR, particularly among those with higher ABRs, no patient had a sustained increase in reported bleeding events after switchover to rFIXFc. Most patients in this study with high ABRs did not have an escalation in dose or frequency of rFIXFc prophylaxis. Clinically, it was felt that many treated bleeding events represented pain related to haemophilic arthropathy rather than an active bleed. Optimising patient education and adherence to already prescribed prophylaxis played an important role in managing patients with reported high ABRs.

Overall, rFIXFc prophylaxis factor consumption was significantly reduced (57 IU/kg/week) compared with SHL rFIX (79 IU/kg/week). Other real-world studies have demonstrated a reduction in factor consumption with rFIXFc prophylaxis.[17,19,20] This study also demonstrated that rFIXFc was effective in the management of bleeds in the acute setting. One or two infusions of rFIXFc resolved 90% of acute bleeds, which is similar to that reported in the phase 3 clinical trial where 97% of bleeding episodes resolved with one or two infusions.[9]

This study is notable for the inclusion of a national cohort of adult patients following an en-masse switch of all Irish PWSHB and a full two-year data set before and after switching, with paired, intra-individual comparison to minimise any effect of reporting bias. In addition, patient bleeding outcomes and factor usage were primarily electronically reported via a haemophilia-specific smartphone diary, with data recorded in real time by the patient. However, this study has some limitations, including retrospective data collection, the lack of objective confirmation of bleeding events and lack of data on the cause of bleeding, i.e. whether spontaneous or traumatic. The fluctuation of ABRs over time, as illustrated in this study, demonstrates the importance of longitudinal real-world data. Furthermore, the results are representative of real-world haemophilia care in a high resource country and consistent with previously published clinical trials and real-world evidence. Real-world outcomes from Irish children with severe haemophilia B who have switched to prophylaxis with rFIXFc would augment this study. Clinical trial data in paediatric cohorts [14,15,19] have demonstrated efficacy and safety, but more data are needed to support this in the real-world setting.

5 | CONCLUSION

This retrospective cohort study analysing the first two years of rFIXFc prophylaxis is real-world evidence that prophylaxis is feasible in a high proportion of unselected PWSHB and facilitates a switch from episodic treatment in people with challenging venous access. Prophylaxis with rFIXFc results in a reduction in bleeding episodes despite reduced infusion frequency and overall lower FIX concentrate consumption. In a rare disease such as haemophilia B, reporting of real-world outcomes is important, particularly as these novel treatments become more widely used. Continued longitudinal follow-up of prophylaxis outcomes, including patient-reported outcomes and health-related quality of life data, will provide further valuable information to allow clinicians and PWSHB to make informed decisions about switching to rFIXFc prophylaxis.

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AUTHOR CONTRIBUTIONS

Contribution: M.O'D and N.M.O'C designed the study. M.O'D was responsible for collection of the data. M.O'D, N.M.O'C, E.Q. and C.B. were responsible for data analysis and interpretation. M.O'D wrote the manuscript, and all authors were involved in reviewing and revising the manuscript, with all authors granting final approval for the manuscript.

DISCLOSURES

This investigator-sponsored study was supported by a research grant from Sobi. M.O'D has received research support from Sobi. N.M.O'C has received research support/PI from Freeline, Sobi, Takeda and Uniqure and has received speaker's fees from Bayer, Bristol-Myers Squibb, Novo Nordisk, Pfizer, Roche and Sobi. She has also served on the scientific advisory board for Bristol-Myers Squibb, Freeline, Pfizer, Roche, Sobi, Takeda and Uniqure. J.S.O'D has served on the speaker's bureau for Baxter, Bayer, Sobi, Novo Nordisk, Boehringer Ingelheim, Leo Pharma, Takeda and Octapharma. He has also served on the advisory boards of Baxter, Bayer, Octapharma CSL Behring, Daiichi Sankyo, Sobi, Boehringer Ingelheim, Takeda and Pfizer. J.S.O.D has received research grant funding awards from Baxter, Bayer, Pfizer, Shire (now part of Takeda), Takeda, 3 M and Novo Nordisk.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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