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ORPHEE: A Real-World Study on rIX-FP Prophylaxis Use in Adolescent/Adult Patients With Hemophilia B

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ABSTRACT

Objectives: To assess the real-world efficacy and safety of recombinant factor IX albumin fusion protein (rIX-FP) in patients with hemophilia B (HB) in France.

Methods: Data on dosing frequency, weekly consumption, and bleeds before-and-after switching to rIX-FP, were collected from December 2021 to February 2024. Annualized (spontaneous) bleeding rates [A(s)BRs] were calculated only in patients on prophylaxis with a follow-up ≥ 6 months.

Results: This interim analysis focused on 77 patients ≥ 12 years; 62 (81%) had severe HB. After switching to rIX-FP, the infusion interval was 14 (7–14) days. Weekly consumption was 43 (35.5–53) IU/kg. ABRs and AsBRs were 0.5 (0–1.9) and 0 (0–0.7) ($n = 63$) at 18.2 (12.3–21.9) months of follow-up. Prophylactic efficacy of rIX-FP was considered 'Excellent'/'Good' in 65/68 (95%) patients. Among the 43 patients previously treated with rFIXFc, 21 increased the infusion interval from 7 (7–11) days with rFIXFc to 14 (7–14) days with rIX-FP; 33/43 (77%) reduced weekly factor IX (FIX) consumption from 59.95 (46.35–77.93) to 42.5 (35.88–50.25) IU/kg. Patients maintained good protection against bleeds.

Conclusion: This analysis confirmed that switching to rIX-FP allows for reducing injection frequency and FIX consumption while maintaining good bleed protection.

1 | Introduction

Hemophilia B (HB) is a rare X-linked congenital disorder characterized by coagulation factor IX (FIX) deficiency. Patients with severe HB (FIX < 1 IU/dL) experience bleeds in joints, muscles, and internal organs. Repeated bleeds can lead to hemophilic arthropathy, progressive chronic joint damage, and reduced quality of life [1]. For these patients, and patients with moderate HB (FIX 1–5 IU/dL) and a severe bleeding phenotype, the standard of care is prophylaxis to prevent bleeds and maintain musculoskeletal health [1].

Initially, the objective of standard prophylaxis was to convert patients with severe HB to a bleeding phenotype typical of moderate/mild HB by maintaining FIX levels > 1 IU/dL. However, it has been increasingly recognized that trough FIX levels of 1–3 IU/dL are insufficient to totally prevent bleeds, resulting in the gradual progression of joint disease [1–3]. Extended half-life (EHL) FIX concentrates allow prophylaxis treatment with trough FIX levels maintained in the mild HB range (5–40 IU/dL) [1]. EHL FIX concentrates also offer flexible dosing with high trough levels and good clinical efficacy, which may result in improved clinical outcomes for patients with HB [4].

Among the EHL FIX concentrates, rIX-FP (albutrepenonacog alfa, IDELVION, CSL Behring) is a recombinant fusion protein [5, 6] that provides effective hemostasis in patients with moderate-to-severe HB for up to 21 days in ≥ 18-year-old patients and 14 days in patients aged 12–18 [7]. In the PROLONG-9FP clinical trial program, rIX-FP showed good dosing flexibility with 7–14 day intervals between prophylactic infusions, resulting in a median annualized spontaneous bleeding rate (AsBR) of zero. Furthermore, 96.2% of steady state trough FIX measurements were > 5 IU/dL across all doses and dose intervals, consistent with a mild hemophilia phenotype [8]. The extension study confirmed the phase III trial results and showed that a 21-day regimen may be an alternative option to minimize treatment burden, individualize treatment, and maintain effective protection against bleeds [9, 10].

Pre-approval clinical trials gave robust efficacy and safety data; however, when evaluating FIX products in clinical practice, real-world utilization and outcomes obtained in post-marketing studies also need to be considered, especially in rare diseases such as hemophilia [11]. Previously, real-world studies only analyzed switching from standard half-life FIX products to recombinant FIX albumin fusion protein (rIX-FP) [12–15], while the debate is currently focused on the choice among different EHL FIX products and their clinical efficacy [16, 17].

The ORPHEE study was designed to follow patients with inherited HB who are currently receiving rIX-FP for long-term prophylaxis, one-off prevention in periods with high bleeding risk including surgeries, and on-demand treatment. Here, we carried out an interim analysis of long-term prophylaxis with rIX-FP in adolescent/adult patients with HB.

2 | Methods

The ORPHEE study (NCT05086575) is a French real-world multicenter, noninterventional, prospective, and longitudinal cohort study designed following the STROBE checklist for observational studies (https://www.strobe-statement.org/checklists/).

2.1 | Study Population

Patients (any age) with inherited HB, treated or previously treated with rIX-FP, were consecutively enrolled at French Hemophilia Treatment Centers (HTC). This interim analysis examined data from adolescent/adult patients included between December 2021 and February 2024 and treated with rIX-FP for prophylaxis.

Data on previous treatment regimens were collected retrospectively for the year preceding the switch to rIX-FP. A prophylactic regimen was defined as at least one injection per month for ≥ 3 consecutive months and based on the World Federation of Hemophilia (WFH) definition [1]. Patients had no FIX inhibitors and/or were not undergoing immune tolerance induction at the time of study inclusion. All patients gave their written informed consent before participation. Patients were followed for 3 years after study inclusion. This post-marketing observational study did not affect the participants' usual management and did not require any additional visit/investigation. Follow-up visits were completed according to the patients' usual schedules. Prophylactic regimens were chosen by the investigator based on the patient's bleeding phenotype and preferences.

2.2 | Clinical Data Collection

Data on annualized bleeding rate (ABR), AsBR, annualized joint bleeding rate (AjBR), dosing frequency, FIX consumption, and pharmacokinetic (PK) parameters (incremental recovery [IR] and half-life) were collected, when possible, before-and-after switching to rIX-FP.

ABR, AsBR, and AjBR were calculated only in patients on prophylaxis with a follow-up period of ≥ 6 months. Data on rIX-FP hemostatic efficacy for preventing and treating nonsurgical and surgical bleeding events were collected. Data on damaged joints were collected on a declarative basis; damaged joints were considered as joints that are painful, bleed easily, require special attention, or are target joints. Trough levels were also collected; however, according to international consensus recommendations on the management of people with HB and based on the

French guidelines [18, 19], only FIX activity (FIX:C) measured by one-stage assay was taken into consideration in our analysis for all FIX concentrates.

Clinical effectiveness and safety were assessed by the investigators. Clinical effectiveness was assessed on a four-point scale (none, moderate, good, and excellent) according to the WFH definition [1]. Safety was evaluated using a two-point scale (good or bad), and included reporting of adverse events (AEs), thrombotic events, and inhibitor development, according to the clinical development program [20].

Annualized infusion rate and annualized FIX consumption were calculated as the number of weekly injections and weekly consumption, respectively, multiplied by 52.

2.3 | Statistical Analysis

For descriptive statistics, percentages, medians, means, standard deviation (SD), interquartile ranges (IQR) or minimum–maximum ranges were used.

Differences in injection frequency, FIX consumption, damaged joints, and ABR/AsBR/AjBR were assessed using data from a population of <50 patients with available pre- and post-switch data, using the Wilcoxon signed-rank test for matched pairs. The effect of the longer interval between injections on FIX consumption was evaluated using the nonparametric Kruskal-Wallis test. A p-value <0.05 was considered significant.

Patients with missing data for a variables were excluded from the analyses that required that/those variables; however, they were included in analyses for which they had all data.

Statistical analyses were performed with GraphPad Prism 7.05 (GraphPad Software Inc.).

3 | Results

3.1 | Study Population

A total of 166 patients treated with rIX-FP from 29 HTCs were included in the ORPHEE study between December 2021 and February 2024 (Figure S1). In this cohort, 106 (64%) patients received rIX-FP for prophylaxis; 77 (73%) were adolescents/adults (≥12 years of age) and 29 (27%) were pediatric patients (<6 years of age).

This analysis focused only on adolescent/adult patients on prophylaxis ($n=77$). Their characteristics are described in Table 1. Twenty-three (30%) patients had at least one damaged joint (mean ± SD; median [range]: 1.7 ± 1.3; 1.0 [1.0–5.0]) at inclusion. Among these 23 patients, 13 (57%) were previously on prophylaxis: 11 with recombinant FIX Fc fusion protein (rFIXFc) and two with a standard half-life FIX concentrate (rFIX and pdFIX, respectively).

TABLE 1 | Baseline demographic data and clinical characteristics.

	***n* = 77**
Age [years], median (range)	39 (12–77)
Boys/men, *n* (%)	77 (100)
Body weight [kg], median (range)	73 (42–121)
History of FIX inhibitors, *n* (%)	0 (0)[a]
Hemophilia severity, *n* (%)	
Mild [5–40 IU/dL]	1 (1)
Moderate [1–5 IU/dL]	14 (18)
Severe [<1 IU/dL]	62 (81)
At least one damaged joint, *n* (%)	23 (30)
Previously treated on demand, *n* (%)	22 (29)
Previously treated on prophylaxis, *n* (%)	55 (71)
pdFIX	2 (4)
rFIX	10 (18)
rFIXFc	43 (78)

Abbreviations: FIX, factor IX; pdFIX, plasma-derived factor IX; rFIX, recombinant factor IX; rFIXFc, recombinant factor IX Fc fusion protein.
[a]Data missing for one patient.

3.2 | Description of the Population on Prophylaxis With rIX-FP

3.2.1 | Dosing Regimen and FIX Consumption With rIX-FP

Dosing regimen and injection frequency were reported for all 77 patients on prophylaxis during a mean ± SD (median; IQR) observation period of 14.9 ± 7.8 (16.1; 9.0–19.8) months, that is, 95.6 patient-years. The mean ± SD (median; IQR) interval between injections was 11.5 ± 4.6 (14; 7–14) days; 30 (39.0%) patients were treated weekly, seven (9.0%) every 10 days, 35 (45.5%) every fortnight, and five (6.5%) every ≥21 days, at the last study visit (Table 2).

Overall, the mean ± SD (median; IQR) weekly FIX consumption on prophylaxis with rIX-FP was 45 ± 15 (43; 35.5–53) IU/kg. The Kruskal-Wallis test showed that the weekly FIX consumption was negatively correlated with the length of the interval between rIX-FP doses ($p<0.0001$). Specifically, it decreased from 57 ± 15 (53.5; 47–61) IU/kg in patients with weekly treatment to 48 ± 8 (52; 46–53) IU/kg/week in patients treated every 10 days, to 37 ± 6 (36; 34–39) IU/kg/week in patients treated every fortnight, and to 24 ± 9 (23; 17–32) IU/kg/week in patients treated every ≥21 days.

3.2.2 | PK Data

The IR and half-life of rIX-FP could be assessed in 44 and 15 patients, respectively. The mean ± SD (median; IQR) IR was

TABLE 2 | Summary of FIX consumption, FIX trough levels, and efficacy in patients on prophylaxis with rIX-FP classified in function of the between-injection interval.

	Every 7 days	Every 10 days	Every 14 days	Every ≥ 21 days
n (%)	30 (39.0)	7 (9.0)	35 (45.5)	5 (6.5)
Dose per injection (IU/kg)	53.5 (47.0–61.6)	74 (65.0–75.0)	72 (67.9–78.0)	77 (53.5–106.0)
Annualized rIX-FP consumption (IU/kg)	2782 (2444–3201)	2694 (2366–2730)	1872 (1765–2028)	1189 (872–1647)
FIX:C trough levels (IU/dL)	17 (14–21) $n=12$	15 (8–21) $n=2$	7 (5–10) $n=16$	4 $n=1$
Efficacy:				
'Excellent' or 'Good' (%)	24 (96)	7 (100)	30 (97)	4 (80)
Follow-up				
≥ 6 months, *n*	25	5	29	4
Duration, months	19.0 (12.0–20.0)	15.9 (9.8–25.1)	17.3 (13.0–21.0)	24.2 (11.0–25.0)
Total bleeds (ABR)				
Median (IQR)	0.0 (0.0–2.0)	0.0 (0.0–0.8)	0.7 (0.0–3.1)	1.4 (0.3–3.1)
Mean ± SD	1.0 ± 1.2	0.3 ± 0.7	1.7 ± 2.4	1.5 ± 1.5
Patients with 0 bleeds, *n* (%)	13 (52)	4 (80)	12 (41)	1 (25)
Spontaneous bleeds (AsBR)				
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–0.4)	0.0 (0.0–0.9)	0 (0–1.5)
Mean ± SD	0.6 ± 1.0	0.2 ± 0.4	0.9 ± 2.1	0.5 ± 1.0
Patients with 0 bleeds, *n* (%)	17 (68)	4 (80)	20 (69)	3 (75)
Joint bleeds (AjBR)				
Median (IQR)	0.0 (0.0–1.4)	0.0 (0.0–0.8)	0.0 (0.0–0.7)	0.8 (0.0–1.9)
Mean ± SD	0.6 ± 1.0	0.3 ± 0.7	0.5 ± 1.1	0.9 ± 1.1
Patients with 0 bleeds, *n* (%)	16 (64)	4 (80)	21 (72)	2 (50)

Note: Data are presented as median (IQR) or *n* (%).
Abbreviations: ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate; AjBR, annualized joint bleeding rate; FIX, factor IX; FIX:C, factor IX activity; IQR, interquartile range; rIX-FP, recombinant factor IX albumin fusion protein; SD, standard deviation.

1.25 ± 0.29 (1.21; 1.02–1.47) IU/dL per IU/kg. The mean ± SD (median; IQR) half-life of rIX-FP was 126 ± 17 (120; 120–129) hours. The mean ± SD (median; IQR) FIX trough level was 11 ± 6 (10; 6–17) IU/dL ($n=31$). Trough levels were higher in patients treated every 7 days than every fortnight or more (Table 2).

3.2.3 | Bleeding Protection

Overall, 63 (82%) patients had a follow-up of ≥ 6 months with rIX-FP and the mean ± SD (median; IQR) follow-up duration was 17.3 ± 5.9 (18.2; 12.3–21.9) months. During this period, 30 (48%) patients did not experience any bleed, 44 (70%) did not experience any spontaneous bleed, and 43 (68%) did not experience any joint bleed. Their ABR, AsBR, and AjBR (mean ± SD) were 1.3 ± 1.9, 0.7 ± 1.6, and 0.6 ± 1.0, respectively.

The analysis of ABRs according to the dosing regimen showed that ABR, AsBR, and AjBR were not different in patients treated every 7, 10, 14, and ≥ 21 days (Table 2).

In addition, follow-up data were available for 19/23 patients who reported a damaged joint at inclusion. After switching to rIX-FP for prophylaxis, eight (42%) patients resolved all damaged joints ($n=5$ previously on demand, $n=2$ previously on prophylaxis with rFIXFc, and $n=1$ previously on prophylaxis with pdFIX) and four (21%) resolved some, but still had at least one damaged joint ($n=3$ previously on prophylaxis with rFIXFc and $n=1$ previously on demand). The damaged joint number did not increase in any patient. At the last completed visit, the mean ± SD (median; range) number of damaged joints per patient was significantly decreased to 0.7 ± 0.7 (1.0; 0.0–2.0) compared to inclusion ($p<0.01$ in Mann–Whitney test).

The efficacy of rIX-FP for prophylaxis was assessed by the investigators in 68 patients. Efficacy was considered 'Excellent' or 'Good' in 65 (96%) patients. Efficacy was similar regardless of the administration frequency (Table 2).

3.2.4 | Bleed Management

A total of 124 bleeding events were reported in 35/77 patients (45%). Bleeding events were mainly joint bleeds (52; 42%), hematomas (25; 20%), and hematuria (14; 11%). They occurred after a mean ± SD (median; IQR) of 9.4 ± 6.2 (8.8; 4.2–14.3) months (missing data: seven bleeds) following the switch to rIX-FP for prophylaxis, and 39/117 (33%) occurred in the first 6 months. Moreover, 56% of all joint bleeds (29/52) occurred in a damaged joint known before inclusion. A patient reported 17 bleeding events, including seven in joints. This patient was receiving long-term treatment with a drug that may alter hemostasis.

Overall, 17 (14%) bleeds did not require any additional rIX-FP injection. The 107 treated bleeds required a mean ± SD (median; IQR) of 1.5 ± 1.3 (1; 1–1) injections with a total rIX-FP consumption of 104 ± 96 (72; 57–100) IU/kg. The mean ± SD (median; IQR) bleed duration was 3 ± 4 (1; 1–3) days ($n = 99$; missing data: eight bleeds). The hemostatic efficacy of rIX-FP was qualitatively assessed by the investigators in 72 treated bleeding events and was rated as 'Excellent' or 'Good' in 63 (87.5%).

3.2.5 | Safety

Overall safety was assessed in 71 patients and was rated as 'Good' for all. Safety was assessed for 75 treated bleeds and was rated as 'Good' for 74 (99%). Twelve AEs were reported, including three considered related to rIX-FP. One of these three AEs was considered moderate (lack of effectiveness), and two were mild (injection-site reaction). No patient developed FIX inhibitors or thrombosis.

3.3 | Comparison Before/After the Switch to rIX-FP Prophylaxis

3.3.1 | Patients Previously Treated on Demand

Twenty-two (29%) patients were previously treated on demand and switched to rIX-FP prophylaxis: 12 (55%) had severe HB and 10 (45%) reported at least one damaged joint at inclusion. They received one rIX-FP injection every mean ± SD (median; IQR) 12 ± 6 (10; 7–14) days and had a mean ± SD (median; IQR) weekly rIX-FP consumption of 45 ± 16 (40; 36–53.5) IU/kg.

During the previous on-demand period, the ABR, AsBR, and AjBR (mean ± SD) were 6.5 ± 5.2 ($n = 11$), 1.6 ± 2.1 ($n = 9$), and 4.3 ± 4.9 ($n = 11$), respectively. After switching to rIX-FP for prophylaxis, 13 patients had a follow-up period ≥ 6 months. Their mean ± SD (median; IQR) follow-up period was 14.1 ± 5.8 (12.6; 9.9–18.1) months. In these patients, ABR, AsBR, and AjBR (mean ± SD) decreased to 0.5 ± 0.7, 0.3 ± 0.5, and 0.3 ± 0.7, respectively. Among these 13 patients, eight (62%), 10 (77%), and 10 (77%) were free of total, spontaneous, and joint bleeds, respectively.

At inclusion, 10/22 patients reported a mean ± SD (median; min–max) number of damaged joints of 2.0 ± 1.2 (1.5; 1.0–4.0). Follow-up data were available for seven of them. At the last visit, after a mean ± SD (median; IQR) time on prophylaxis with rIX-FP of 14.2 ± 7.8 (12.0; 9.4–23.4) months, damaged joints were fully resolved in five out of seven patients, partially resolved in one patient, and stabilized in one patient. At the last completed visit, the mean ± SD (median; min–max) number of damaged joints per patient was significantly decreased to 0.3 ± 0.5 (0.0; 0.0–1.0) ($p < 0.05$, Wilcoxon signed-rank test).

3.3.2 | Comparison of Patients Previously on Prophylaxis With rFIXFc Who Switched to rIX-FP

Forty-three patients who were previously on prophylaxis with rFIXFc, switched to rIX-FP and were all included in this subgroup analysis. After switching to rIX-FP, injection frequency was reduced in 22/43 (51%) patients. The mean ± SD (median; IQR) between-injection interval was longer with rIX-FP than with rFIXFc (12 ± 4 [14; 7–14] days vs. 9 ± 5 [7; 7–10] days; $p < 0.01$). Three patients who increased the injection frequency with rIX-FP compared with rFIXFc reported a damaged joint at inclusion. The reduction of injection frequency was associated with a 28% reduction in the mean ± SD (median; IQR) weekly FIX consumption, from 63 ± 29 (59; 46–78) with rFIXFc to 45 ± 14 (42.5; 36–50) IU/kg with rIX-FP ($p < 0.0001$). Specifically, 33 (77%) patients reduced their weekly consumption with rIX-FP compared with rFIXFc (see Figure 1 for annualized infusion rates and annualized FIX consumption).

FIX trough levels increased in five of six patients with available data, after switching to rIX-FP (Figure S2).

Thirty-eight (88%) patients had a follow-up ≥ 6 months. During a mean ± SD (median; IQR) follow-up period of 18.7 ± 5.4 (19.3; 15.3–23.6) months after switching to rIX-FP, patients maintained

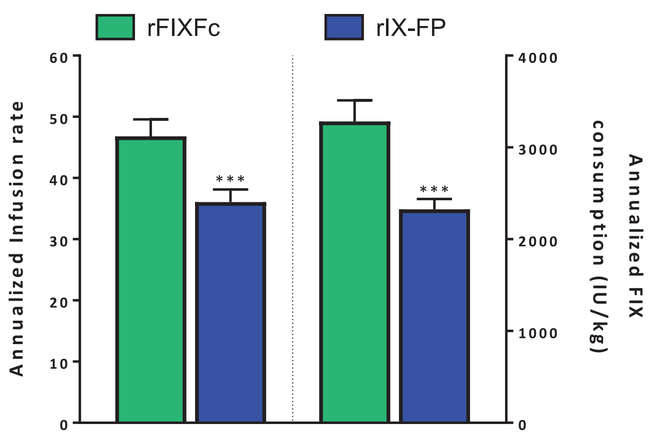

FIGURE 1 | Changes in annualized infusion rate and annualized FIX consumption in patients switching from rFIXFc ($n = 43$) to rIX-FP for prophylaxis. Data are the mean ± standard error of the mean. ***$p < 0.001$ (Wilcoxon signed-rank test). FIX, factor IX.

TABLE 3 | Annualized bleeding rate changes in patients switching from rFIXFc to rIX-FP for prophylaxis.

	rFIXFc	rIX-FP
	$n=43$	$n=38$[a]
Follow-up duration, months		
Median (IQR)	12 (12–12)	19 (16–24)
Mean ± SD	11.7 ± 0.6	18.7 ± 4.3
Total bleeds (ABR)		
Median (IQR)	1.0 (0.0–3.0)	1.0 (0.0–3.0)
Mean ± SD	2.0 ± 2.7	1.7 ± 2.2
Patients with 0 bleeds, *n* (%)	15 (35%)	15 (39%)
spontaneous bleeds (AsBR)		
Median (IQR)	0.0 (0.0–2.0)	0.0 (0.0–0.8)
Mean ± SD	1.0 ± 1.6	0.8 ± 1.9
Patients with 0 bleeds, *n* (%)	23 (53%)	26 (68%)
joint bleeds (AjBR)		
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.2)
Mean ± SD	1.2 ± 1.9	0.6 ± 1.1
Patients with 0 bleeds, *n* (%)	25 (58%)	26 (68%)

Abbreviations: ABR, annualized bleeding rate; AjBR, annualized joint bleeding rate; AsBR, annualized spontaneous bleeding rate; IQR, interquartile range; rFIXFc, recombinant factor IX Fc fusion protein; rIX-FP, recombinant factor IX albumin fusion protein; SD, standard deviation.
[a]Data missing for five patients.

effective protection against bleeding events and median ABR, AsBR, and AjBR values were 0, as during treatment with rFIXFc (Table 3).

Before switching to rIX-FP, 11 (26%) patients reported a mean ± SD (median; range) number of damaged joints of 2 ± 1 (1; 1–5) at inclusion. At the last completed visit ($n=10$), the mean ± SD (median; range) number of damaged joints was 1 ± 1 (1; 0–2) ($p=0.06$).

4 | Discussion

In France, rIX-FP has been commercially available since April 2021 and rFIXFc since 2018. N9-GP is not commercialized due to safety concerns by the French authorities. To date, this study included the largest cohort of patients treated with an EHL FIX [12–15, 21–26], and is also the first study that directly investigated the benefit of switching from rFIXFc to rIX-FP, by comparing before-and-after switch data for each patient.

In agreement with previous studies performed during clinical development [5, 9], rIX-FP had a favorable PK profile in terms of half-life and IR. Thanks to the improved PK profile of rIX-FP, more than half of the assessed patients received one injection every fortnight or more. Therefore, hematologists can tailor treatment according to their patients' profiles. Lengthening the interval between administrations allows for reducing the weekly consumption, as shown during the clinical development of rIX-FP [9, 20]. In this study, the median weekly FIX consumption with rIX-FP was 43 IU/kg/week, in line with the values reported by other European post-marketing studies on rIX-FP [12, 14, 15].

In this study, patients were followed for 3 years. This interim analysis took place at a median follow-up of 18 months (i.e., half of the total follow-up duration) when only 18% of patients had changed their frequency of administration after initiation of prophylaxis with rIX-FP and the last previous regimen. Future analyses should monitor rIX-FP dose changes over time, particularly the potential larger reduction in injection frequency and FIX consumption versus previous FIX products. Further collection of joint status data would be also valuable in assessing the prevention/progression of hemophilic arthropathy.

It is increasingly recognized that factor VIII (FVIII)/FIX trough levels of 3–5 IU/dL are insufficient to totally prevent bleeds in patients with hemophilia, leading to occasional clinical and subclinical bleeds that result in the gradual progression of joint disease [1]. Although several studies have highlighted the importance of the extravascular FIX pool in hemostasis [17, 27], plasma levels are still a valuable criterion for the clinical evaluation of coagulation activity [27, 28]. Indeed, a recent study using data from the Cost of Hemophilia in Europe/USA: Socioeconomic Survey (CHESS) platform found progressively lower ABR with higher FIX levels in men with HB in Europe and the USA [29].

EHL FIX products were developed to reduce prophylaxis treatment burden and to easily maintain through FIX levels > 5 IU/dL, thereby transforming a severe/moderate phenotype into a mild one [1, 30]. According to this objective, in this study, 87% of patients on prophylaxis with rIX-FP had a trough level in the mild hemophilia range.

Besides reducing prophylaxis regimen constraints, rIX-FP for prophylaxis was associated with good protection against bleeding, with median AsBRs equal to 0, regardless of the prophylaxis regimen. It is also important to note that over half of the 23 patients who reported a damaged joint at inclusion resolved or reduced their number of damaged joints with rIX-FP prophylaxis, in accordance with a previous study showing an improvement in joint status with rIX-FP prophylaxis [13].

Therefore, our data confirmed rIX-FP effectiveness observed during the clinical development program [9, 20] and in real-world studies [12–15, 24]. Randomized clinical trials are the gold standard for evaluating the efficacy of new products [31]; however, real-world data are also interesting, particularly because they provide valuable information, especially in rare diseases [11]. Both real-world and clinical study data are essential to provide new insights into hemophilia management [11].

This interim analysis also investigated the effect of switching from on-demand or prophylaxis treatment with another EHL FIX (rFIXFc) to rIX-FP prophylaxis. In patients previously treated on demand, ABR decreased following their switch to rIX-FP for prophylaxis, as previously shown [12, 20].

Given the different pharmacological properties of rFIXFc and rIX-FP, the choice of EHL FIX for prophylaxis should be data-driven [17]. Due to difficulties of generating head-to-head clinical data that directly compare efficacy outcomes of each EHL FIX, real-world evidence assumes increasing importance [17]. To date, rFIXFc and rIX-FP have only been indirectly compared using matching-adjusted indirect comparison analyses of phase III data [32, 33]. One of these two studies concluded that the efficacy of prophylaxis to prevent total bleeding events was comparable between rFIXFc and rIX-FP, despite differences in residual rates between treatments [32]. The other study showed a significant reduction in spontaneous bleeds and in the percentage of patients experiencing bleeding events, spontaneous bleeding events, and joint bleeding events with rIX-FP compared with rFIXFc [33]. This interim analysis of the ORPHEE data is the first to directly investigate the effect of switching from rFIXFc to rIX-FP prophylaxis. Switching to rIX-FP was associated with a significant reduction in the frequency of administration and FIX consumption. This means 26 fewer injections per year for patients on rIX-FP compared with their previous treatment with rFIXFc. In terms of FIX use for a patient weighing 70 kg, prophylaxis consumption was reduced from 214 760 IU to 154 700 IU when switching from rFIXFc to rIX-FP. Moreover, these significant reductions with rIX-FP were associated with excellent bleed protection (Figure 2).

Among the 13 patients who maintained the same frequency of administration between rFIXFc and rIX-FP and for whom follow-up data on bleeding occurrence were available, rIX-FP prophylaxis was associated with decreased AsBR in eight (62%) patients. Among the 11 patients who reported at least one damaged joint at inclusion despite prophylaxis with rFIXFc, the follow-up was complete for 10, and 5 (50%) reported resolution or reduction of the number of damaged joints when on prophylaxis with rIX-FP.

In conclusion, this before-and-after comparison between rFIXFc and rIX-FP highlighted benefits for patients on prophylaxis following the switch to rIX-FP in terms of reduction of the number of injections, good protection against bleeding, and even resolution of damaged joints.

As a retrospective chart review study, potential limitations include selection bias due to the noninclusion of all eligible patients treated at the participant HTCs and the absence of accurate recording of all bleeds in medical records. Moreover, due to the use of different methods (with their own specific coefficients of variation) for FIX quantification by the different HTCs, the intra-individual trough levels of FIX and the PK parameters could not be compared before/after the switch in a fully rigorous manner. However, data were collected prospectively during the different study visits and monitored by an independent contract research organization. Moreover, the study strictly followed the Good Clinical Practice for medical research and was designed according to the recommended STROBE checklist for observational studies (https://www.strobe-statement.org/checklists/).

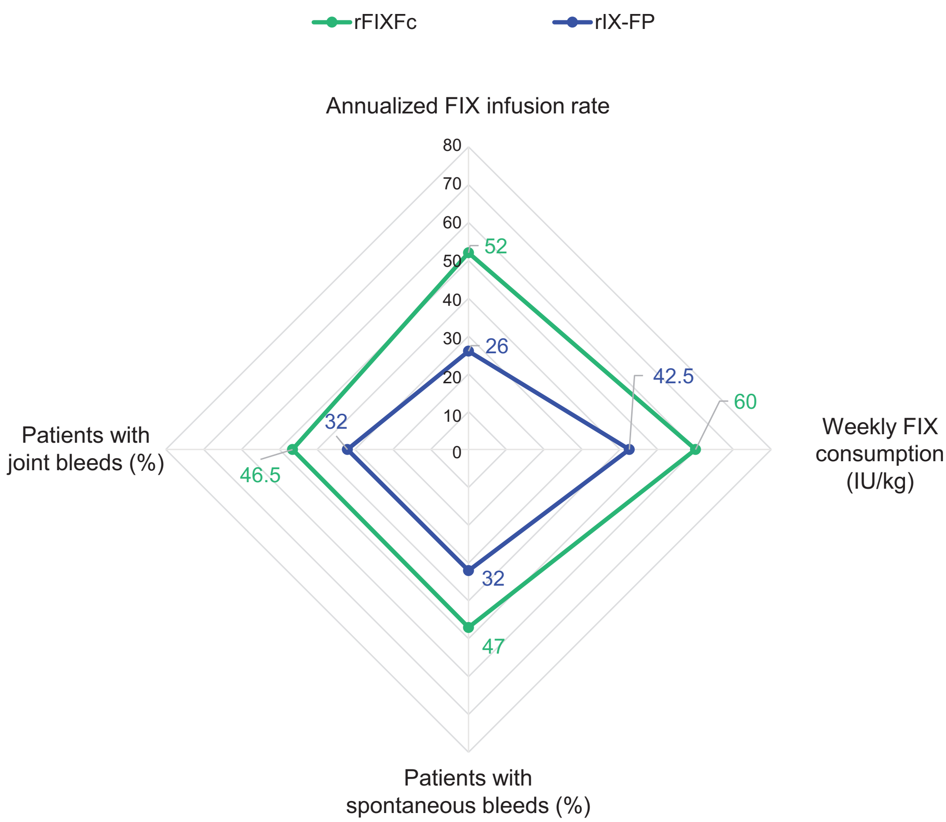

FIGURE 2 | Radar plots summarizing the annualized infusion rate, weekly consumption (IU/kg/week), and percentage of patients with spontaneous or joint bleeds among those who switched from rFIXFc ($n = 43$) to rIX-FP for prophylaxis.

The strengths of the current study include the use of data from 29 French HTCs, thus reflecting the real-world use of rIX-FP in France. The extended assessment period (overall median follow-up of 16 months) provided adequate time to observe changes in outcomes. In addition, real-world evidence provides information on outcomes observed in clinical practice, outside the restrictions imposed by clinical trials.

5 | Conclusion

This interim analysis showed that patients who switched to rIX-FP were well protected against bleeds, regardless of the injection frequency. Switching from rFIXFc to rIX-FP was associated with reduced treatment burden and FIX consumption. This study confirms that rIX-FP allows physicians to tailor prophylaxis to their patients' needs to improve their quality of life and bleed protection.

Author Contributions

B. pan Petesch, Y. Dargaud, A. Rauch, R. d'Oiron, A. Harroche, B. Guillet, C. Martin, and H. Catovic designed the study. B. Guillet, C. Martin, and H. Catovic analyzed data on safety and efficacy and drafted the initial version of the manuscript. All authors critically reviewed and revised the manuscript and approved the final version.

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Ethics Statement

The study was conducted in accordance with French Law no. 2012–300 of 5 March 2012 on research involving human subjects, Order no. 2016–800 of 16 June 2016, and Decree no. 2016–1537 of 16 November 2016 on research involving human subjects and approved by the Personal Data Protection Committee CPP Ile de France VI. All patients gave their written informed consent before participation.

Conflicts of Interest

Fabienne Volot: declares COI from Sobi, Roche, Pfizer, Takeda and CSL Behring. Sabine Castet: received fees as consultant or speaker from CSL Behring, LFB, Novo Nordisk, Sobi, and Roche-Chugai. Alexandra Fournel: declares no COI. Birgit Frotscher: declares COI from Sobi, CSL Behring and Novo Nordisk. Benjamin Gillet: declares COI from Sobi, Roche, Roche-Chugai, Sanofi, and Novo Nordisk. Dominique Desprez: declares COI from Sobi, Roche, Takeda and CSL Behring. Brigitte Tardy: declares COI from Sobi, Roche, CSL Behring, Novo Nordisk, Baxalta, Bayer and Pfizer. Antoine Rauch: received research support for his institution from CSL Behring and Roche-Chugai, participated in clinical trials, advisory boards, and symposia for BioMarin, CSL Behring, LFB, Novo Nordisk, Octapharma, Roche-Chugai, and Sobi. Pierre Chamouni: has been a consultant for Sobi. Christine Biron-Andreani: received funding from CSL Behring, Takeda, Sobi, LFB, and Roche. Jean-Baptiste Valentin: declares COI from CSL Behring, Octapharma, and Sobi. Annie Harroche: participated in clinical trials, advisory boards, and symposia for CSL Behring, Roche, Sobi, LFB, Bayer, Takeda, Octapharma, Novo Nordisk, and Sanofi. Yesim Dargaud: received grants/research support from Bayer, Baxter, Baxalta, Novo Nordisk, CSL Behring, LFB, Pfizer, LEO Pharma, Octapharma, and Stago; an educational grant from Takeda, and honoraria from Bayer, Baxter, Novo Nordisk, CSL Behring, Sobi and Octapharma. Brigitte Pan Petesch: has been a consultant for Sobi, CSL Behring, Takeda, BioMarin, Novo Nordisk and Roche-Chugai. Roseline d'Oiron: has been a consultant for Bayer, Baxter/Baxalta/Shire/Takeda, BioMarin, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi and Spark Therapeutics. Claire Berger: declares COI for Sobi and Octapharma. Claire Reynes: declares COI from Novo Nordisk, CSL Behring and LFB. Thomas Lauvray declares no COI. Emmanuelle de Raucourt: declares COI from Sobi, LFB, CSL Behring, Roche and Takeda. Abel Hassoun: has been a consultant for Bayer, CSL Behring, and Sobi. Aurélien Lebreton: declares COI from Sobi, Takeda, LFB, Novo Nordisk, CSL Behring, Pfizer, Octapharma and Bayer. Vincent Cussac: declares COI from Takeda and Octapharma and is a Novo Nordisk employee. Hasan Catovic: declares CSL Behring employee. Cédric Martin: declares CSL Behring employee. Benoit Guillet: has been a consultant for Baxter/Baxalta/Shire/Takeda, CSL Behring, LFB, Novo Nordisk, Octapharma, Roche-Chugai and Sobi.

Data Availability Statement

CSL will only consider requests to share Individual Patient Data (IPD) that are received from systematic review groups or bona-fide researchers. CSL will not process or act on IPD requests until 12 months after article publication on a public website. An IPD request will not be considered by CSL unless the proposed research question seeks to answer a significant and unknown medical science or patient care question. Applicable country specific privacy and other laws and regulations will be considered and may prevent sharing of IPD. Requests for the use of the IPD will be reviewed by an internal CSL review committee. If the request is approved, and the researcher agrees to the applicable terms and conditions in a data sharing agreement, IPD that has been appropriately anonymized will be made available. Supporting documents including the study protocol and Statistical Analysis Plan will also be provided. For information on the process and requirements for submitting a voluntary data sharing request for IPD, please contact CSL at clinicaltrials@cslbehring.com.

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Supporting Information

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