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ORIGINAL ARTICLE

Recombinant factor IX-Fc fusion protein in severe hemophilia B: Patient-reported outcomes and health-related quality of life

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Abstract

Introduction: In 2017, all people with severe hemophilia B in Ireland switched to recombinant factor IX Fc fusion protein concentrate (rFIXFc) prophylaxis. Patient-reported outcomes (PROs) and health-related quality of life (HRQoL) are important to evaluate with new treatments.

Aims: To assess HRQoL in people with severe hemophilia B and their experience after switching to rFIXFc prophylaxis.

Methods: Participants completed a Patient Reported Outcomes Burden and Experience (PROBE) questionnaire on initiation and following two years of rFIXFc prophylaxis. The PROBE questionnaire has four domains: demographics, general health, haemophilia-specific, and European Quality of Life 5-Dimensions (EQ-5D-5L) questionnaire.

Results: Twenty-three participants completed the questionnaire at both time points. The number of activities where chronic pain occurred and interfered with the activity was reduced by 25% and 33%, respectively ($P < .001$), following two years of rFIXFc prophylaxis. There was a 9% decrease in chronic pain during the second year of rFIXFc prophylaxis compared to baseline, but the rate remained high, at 74%. A 25% reduction in the number of affected activities of daily living (ADLs) was reported following 2 years of rFIXFc prophylaxis ($P = .007$). The most common health problems were arthritis, hypertension, anxiety/depression, and gingivitis. The median EQ-5D-5L score was similar following two years of rFIXFc prophylaxis, 0.76 (range, −0.01 to 0.95), compared to 0.77 (range, 0.36-1) at baseline.

Conclusion: This study of real-world patient experience using PROs demonstrates a reduction in chronic pain and improvement in ADLs in participants after switching to rFIXFc prophylaxis. It provides important insights into patient-identified health care needs and living with severe hemophilia B.

KEYWORDS
extended half-life concentrate, hemophilia B, health-related quality of life, pain, patient-reported outcomes

Essentials

- Severe hemophilia B can affect many aspects of life beyond bleeding events.
- It is important to understand how new treatments for hemophilia B impact on quality of life.
- This study reports improved chronic pain and ADLs following 2 years of treatment with rFIXFc.
- No overall improvement in quality of life was evident.

1 | INTRODUCTION

Hemophilia B is a rare congenital bleeding disorder resulting in bleeding secondary to reduced or absent levels of clotting factor IX (FIX). People with severe hemophilia B (FIX levels <0.01 IU/mL) have hemophilia-specific comorbidities including spontaneous bleeding and joint problems.[1] These comorbidities impact health-related quality of life (HRQoL) by causing pain, mobility problems, and difficulties with activities of daily living (ADLs), and correlate with severity of hemophilia.[2] Hemophilia B remains a lifelong condition, although ongoing clinical gene therapy trials suggest a functional cure may be attainable in the future.[3]

The current standard of care for people with severe hemophilia B is regular infusions of FIX to prevent spontaneous bleeding and protect against the development of hemophilic arthropathy.[4] The availability of extended half-life (EHL) FIX concentrates has expanded the treatment options available to people with hemophilia B.[5-7] Meaningful measurement of clinically relevant outcomes such as bleeding rates and joint health remain important, and a wide variety of tools and methods exist to report these outcome measures.[8] However, as hemophilia treatments become more effective, it is no longer possible to distinguish between treatment options based on bleeding rates alone. Furthermore, direct comparison of trough levels achieved with different EHL FIX products is also misguided given their distinct individual pharmacokinetic properties, particularly regarding biodistribution.[5,9,10] Consequently, outcomes beyond traditional bleeding rates, trough levels, and joint health are also needed to aid physicians and people with hemophilia in choosing the optimum treatment. Patient-reported outcomes (PROs) are recognized as increasingly important to understand the patients' lived experience of their illness and treatments.[11,12]

One of the hopes with EHL FIX prophylaxis is that the reduced infusion frequency, along with achievement of higher trough levels, would translate to an improvement in HRQoL for people with severe hemophilia B.[13,14] In Ireland in 2017, all people with severe hemophilia B switched from standard half-life recombinant FIX (SHL rFIX) to recombinant factor IX Fc fusion protein concentrate (rFIXFc, Alprolix, Bioverativ Therapeutics, Inc., Waltham, MA, USA) prophylaxis. Initial evaluation of our real-world data following two years of rFIXFc prophylaxis has illustrated reduced annualized bleeding rates, factor consumption, and infusion frequency,[15] as well as demonstrating efficacy and safety of rFIXFc in the perioperative management of people with hemophilia B. Real-world published HRQoL data with rFIXFc prophylaxis are limited, with a single study demonstrating similar scores for SHL rFIX and rFIXFc prophylaxis.[16] Data from the pivotal clinical trials of EHL rFIX have demonstrated improved HRQoL in pediatric populations.[17,18] Adult clinical trials have reported improvements in the domains of Sport, Feeling, and Partnership and in Physical Health and Sport using Haemophilia Quality of Life Questionnaire (HAEM-A-QOL), with nonacog beta pegol[19] and rFIXFc[20] prophylaxis, respectively.

The aim of this study is to assess HRQoL in the real-world setting in an unselected cohort of adults with severe hemophilia B after switching to rFIXFc prophylaxis from SHL rFIX.

2 | METHODS

This prospective study was approved by the institutional ethics committee and the local research and innovation center and carried out in collaboration with the Irish Haemophilia Society. People with severe hemophilia B (FIX:C < 0.01 IU/mL) ≥18 years who switched from SHL rFIX to rFIXFc prophylaxis and attend the National Coagulation Centre (NCC) in Dublin were invited to participate and provided informed written consent. The NCC is a hemophilia comprehensive care center providing care to adults (≥16 years) with hemophilia and other bleeding disorders. Participants were requested to complete a Patient Reported Outcomes Burdens and Experience (PROBE) questionnaire at the time of switching treatment (2017) from SHL rFIX and after two years of prophylaxis with rFIXFc (2019).

The PROBE questionnaire is a hemophilia-specific questionnaire developed using outcomes identified by people with hemophilia as important and has undergone psychometric validation,[21] test-retest analysis,[22] and cross-cultural validity assessment.[23] It consists of 29 questions and takes approximately 15 minutes to complete. Section 1 relates to demographic information including age, diagnosis, education, and relationship status. Section 2, the core section covering PRO, focuses on general health-related problems, mobility issues, pain and analgesia usage, and ADLs, as well as school/work life. Section 3 contains hemophilia-specific questions regarding joint problems, bleeding events, and current and past hemophilia treatment regimens. Answers are provided in different formats including a seven-item Likert scale, yes/no questions, and free text options.

Finally, section 4 is the European Quality of Life 5-Dimensions 5-Level questionnaire (EQ-5D-5L). The EQ-5D-5L is a self-administered, standardized questionnaire that measures HRQoL in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[24] Each dimension has five possible response levels: no problems, slight problems, moderate problems, severe problems, and extreme problems/unable to do. A single index score is derived from responses to each dimension using country-specific value sets. The EQ-5D score ranges from <0 (health score worse than death) to 1 (best possible health state). It also includes a visual analog scale (VAS) requiring self-rating of global health status on the day of assessment, ranging from 0 (worst health imaginable) to 100 (best health imaginable). Participants completed the PROBE questionnaires in the comprehensive care center when attending for routine clinic appointments. The completed questionnaires were then transcribed into a database to permit analysis.

Statistical analyses were primarily descriptive and correlative. Comparison between time points was carried out on paired data using Wilcoxon signed-rank test for ordinal values while the paired *t* test was used for continuous variables. The chi-squared test and Fisher's exact test were used for analysis of categorical data. Health state from the EQ-5D-5L was calculated using the Irish derived value set.[25]

3 | RESULTS

3.1 | Patient population

Twenty-seven adult males with severe hemophilia B enrolled in the study with final analysis of 23 participants (Table 1); 2 participants emigrated before study end, and 2 participants did not complete questionnaires at both required time points (Figure 1). All patients received prophylaxis after switching to rFIXFc, and all continued prophylaxis at two years. Not every participant answered every question, and only paired responses for each question were analyzed and reported (Table S1).

3.2 | EuroQol EQ-5D-5L

There was no significant change in the median reported EQ-5D-5L score following two years of rFIXFc prophylaxis, 0.76 (range −0.01 to 0.95), compared to 0.77 (range 0.36-1) at baseline. Most participants (≈70%) reported no or slight problems overall. On subgroup analysis, an improvement in the median EQ-5D-5L score following two years of rFIXFc prophylaxis was seen for participants who switched from episodic treatment with SHL rFIX (0.62 vs 0.76). The worst scores were reported for pain and mobility at both time points. Of note, participants reported considerably poorer scores in these domains compared to a baseline Irish male population[26] (Figure 2A). The EQ VAS score was similar at both time points, with a median score of 72.5 (range 45–90) at baseline versus 75 (range 40–93) following two years of rFIXFc prophylaxis (Figure 2B).

TABLE 1 Participant demographic data

Participants, n	23
Baseline factor IX level, IU/mL	<0.01
Age, y, median	47
Range	(20-70)
Education duration, y, median	16
Range	6-24
Race	
White Irish	23
HJHS, median	25
Range	0-53
Treatment regimen before rFIXFc prophylaxis	
Prophylaxis	17
Episodic treatment	6

Abbreviations: HJHS, Hemophilia Joint Health Score; rFIXFc, recombinant factor IX Fc fusion protein concentrate.

3.3 | Pain and analgesia usage

The majority of participants answered the questions on acute pain, chronic pain, and analgesia use at both time points (Table 2). A 25% reduction in the number of activities when chronic pain occurred ($P < .001$) and a 33% reduction in the number of activities that chronic pain interfered with ($P < .001$) was reported following two years of rFIXFc prophylaxis. There was a 9% decrease in chronic pain during the second year of prophylaxis with rFIXFc compared to baseline, but despite this, rates following two years of rFIXFc prophylaxis remained high (74%). Chronic pain occurred during a wide variety of activities and impacted on many aspects of daily life.

Participants reported a 19% increase in acute pain during the second year of rFIXFc prophylaxis compared to baseline. There was no significant relationship between acute pain and number of bleeds. Similar to chronic pain, acute pain also occurred during a wide range of activities, most commonly while walking but also at rest and at night. Following two years of rFIXFc prophylaxis, those experiencing acute pain reported that multiple aspects of their lives were adversely affected including walking ability (86%), general activities (71%), enjoyment of life (57%), mood (50%), sleep (50%), sports (29%), work (21%), and relationships (14%).

Analgesia requirements among participants were high, with 86% reporting analgesia use in the year before switching to rFIXFc, and 95% during the second year of prophylaxis with rFIXFc (Table 2).

3.4 | Activities of daily living

There was a reduction in the number of affected ADLs following two years of rFIXFc prophylaxis compared to baseline (71 vs 95; $P = .007$). The greatest improvement was reported in the areas of doing heavy domestic tasks (17% improvement), walking (13% improvement), bending (13% improvement), and going up stairs (13%

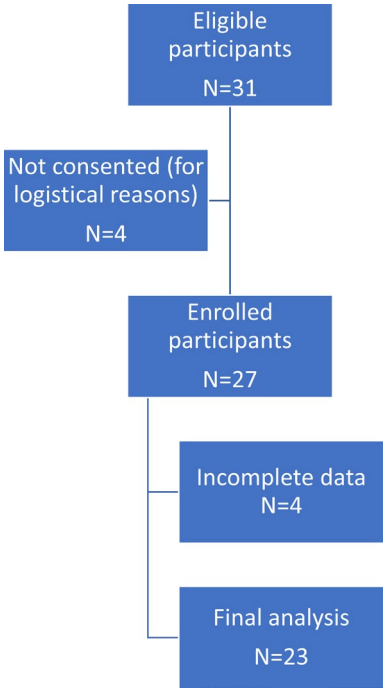

FIGURE 1 Participant enrollment

improvement). However, ADLs that disimproved at the second time point included getting up from sitting, sexual intimacy, doing light domestic tasks, and getting in and out of a car. A high proportion of participants reported difficulty with at least one ADL at both baseline (57%) and after two years of rFIXFc prophylaxis (52%) (Figure 3).

3.5 | General health problems

At both time points, most participants reported at least one health problem, with musculoskeletal issues being the most reported free-text problem (Table 3). The most common health problems reported from a specified list following two years of rFIXFc prophylaxis were arthritis (44%), mental health issues (anxiety and depression) (28%), hypertension (28%), and gingivitis (17%).

3.6 | Joint health and mobility

There was a significant reduction in reported target joints (three or more spontaneous bleeds into any one joint in the past six months[27]) ($P = .006$), with 10% reporting a target joint during the second year of rFIXFc prophylaxis, compared to 48% at the time of switching to rFIXFc prophylaxis. Nearly all participants reported reduced range of motion in a joint secondary to hemophilia, with a median of three joints affected at both time points.

Participants reported much higher rates of target joints when asked, "Do you currently have a target joint?" with no definition of a target joint included in the question. At baseline, 82% reported a target joint and 73% following two years of rFIXFc prophylaxis.

Fifty-two percent reported using a mobility aid/assistive device at some point in the year before switching to rFIXFc prophylaxis, including orthotic shoes (39%), crutches (26%), compression bandages (22%), orthopedic brace (9%), walking stick (9%), sling (4%), and walker (4%). The frequency of use of each mobility aid/assistive device varied, with only orthotic shoes or insert use reported >50% of the time. There was a 22% increase in mobility aid/assistive device use reported during the second year of rFIXFc prophylaxis, with orthotic shoes or inserts (61%) being most used, and more than half using them >75% of the time.

3.7 | Bleeding events

There was a significant reduction in reported annualized bleeding rate (ABR) with rFIXFc prophylaxis ($P = .002$). Following two years of rFIXFc prophylaxis 86% participants reported ABR < 3, with 32% reporting zero bleeds, compared to 50% of participants reporting ABR < 3 with SHL rFIX and 9% no bleeding events (Figure 4).

3.8 | Hemophilia treatments

All participants were on regular prophylaxis at the second time point, compared to 73% before the switchover. There was a decrease in the reported frequency of prophylaxis infusions between SHL rFIX (weekly mean number of infusions, 2.06) and rFIXFc (weekly mean number of infusions, 0.88) ($p < 0.001$). The average age to start prophylaxis in the youngest age group, 18 to 29 years, was 2.5 years, getting progressively later, with mean age 27 years reported by participants in the age group 30-50 years and 47 years in the 51-70 years age group.

4 | DISCUSSION

This study provides sobering insights into the patient experience of living with severe hemophilia B, despite residing in a high-income country with free access to prophylaxis and health care. PROs demonstrate high rates of acute and chronic pain, high rates of analgesia use, and functional impairment, with many using mobility/assistive devices.

HRQoL, assessed by EQ-5D-5L, did not demonstrate a significant change after switching from SHL rFIX to rFIXFc prophylaxis. However, an improvement is seen in the subgroup of participants who switched from episodic treatment with SHL rFIX to regular prophylaxis with rFIXFc. Real-world EQ-5D-5L scores in a UK study with low-dose rFIXFc prophylaxis reported similar results.[16] In the clinical trial setting, nonacog beta pegol prophylaxis has demonstrated significant improvement in EQ-5D score from baseline, although using a three-level EQ-5D tool rather than the five-level version used in our study.[19] It is also worth noting that the EQ VAS and EQ-5D-5L scores reported in our study at both time points are markedly worse

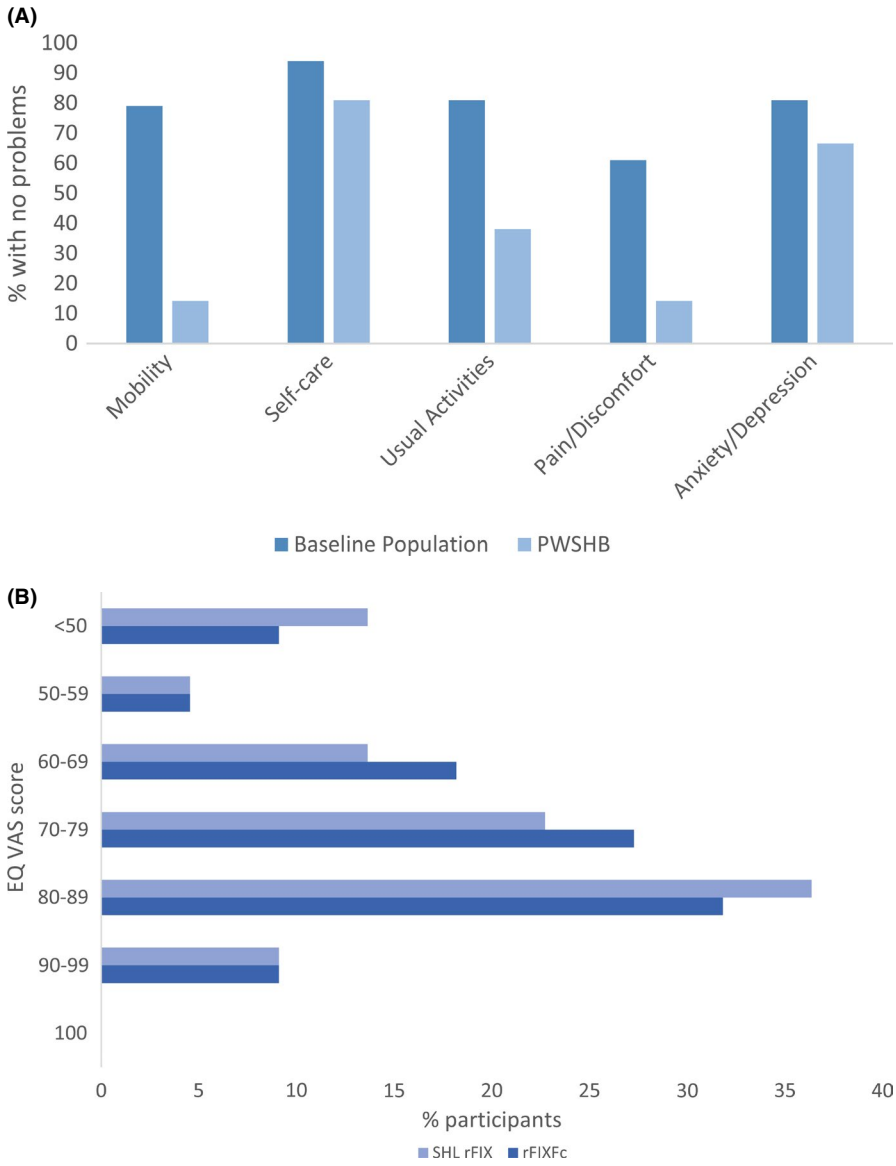

FIGURE 2 (A) Proportion of people with severe hemophilia B (PWSHB) reporting no problems in each European Quality of Life 5-Dimensions (EQ-5D-5L) domains compared to baseline Irish male population. (B) EuroQol visual analog scale (EQ VAS) scores at baseline and after two years of recombinant factor IX Fc fusion protein concentrate (rFIXFc) prophylaxis. SHL, standard half-life

than the population norms for the Irish male population.[26] This is most notable in three domains: no pain/discomfort (61% vs 14%), no mobility problems (79% vs 14%), and no difficulties with usual activity (81% vs 38%).

The PROBE questionnaire is an invaluable tool to capture detailed PROs and provide more meaningful insight into the areas of particular concern highlighted by the EQ-5D-5L scores. Firstly, although rates of reported chronic pain are high, importantly, our study demonstrates a significant reduction in the number of daily activities impacted by chronic pain following two years of rFIXFc prophylaxis. Many studies have highlighted the high prevalence of pain in adult people with hemophilia,[28-30] with 89% of people with hemophilia in a large international study reporting chronic pain that interfered with ADLs.[31] Routine childhood prophylaxis is critical to minimize joint damage and establishment of hemophilic arthropathy, which is a major contributory factor to high rates of chronic pain.[32] Most of this study cohort did not receive regular prophylaxis until adulthood. In the current era of hemophilia care, which emphasizes the importance of prophylaxis from a young age, our hope would be that future studies of the Irish hemophilia population would report lower rates of chronic pain.

Rates of reported acute pain were also high, and despite reduced bleeding episodes an increase in acute pain was reported during the second year of rFIXFc prophylaxis compared to baseline (45% vs 63%). This is counterintuitive, but it is possible that knowledge of higher trough levels may have encouraged change in behavior or activity levels, resulting in more injuries but not associated with bleeding. There may also be a recall bias as participants are asked to report acute pain for a one-year period. Rates of analgesia use were high, with the associated challenges of analgesia management in people with hemophilia.[4,30,33] The increase in analgesia use reported in this study may reflect patient confidence in their prophylaxis, which subsequently allowed patients to manage joint or arthropathy pain with analgesia, rather than treating as a potential bleed with clotting factor concentrate. The difficulty in differentiating between hemarthrosis and hemophilic arthropathy is well recognized.[34] The burden

TABLE 2 Acute and chronic pain, and analgesia use at baseline and following two years of rFIXFc prophylaxis

	Baseline in year before switching to rFIXFc prophylaxis	During the second year of rFIXFc prophylaxis
Acute pain		
% reporting acute pain	45	64
Median number of activities when acute pain occurs	0 (0-7)	1 (0-6)
Median number of activities affected by acute pain	0 (0-9)	1.5 (0-8)
Chronic pain		
% reporting chronic pain	83	74
Median number of activities when chronic pain occurs	3 (0-8)	2 (0-7)
Median number of activities affected by chronic pain	5 (0-10)	2 (0-10)
Analgesia usage	%	%
Never (0% of the time)	14	5
Sometimes (1%-50% of the time)	55	64
Frequently (51%-99% of the time)	18	18
Always (100% of the time)	14	14

Abbreviations: rFIXFc, recombinant factor IX Fc fusion protein concentrate.

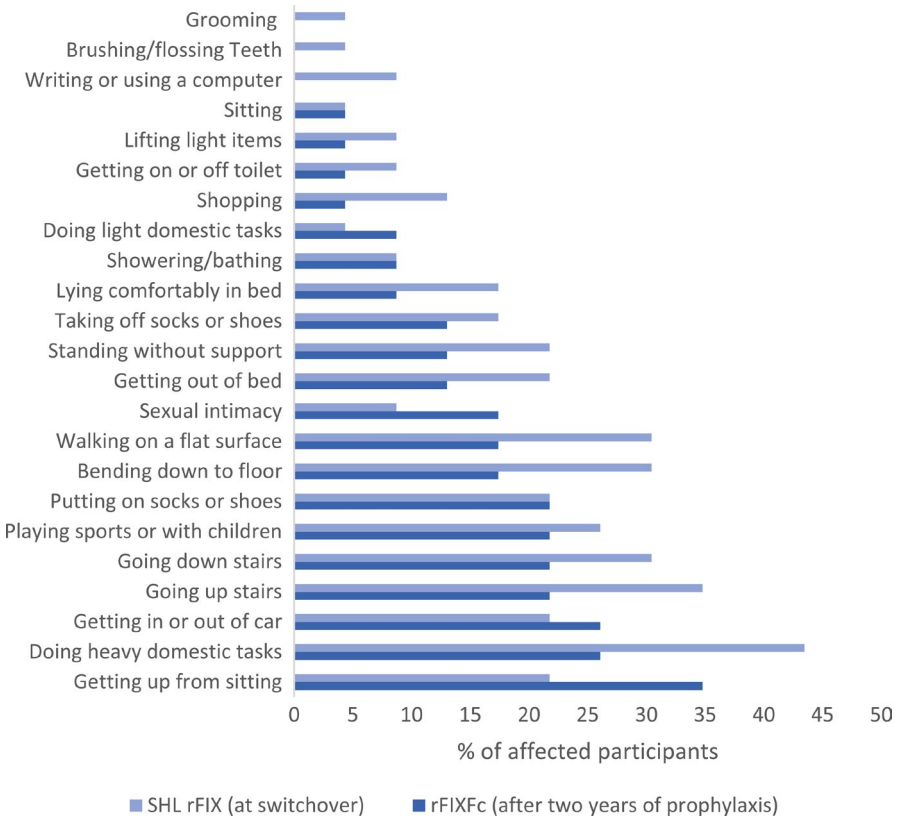

FIGURE 3 Difficulties with activities of daily living. Abbreviations: rFIXFc, recombinant factor IX Fc fusion protein concentrate; SHL rFIX, standard half-life recombinant factor IX

of pain for people with severe hemophilia B is highlighted further when compared to a population without haemophilia. A population with no bleeding disorders (NoBD) who completed PROBE questionnaires, reported much lower rates of chronic pain (29%), acute pain (33%), and analgesia use (65%).[35]

PROs also provided greater insight into problems with mobility captured more crudely by the EQ-5D-5L. High numbers of participants reported musculoskeletal problems such as arthritis, reduced range of motion in joints, and needing a mobility aid or assistive device. There was a significant reduction in reported target joints

TABLE 3 Health-related problems

Number of health-related problems in past 12 months	At switchover (%)	Following 2 years of rFIXFc prophylaxis (%)
0 problems	39	30
1 problem	17	26
2 problems	35	30
3 problems	9	13
System affected		
Musculoskeletal	43	48
Bleeding	13	13
Gastrointestinal	4	13
Neurological	4	13
Urological	9	4
Other	4	4

Abbreviations: rFIXFc, recombinant factor IX Fc fusion protein concentrate.

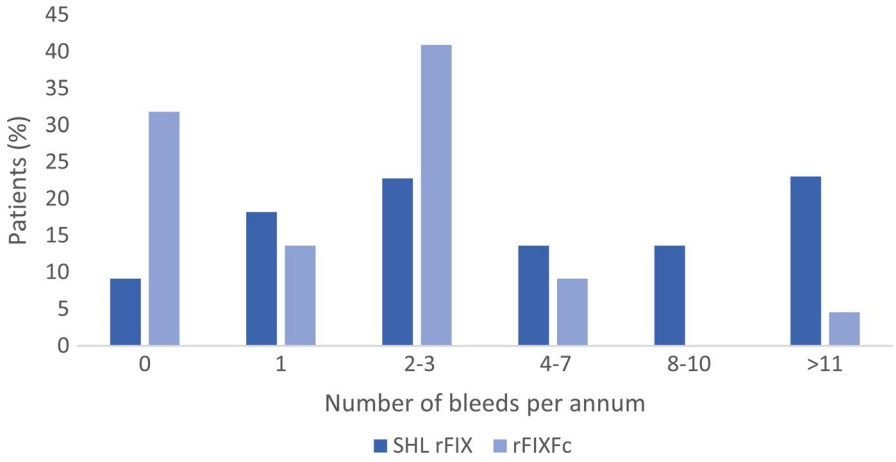

FIGURE 4 Annualized bleeding rate for the year before switching to recombinant factor IX Fc fusion protein concentrate (rFIXFc) prophylaxis and for the second year of rFIXFc prophylaxis. SHL, standard half-life

(three or more spontaneous bleeds into any one joint in the past six months) during the second year of rFIXFc prophylaxis, but joint health remained problematic. It is worth noting the patient interpretation of the term *target joint* highlighted by the responses to the PROBE questionnaire. When asked, "Do you currently have a target joint?" 73% reported a target joint. In contrast, when asked about three or more spontaneous bleeds in any one joint, only 10% reported a target joint. People with hemophilia often use the term *target joint* to refer to a joint that causes problems, including pain, bleeding, or functional impairment. Finally, a significant reduction in the number of ADLs affected following two years of rFIXFc prophylaxis was reported, although approximately half of participants reported at least one affected ADL at both time points. In comparison, in a NoBD population, only 10% reported any problems with ADLs.[35]

The expectation that EHL FIX products will result in improved HRQoL for people with severe hemophilia B due to a reduced burden of treatment[13,14] is overly simplistic. The presence of the disability paradox among people with hemophilia has been recently described, with people with hemophilia reporting higher health states than the general population when assessed with the EQ-5D.[36] Other important factors such as pain, joint disease, and ability to perform ADLs also impact on HRQoL,[37,38] and the PROs in this study illustrate the high disease burden experienced by Irish adults with severe hemophilia B. The majority of this study population did not receive childhood prophylaxis and problems secondary to chronic muscle and joint deterioration may not demonstrate improvement, particularly with a short observation period. In fact, prophylaxis with rFIXFc represents tertiary prophylaxis for most participants in this study. The PRO data gathered by the PROBE questionnaire also highlights other health problems faced by those with severe hemophilia B. These data provide opportunities to sustain and expand the care offered to people with severe hemophilia B in Ireland. It further supports the importance of specialized physiotherapists, clinical psychologists, occupational therapists, and dentists as part of the multidisciplinary comprehensive care team.[4]

A limitation of this study is the small sample size, a common issue in rare disease research, and may limit the ability to demonstrate a significant improvement in HRQoL despite the significant reduction in reported bleeding events, target joints, and infusion frequency with rFIXFc prophylaxis. Although there is no significant change in EQ-5D-5L after switching to rFIXFc prophylaxis, there are PROs that demonstrate improvements. Importantly, changes in PROs that are not statistically significant can still be meaningful to the patient. The core PRO in the PROBE questionnaire (pain, mobility issues, ADLs, health problems) can be affected by conditions other than hemophilia, so an improvement in hemophilia management does not necessarily

translate to an improvement in these PROs. The PROBE questionnaire instead provides a more holistic approach to a person with hemophilia and in that setting offers valuable insights. Semistructured qualitative interviews may offer an alternative approach to evaluating the specific impact of switching to a new treatment.

5 | CONCLUSION

This study provides important insight into patient-reported experiences of living with severe hemophilia B. It emphasizes the high rates of chronic pain and analgesia use in this population, which persist despite lower bleed rates and higher FIX trough levels achieved with rFIXFc prophylaxis. It also highlights the health problems affecting people with severe hemophilia B and the need for a sustained multidisciplinary approach in hemophilia health care. It reiterates findings of reduced ABRs, target joints, and infusion frequency with rFIXFc prophylaxis reported in clinical trials and from the real world. There is a need for further exploration of the patient experience of switching to an EHL FIX product.

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AUTHOR CONTRIBUTIONS

NMOC designed the study. MOD, KJ, and ES were responsible for collection of the data. MOD, EQ, and NMOC were responsible for data analysis and interpretation. MOD wrote the manuscript, and all authors were involved in reviewing and revising the manuscript, with all authors granting final approval for the manuscript.

RELATIONSHIP DISCLOSURE

MOD has received research support from Sobi. NMOC has received research support/principal investigator from Freeline, Sobi, Takeda, 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. JSOD 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. JSOD has received research grant funding awards from Baxter, Bayer, Pfizer, Shire (now part of Takeda), Takeda, 3 M, and Novo Nordisk.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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