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ORIGINAL RESEARCH

Real-World Prophylaxis Outcomes with rIX-FP and rFIXFc for Males with Hemophilia B: Pooled Analysis of Medical Chart Data from Germany and Italy

Johannes Oldenburg · Martin Olivieri · Songkai Yan · Ying Yang · Radovan Tomic · Xiang Zhang · Douglass Drelich · Natalie Jakobs · Mariasanta Napolitano

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ABSTRACT

Introduction: The current standard of care for people with severe hemophilia B is prophylaxis with factor IX (FIX) products. This analysis assessed the effectiveness of prophylaxis for people with hemophilia B (PwHB) receiving rIX-FP or rFIXFc prophylaxis in Germany and Italy.

Methods: A retrospective, de-identified chart review included PwHB ≥ 12 years with severe/moderate hemophilia B from Germany or Italy, receiving prophylaxis with rIX-FP or rFIXFc for ≥ 12 months. The primary outcome was FIX consumption; the secondary outcomes were dosing interval, annualized bleeding rate (ABR), annualized spontaneous bleeding rate (AsBR), and annualized joint bleeding rate (AjBR). These outcomes were also explored in PwHB with pre- and post-rIX-FP switch data.

Results: Of 194 PwHB, 107 and 87 received rIX-FP and rFIXFc prophylaxis, respectively. The mean FIX consumption of rIX-FP was significantly lower compared to rFIXFc (42.4 vs. 65.2 IU/kg/week, $p = 0.0001$), with mean dosing intervals of 9.5 days (rIX-FP) and 7.9 days (rFIXFc). The mean bleeding rates for rIX-FP versus rFIXFc, respectively, were: ABR 0.7 versus 1.1 ($p = 0.6704$), AsBR 0.1 versus 0.3 ($p = 0.3427$), and AjBR 0.3 versus 0.4 ($p = 0.5296$). Subgroup analyses for PwHB with severe and moderate hemophilia B separately showed similar numerical patterns when comparing these outcomes. In the 18 patients with switch data, a significant reduction in FIX consumption was observed (median 51.7 to 33.3 IU/kg/week, $p = 0.0069$), and the mean dosing interval was extended (7.2–9.5 days). The ABR (median 1.6–0.0, $p = 0.0172$; $n = 18$) and AjBR (median 0.6–0.0, $p = 0.0200$; $n = 14$) decreased significantly, while the AsBR

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J. Oldenburg
Institute of Experimental Hematology and Transfusion Medicine, University Hospital Bonn, Medical Faculty, University of Bonn, Bonn, Germany

M. Olivieri
Paediatric Thrombosis and Haemostasis Unit, Dr. Von Hauner Children's Hospital LMU Munich, Munich, Germany

S. Yan (✉) · X. Zhang · D. Drelich
CSL Behring, King of Prussia, PA, USA
e-mail: songkai.yan@cslbehring.com

Y. Yang · N. Jakobs
Adivo Associates LLC, San Francisco, CA, USA

R. Tomic
CSL Behring, Milan, Italy

M. Napolitano
PROMISE Department, University of Palermo, Palermo, Italy

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decreased but not significantly (median 0.2–0.0, $p = 0.1460$; $n = 14$).
***Conclusion*:** rIX-FP prophylaxis was associated with reduced FIX consumption versus rFIXFc and offered equally effective or potentially improved bleed protection. Additionally, PwHB who switched to rIX-FP achieved significant decreases in FIX consumption, ABR, and AjBR compared with their prior FIX product.

PLAIN LANGUAGE SUMMARY

Hemophilia B is a rare inherited bleeding disorder. People with hemophilia are more likely to bleed compared to people without hemophilia; these bleeds can occur either spontaneously or as a result of trauma. People with hemophilia are treated with medication to reduce the risk of bleeds occurring. There are various medications on the market, including coagulation factors. Most of the evidence supporting the use of these medications comes from clinical trials, which are often strictly controlled. Collecting data on the real-world use of medications is also important; however, data comparing different treatments for hemophilia B are currently limited. This study looked at the use of two medications [recombinant factor IX albumin fusion protein (rIX-FP) and recombinant factor IX Fc fusion protein (rFIXFc)] commonly used to treat people with hemophilia B in Germany and Italy. Data were collected from medical records of people with hemophilia, including how much medication was received and how often (by intravenous infusion), as well as how many bleeds occurred. The results of this study suggest that the use of one particular medication (rIX-FP) may lead to fewer infusions and reduced product usage, while providing a similar level of bleed control, compared with the other (rFIXFc). For people with hemophilia, reduced infusion frequency decreases treatment burden and, coupled with fewer bleeds, may provide meaningful improvements in the quality of life. This type of real-world study can be useful to provide clinicians with data on how different medications are used in daily clinical practice.

Keywords: Annualized bleeding rates; Dosing interval; Factor consumption; Hemophilia B; Joint bleeding rates; Prophylaxis; Real world; rFIXFc; rIX-FP; Spontaneous bleeding rates

Key Summary Points

Why carry out this study?

Hemophilia B is a rare congenital bleeding disease which, depending on severity, can result in frequent spontaneous bleeds, arthropathy, and a decrease in quality of life. Previous treatment standards included standard half-life factor IX (FIX) products which are still used for hemophilia B prophylaxis; however, there has been a shift towards using extended half-life FIX products.

There is a need for real-world data comparing the effectiveness and use patterns of extended half-life products in people with hemophilia B.

This retrospective analysis collected medical chart data in Germany and Italy to compare real-world FIX consumption and bleeding outcomes for rIX-FP and rFIXFc when used for prophylaxis in people ≥ 12 years with severe or moderate hemophilia B.

What was learned from this study?

rIX-FP prophylaxis was associated with reduced FIX consumption compared to rFIXFc prophylaxis, and was equally effective for, or potentially improved, bleed protection; switching to rIX-FP prophylaxis from prior FIX products can also reduce FIX consumption and bleeding rates.

The results of this study are in line with the findings of other non-interventional real-world studies from Germany and Italy.

INTRODUCTION

Hemophilia B, a rare congenital bleeding disorder, is characterized by factor IX (FIX) deficiency

[1]. Depending on the severity, people with hemophilia B (PwHB) can suffer from frequent spontaneous bleeds and increased trauma-related bleeding, leading to pain, arthropathy, decreased quality of life, and, in serious cases, death [1].

For people with severe hemophilia B, prophylaxis with FIX concentrates is the current standard of care [1, 2]. Extended half-life (EHL) FIX products offer prolonged dosing intervals compared to the standard half-life (SHL) products, which can help to alleviate the treatment burden for PwHB and caregivers [1, 2]. The introduction of EHL products has also enabled PwHB to improve their treatment adherence and quality of life, compared to SHL product use [1, 2].

There are two EHL FIX products widely used in Germany and Italy. Recombinant factor IX albumin fusion protein (rIX-FP; albutrepenonacog alfa, IDELVION®, CSL Behring) is a product containing a highly purified recombinant FIX (rFIX) fused to human recombinant albumin [3, 4]. Recombinant factor IX Fc fusion protein (rFIXFc; eftrenonacog alfa, ALPROLIX®, Sobi) is a protein consisting of the dimeric Fc fragment of immunoglobulin G covalently fused to rFIX [5]. Compared to SHL FIX products, both EHL products have significantly improved half-life, with a mean terminal half-life of 102 and 82 h for rIX-FP and rFIXFc, respectively [5, 6]. Another EHL FIX product, N9-GP (nonacog beta pegol, Refixia®, Novo Nordisk), has also been approved; however, the clinical utilization of this product is limited in Italy and is therefore excluded from this study.

Although several post-marketing studies of prophylaxis with rIX-FP and rFIXFc have been published, they typically evaluate the difference in clinical outcomes compared with a prior SHL FIX product after switching [7–11]. The results of post-marketing analyses assessing the effectiveness and safety of rIX-FP in PwHB who switched from a prior SHL FIX product showed that the switch to rIX-FP was associated with reduced FIX consumption and improved hemostasis [7–10, 12]. Similarly, the findings from a non-interventional study (PREVENT) in Germany demonstrated that a transition from a previous FIX product to rFIXFc prophylaxis was associated with a reduced number of infusions while maintaining bleed protection [11].

Real-world studies comparing clinical outcomes in PwHB treated with rIX-FP versus other EHL products in Europe are sparse. This retrospective analysis utilized medical chart data from Germany and Italy. Pooled data were used to compare real-world FIX consumption and bleeding outcomes for rIX-FP and rFIXFc prophylaxis in PwHB ≥ 12 years with severe or moderate hemophilia B. Furthermore, prophylaxis with rIX-FP was compared with previous FIX therapy to determine the impact of switching.

METHODS

A retrospective, de-identified chart review was conducted for PwHB aged ≥ 12 years with moderate or severe hemophilia B (1–5% or < 1% of normal FIX levels, respectively) prophylactically treated with rIX-FP or rFIXFc in German or Italian Hemophilia Treatment Centers (HTCs).

Ethical Approval

Following institutional review board (IRB) evaluation, the study was determined to be exempt from IRB oversight as it was secondary research using non-identifiable information for which informed consent is not required.

Study Population

Male PwHB who had been receiving rIX-FP or rFIXFc for prophylaxis were included in the analysis. Data were also collected on PwHB receiving N9-GP (nonacog beta pegol, Refixia®, Novo Nordisk); however, N9-GP has only been available in Italy since September 2022. Therefore, this analysis only includes comparison of prophylaxis with rIX-FP and rFIXFc in Germany and Italy, while data for rIX-FP, rFIXFc and N9-GP use in Germany will be reported elsewhere. To be included in this analysis, all PwHB were required to be on prophylaxis for at least 1 year during the data period of January 1, 2020, to January 31, 2023. Additionally, to be included in the switch analysis, a minimum of 1 year on

prior therapy was also required, therefore a data period of January 1, 2019, to January 31, 2023 was required. PwHB with inhibitors to FIX, any known coagulation disorder other than hemophilia B, and an unknown number of bleeding events were excluded from the analysis.

Measures were taken to minimize center bias and ensure robust and generalizable data were collected. Overall, 31 HTCs from Germany and 16 HTCs from Italy participated, representing geographically balanced data in each country. The protocol for data collection across all centers was standardized to ensure consistency in data entry and result comparability. Participating healthcare professionals (HCPs) were instructed to randomly select charts from all eligible PwHB. The distribution of centers was regularly assessed, and, if necessary, the recruitment strategies were adjusted to ensure a geographically balanced representation of centers throughout the study. The study sponsor remained anonymous to the participating HCPs during the sample collection to avoid potential bias in patient or brand selection.

Outcomes Assessed

The primary outcome was FIX consumption (IU/kg/week) and was calculated based on the most recently prescribed dosing regimen (i.e., dose and dosing frequency) during the observation period. The secondary outcomes were compared between prophylaxis with rIX-FP and rFIXFc: annualized bleeding rate (ABR), annualized spontaneous bleeding rate (AsBR), annualized joint bleeding rate (AjBR) (all bleed rates were calculated by annualizing the number of bleeding episodes during the observation period), and the percentage of PwHB with zero total bleeds, zero spontaneous bleeds, zero joint bleeds, and dosing interval. Data for ABR were available for all PwHB; however, data were not available for some PwHB to calculate AsBR or AjBR.

Exploratory outcomes included evaluating FIX consumption, dosing frequency, ABR, AsBR, AjBR, and zero total bleeds, zero spontaneous bleeds, and zero joint bleeds for rIX-FP prophylaxis compared with previous FIX treatment.

Statistical Analyses

Based on the distributions, generalized linear model (GLM) regression was used to compare the differences between rIX-FP and rFIXFc prophylaxis in mean FIX consumption and mean ABR, AsBR, and AjBR. The GLM model for FIX consumption included age, weight, country, and disease severity as covariates, and the Gaussian family with an identity link function was used. The GLM models for ABR, AsBR, and AjBR included age, weight, country, disease severity, and FIX consumption as covariates, and the negative binomial family was chosen with a log link function. To compare the two products for the presence of total bleeds, spontaneous bleeds, and joint bleeds, logistic regression models were used and age, weight, disease severity, country, and FIX consumption were included as covariates. Adjusted p values from these models were obtained to compare the two products.

Wilcoxon signed-rank tests were used to assess the statistical significance of differences in median FIX consumption, ABR, AsBR, and AjBR before and after switching to rIX-FP prophylaxis from a prior FIX product.

Stata® (17.0 or later version) software was used to perform the statistical analyses.

RESULTS

Study Population

Overall, data were collected for 194 PwHB receiving FIX prophylaxis (Table 1). In total, 107 PwHB were treated with rIX-FP prophylaxis and 87 were treated with rFIXFc. The mean age was 31.3 and 32.6 years for PwHB receiving rIX-FP and rFIXFc, respectively. The mean weight for PwHB receiving rIX-FP was 73.4 kg, and for PwHB receiving rFIXFc was 72.7 kg. The proportions of people with severe hemophilia B were similar across the two products [rIX-FP: 70.1% (75/107) versus rFIXFc: 69.0% (60/87), respectively]. The mean observation period for the two products was 30.2 months for rIX-FP and 30.5 months for rFIXFc.

Table 1 Study population characteristics

FIX product	rIX-FP (*n* = 107)	rFIXFc (*n* = 87)
Age (years)		
Mean (SD)	31.3 (16.1)	32.6 (19.1)
Male, n (%)	107 (100)	87 (100)
Weight (kg)		
Mean (SD)	73.4 (13.5)	72.7 (13.2)
Hemophilia B severity, *n* (%)		
Severe (FIX < 1%)	75 (70.1)	60 (69.0)
Moderate (FIX > 1–5%)	32 (29.9)	27 (31.0)
Observation period (months)		
Mean (SD)	30.2 (8.5)	30.5 (9.0)

FIX factor IX, *SD* standard deviation

FIX Consumption and Dosing

Results for FIX consumption are presented in Table 2. PwHB receiving rIX-FP prophylaxis had significantly lower mean FIX consumption compared with those receiving rFIXFc prophylaxis (42.4 versus 65.2 IU/kg/week, $p = 0.0001$). In people with severe disease ($n = 135$), mean FIX consumption was 45.4 versus 70.8 IU/kg/week ($p = 0.0016$) for rIX-FP and rFIXFc, respectively. In people with moderate disease ($n = 59$), mean FIX consumption was 35.4 versus 52.8 IU/kg/week ($p = 0.0268$), for rIX-FP and rFIXFc, respectively.

The mean dosing interval for rIX-FP was 9.5 days and 7.9 days for rFIXFc (Fig. 1). For both products, the dosing frequency for the majority of PwHB was once weekly or once within a week. The proportion of PwHB dosed every 9–12 days was 19.6% for rIX-FP versus 23.0% for rFIXFc. The percentage of PwHB dosed every 14–15 days was 24.3% of those receiving rIX-FP prophylaxis compared with 10.3% of those receiving rFIXFc prophylaxis. The percentage of PwHB dosed every 21 days was 5.6% of those receiving rIX-FP prophylaxis, whereas no PwHB receiving rFIXFc prophylaxis were dosed every 21 days.

Bleeding Rates

Bleeding rates are presented in Table 3. PwHB receiving rIX-FP or rFIXFc prophylaxis had a mean ABR of 0.7 and 1.1, respectively ($p = 0.6704$). The proportion of PwHB with zero ABR was 37.4% for the rIX-FP group and 41.4% for the rFIXFc group ($p = 0.2268$). In people with severe hemophilia B ($n = 135$), mean ABR was 0.7 versus 0.9 for rIX-FP and rFIXFc, respectively. For people with moderate disease ($n = 59$), mean ABR was 0.6 versus 1.5 for rIX-FP and rFIXFc, respectively.

The data required for calculating AsBR and AjBR were available for 159 of 194 PwHB. Mean AsBR was 0.1 and 0.3 for all PwHB receiving rIX-FP and rFIXFc prophylaxis, respectively ($p = 0.3427$). Overall, 80.7% of PwHB receiving rIX-FP and 73.2% of those treated with rFIXFc had zero AsBR ($p = 0.3370$). For those with severe hemophilia B ($n = 114$), mean AsBR was 0.2 versus 0.4, for rIX-FP and rFIXFc, respectively. In those with moderate disease ($n = 45$), mean AsBR was 0.0 versus 0.2, for rIX-FP and rFIXFc, respectively.

Mean AjBR was 0.3 and 0.4 for all PwHB receiving rIX-FP and rFIXFc prophylaxis, respectively ($p = 0.5296$). Overall, 62.5% and 62.0% of PwHB receiving rIX-FP and rFIXFc achieved

Table 2 Summary of FIX consumption

Consumption (IU/kg/week)		
FIX product	**rIX-FP (*n* = 107)**	**rFIXFc (*n* = 87)**
All PwHB		
Consumption (IU/kg/week)		
Mean (SD)	42.4 (25.1)	65.2 (48.6)
Median (min, max)	35.7 (7.5, 140.9)	50.0 (14.0, 385.7)
p value for mean FIX consumption comparison vs. rIX-FP[a]	NA	0.0001*
People with severe hemophilia B		
FIX product	**rIX-FP (*n* = 75)**	**rFIXFc (*n* = 60)**
Consumption (IU/kg/week)		
Mean (SD)	45.4 (27.1)	70.8 (51.3)
Median (min, max)	36.6 (7.5, 140.9)	54.4 (33.3, 385.7)
People with moderate hemophilia B		
FIX product	**rIX-FP (*n* = 32)**	**rFIXF (*n* = 27)**
Consumption (IU/kg/week)		
Mean (SD)	35.4 (18.4)	52.8 (40.3)
Median (min, max)	30.4 (9.7, 87.5)	45.2 (14.0, 211.8)

FIX factor IX, *IU* international units, *max* maximum, *min* minimum, *NA* not applicable, *PwHB* people with hemophilia B, *SD* standard deviation

*Represents a statistical significance ($p < 0.05$)

[a]From comparisons of products within the generalized linear model for mean FIX consumption incorporating age, weight, country, and disease severity as covariates

zero AjBR bleeds ($p = 0.9093$). Those with severe hemophilia B ($n = 114$) receiving either rIX-FP or rFIXFc had a mean AjBR of 0.3. People with moderate hemophilia B ($n = 45$) receiving rIX-FP or rFIXFc had a mean AjBR 0.1 and 0.6, respectively.

Switch Analysis

Overall, data were collected from 18 PwHB (11 from Germany and seven from Italy) who switched to rIX-FP prophylaxis from a prior FIX product (Table 4). Most PwHB switched from a recombinant FIX product (rFIXFc, 61.1%, $n = 11/18$; rFIX, 27.8%, $n = 5/18$; N9-GP, 5.6%, $n = 1/18$). One PwHB switched from a plasma-derived FIX product (human plasma coagulation factor IX, 5.6%). There were nine PwHB with severe disease and nine with the moderate form of disease. The mean observation period was 27.4 months before and 19.3 months after the switch.

Following the switch to rIX-FP prophylaxis from a prior FIX product, consumption reduced from a mean of 51.9 IU/kg/week to 34.4 IU/kg/week, with the median significantly reduced from 51.7 to 33.3 ($p = 0.0069$; Table 4).

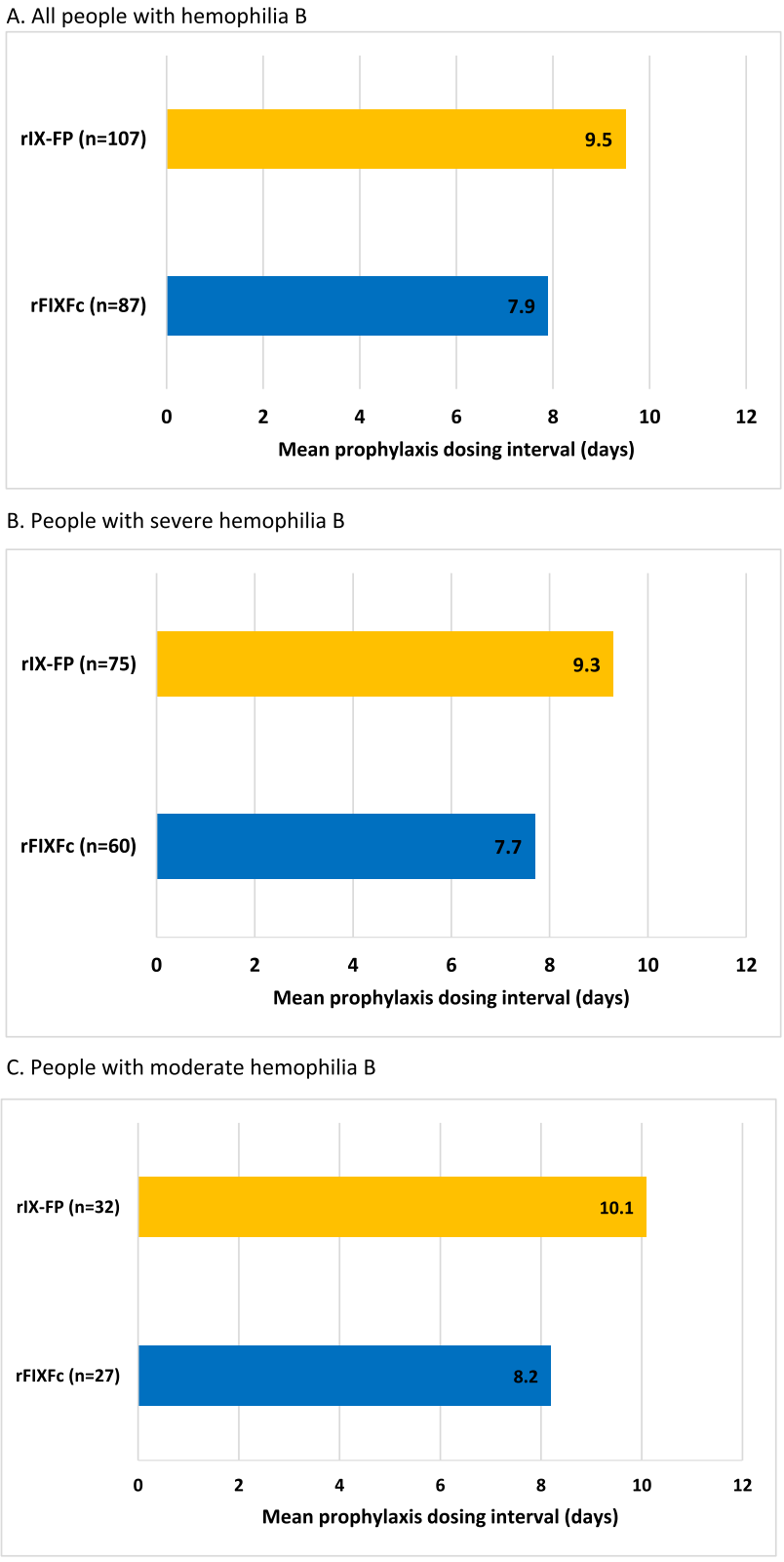

Fig. 1 The mean dosing interval by product. **A** All people with hemophilia B. **B** People with severe hemophilia B. **C** People with moderate hemophilia B

Table 3 Summary of bleeding rates (ABR, AsBR, and AjBR)

FIX product All PwHB	rIX-FP	rFIXFc
ABR		
n	107	87
Mean (SD)	0.7 (0.9)	1.1 (2.5)
Median (min, max)	0.3 (0.0, 5.2)	0.3 (0.0, 20.3)
PwHB with zero ABR, *n* (%)	40 (37.4)	36 (41.4)
p value for mean ABR comparison vs. rIX-FP[a]	NA	0.6704
p value for percentage of PwHB with zero total bleeds vs. rIX-FP[b]	NA	0.2268
AsBR		
n	88	71
Mean (SD)	0.1 (0.4)	0.3 (0.8)
Median (min, max)	0.0 (0.0, 3.2)	0.0 (0.0, 6.0)
PwHB with zero AsBR, *n* (%)	71 (80.7)	52 (73.2)
p value for mean AsBR comparison vs. rIX-FP[a]	NA	0.3427
p value for percentage of PwHB with zero spontaneous bleeds vs. rIX-FP[b]	NA	0.3370
AjBR		
n	88	71
Mean (SD)	0.3 (0.7)	0.4 (0.8)
Median (min, max)	0.0 (0.0, 5.2)	0.0 (0.0, 3.3)
PwHB with zero AjBR, *n* (%)	55 (62.5)	44 (62.0)
p value for mean AjBR comparison vs. rIX-FP[a]	NA	0.5296
p value for percentage of PwHB with zero joint bleeds vs. rIX-FP[b]	NA	0.9093
People with severe hemophilia B		
ABR		
n	75	60
Mean (SD)	0.7 (0.9)	0.9 (2.7)
Median (min, max)	0.4 (0.0, 5.2)	0.3 (0.0, 20.3)
PwHB with zero ABR, *n* (%)	26 (34.7)	27 (45.0)
AsBR		
n	64	50
Mean (SD)	0.2 (0.5)	0.4 (1.0)

Table 3 continued

People with severe hemophilia B		
Median (min, max)	0.0 (0.0, 3.2)	0.0 (0.0, 6.0)
PwHB with zero AsBR, *n* (%)	48 (75.0)	35 (70.0)
AjBR		
n	64	50
Mean (SD)	0.3 (0.7)	0.3 (0.7)
Median (min, max)	0.0 (0.0, 5.2)	0.0 (0.0, 3.3)
PwHB with zeroAjBR, *n* (%)	37 (57.8)	35 (70.0)
People with moderate hemophilia B		
ABR		
n	32	27
Mean (SD)	0.6 (0.9)	1.5 (2.2)
Median (min, max)	0.3 (0.0, 3.5)	0.3 (0.0, 8.5)
PwHB with zero ABR, *n* (%)	14 (43.8)	9 (33.3)
AsBR		
n	24	21
Mean (SD)	0.0 (0.2)	0.2 (0.4)
Median (min, max)	0.0 (0.0, 1.0)	0.0 (0.0, 1.3)
PwHB with zero AsBR, *n* (%)	23 (95.8)	17 (81.0)
AjBR		
n	24	21
Mean (SD)	0.1 (0.2)	0.6 (0.8)
Median (min, max)	0.0 (0.0, 1.0)	0.3 (0.0, 2.7)
PwHB with zero AjBR, *n* (%)	18 (75.0)	9 (42.9)

ABR annualized bleeding rate, *AjBR* annualized joint bleeding rate, *AsBR* annualized spontaneous bleeding rate, *max* maximum, *min* minimum, *NA* not applicable, *PwHB* people with hemophilia B, *SD* standard deviation

[a]From comparisons of products within the generalized linear model for ABR, AsBR and AjBR incorporating age, weight, country, disease severity, and FIX consumption

[b]From comparisons of products within the logistic regression models incorporating age, weight, disease severity, country, and FIX consumption as covariates

The mean dosing interval was extended from 7.2 days (pre-switch) to 9.5 days after the switch to rIX-FP. Overall, 94.4% (*n* = 17/18) of PwHB were dosed weekly or less frequently after the switch versus pre-switch (66.7%, *n* = 12/18). For 50.0% (*n* = 9/18) of PwHB, the post-switch dosing interval was ≥ 10 days compared with 16.7% (*n* = 3/18) of PwHB pre-switch.

Table 4 Dosage and hemostatic effectiveness in PwHB included in the switch analysis

	Before switching to rIX-FP (*n* = 18)	**After switching to rIX-FP (*n* = 18)**	***p* value**
Consumption (IU/kg/week)			
Mean (SD)	51.9 (28.5)	34.4 (11.9)	
Median (min, max)	51.7 (6.6, 140.6)	33.3 (9.7, 59.2)	0.0069*
Dosing intervals (days)			
Mean (SD)	7.2 (3.7)	9.5 (3.2)	–
PwHB dosed once weekly or less, *n* (%)	12 (66.7)	17 (94.4)	–
ABR			
Mean (SD)	1.3 (1.1)	0.4 (0.9)	
Median (min, max)	1.6 (0.0, 3.6)	0.0 (0.0, 3.5)	0.0172*
PwHB with zero bleeds, *n* (%)	4 (22.2)	11 (61.1)	–
	Before switching to rIX-FP (*n* = 14)	**After switching to rIX-FP (*n* = 14)**	***p* value**
AsBR			
Mean (SD)	0.4 (0.6)	0.1 (0.2)	
Median (min, max)	0.2 (0.0, 1.8)	0.0 (0.0, 0.7)	0.1460
AjBR			
Mean (SD)	0.8 (1.0)	0.1 (0.3)	
Median (min, max)	0.6 (0.0, 3.6)	0.0 (0.0, 1.0)	0.0200*

ABR annualized bleeding rate, *AjBR* annualized joint bleeding rate, *AsBR* annualized spontaneous bleeding rate, *IU* international units, *max* maximum, *min* minimum, *PwHB* people with hemophilia B, *SD* standard deviation

*Represents a statistical significance ($p < 0.05$)

ABR was reduced following the switch to rIX-FP prophylaxis from a previous FIX product (mean from 1.3 to 0.4; median significantly from 1.6 to 0.0, $p = 0.0172$). The percentage of PwHB with zero bleeds was 22.2% prior to the switch to rIX-FP versus 61.1% following the switch (Table 4).

The data required for calculating AsBR and AjBR were only available for 14/18 PwHB who were included in the switch analysis. Prior to the switch to rIX-FP, the mean (median) AsBR was 0.4 (0.2) compared with 0.1 (0.0) following the switch (reduction in median was not significant, $p = 0.1460$); mean (median) AjBR decreased from 0.8 (0.6) to 0.1 (0.0) and the reduction in median was significant ($p = 0.0200$).

DISCUSSION

This is one of the largest real-world studies assessing FIX consumption and effectiveness of prophylactic use of rIX-FP compared to rFIXFc in people with moderate or severe hemophilia B in Germany and Italy [7, 10]. PwHB receiving rIX-FP had a significantly lower FIX consumption (42.4 IU/kg/week) than those receiving rFIXFc (65.2 IU/kg/week; $p = 0.0001$). The mean weekly rIX-FP consumption was within the range of a rIX-FP prophylaxis dose recommended by the Summary of Product Characteristics (EU) (35–50 IU/kg/week) [13].

The mean dosing interval for rIX-FP was numerically longer, compared to rFIXFc. PwHB treated with rIX-FP had numerically lower bleeding rates compared to rFIXFc, and the proportion of all PwHB with zero bleeds was numerically higher for the rIX-FP treatment group versus the rFIXFc group. After the switch to rIX-FP from a prior FIX product, the median FIX consumption, ABR, and AjBR decreased significantly, with a sizeable extension of the dosing interval.

Compared to SHL FIX products, EHL FIX products allow PwHB to extend their dosing intervals and reduce infusion frequency due to the higher FIX levels achieved [1, 14]. This dosing interval extension allows PwHB to tailor their dosing regimen to meet their specific needs based on their lifestyle [1, 14]. The present study showed that, compared to another widely used EHL FIX product, rIX-FP prophylaxis in PwHB aged ≥ 12 years allows longer dosing intervals with decreased FIX consumption while allowing (or ensuring) a similar or potentially better hemostasis. As a result, this may reduce the treatment burden on PwHB and their caregivers while maintaining protection from bleeds. The outcomes from this study align with the results of clinical trials with rIX-FP demonstrating that the dosing frequency can be extended to up to 10 or 14 days (or 21 days in selected adult PwHB) while maintaining effective hemostasis [6, 15]. The current study outcomes also align with the clinical trials with rFIXFc, where the majority of patients were treated on weekly prophylaxis or on individualized prophylaxis varying between every 8–16 days (median dosing interval of 14 days), patients treated on either regimen were able to maintain effective hemostasis [16]. The outcomes of this study are also in line with the real-world data from Germany and Italy comparing rIX-FP to SHL products [7–9], and in line with real-world data from Germany comparing rFIXFc to SHL products [11]. Similarly to PwHB in other real-world studies, those who switched from a prior FIX product to rIX-FP in this study had significantly reduced weekly FIX consumption and numerically lower ABR than their previous treatment [7, 10].

Compared with participants in clinical trials, who must meet strict inclusion and exclusion criteria, such as selected ranges of hemophilia severity and restrictions on inhibitor status [6, 17, 18], the cohorts analyzed in real-world studies are typically more diverse (including potential comorbidities and demographic diversity). Therefore, demonstrating clinical effectiveness in real-world settings is needed to confirm the results of clinical trials and might enable more generalizable results than clinical trials.

Limitations

Limitations of the current study include a potential selection bias due to center distribution, and because PwHB were not randomized and HCPs were not blinded due to the retrospective and observational nature of the study. Specific procedures for randomization of chart selection were not possible to enforce, therefore each study center utilized their own criteria to identify eligible charts, independent of any influence from the authors. Thus, the findings may not be fully generalizable to the overall hemophilia B population. There may also be a potential variation in PwHB management in practices across participating centers, and we are unable to evaluate its effect on the results. Some centers only report data on one product. Despite this, the distribution of patients using the two products across broad geographic regions within each country helps to mitigate concerns regarding product-specific bias. Notably, no consistent trends were observed that would indicate a systematic bias favoring either product. We also acknowledge that patient chart studies include the risk of incomplete or inaccurate documentation and often involve relatively small sample sizes for rare diseases such as hemophilia B. There are also limitations in assessing the impact of potential confounding variables in this study, for example, due to the multiple-year history of the two products in both countries, baseline joint health and bleeding rates before initiating the products were not available for many patients, and assessment of physical activity data is often not well reported. Additionally, bleeding outcomes, particularly percentage of PwHB with no bleeds calculated for each product, may be affected by differences in the mean duration of observation periods for every product.

Finally, FIX consumption may not accurately reflect the actual FIX consumption by PwHB, as it was calculated based on the dosing regimen from prescriptions recorded in medical charts. While recognizing the study limitations, the findings of this study align with the results of the other non-interventional real-world studies from Germany and Italy [7–9, 11]. The design of the current study also aligns with other chart review studies in hemophilia A [19–22]. Due to the X-linked nature of hemophilia B, the majority of patients receiving treatment for moderate and severe disease are male. As such, this current study included only male patients. As the goals of treatment for PwHB move towards total control of disease, regardless of disease severity, future studies of female patients are needed to ensure fair representation within the treatment space [1, 23].

CONCLUSION

rIX-FP prophylaxis was associated with reduced FIX consumption versus rFIXFc and offered equally effective or potentially improved bleed protection. Additionally, PwHB who switched to rIX-FP achieved significant decreases in FIX consumption, ABR, and AjBR compared with their prior FIX product.

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Data Availability. These data from this study have not been published in a repository; contact the corresponding author for additional information.

Declarations

Conflict of interest. Johannes Oldenburg has received research funding from Bayer, Biotest, CSL Behring, Octapharma, Pfizer, Swedish Orphan Biovitrum and Takeda; consultancy, speakers bureau, honoraria, scientific advisory board and travel expenses from Bayer, Biogen Idec, BioMarin, Biotest, Chugai, CSL Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Spark Therapeutics, Swedish Orphan Biovitrum and Takeda; Martin Olivieri has received grants/research support from Bayer, Biomarin, Biotest, Takeda, CSL Behring Octapharma, Pfizer, Shire, Roche, Stago and Swedish Orphan Biovitrium, consultancy and speaker fees from Bayer, BioMarin, Biotest, Novo Nordisk, Takeda, CSL Behring, Pfizer, Roche and Swedish Orphan Biovitrium; Songkai Yan, Radovan Tomic, Xiang Zhang and Douglass Drelich are employees of CSL Behring; Ying Yang and Natalie Jakobs are employees of Adivo Associates; Mariasanta Napolitano has acted as consultant for Bayer, Novo Nordisk, Sobi, Kedrion, and has received speaker fees from Takeda, CSL Behring, Bayer, Novo Nordisk, Kedrion, Novartis, Amgen, Sobi, Sanofi Genzyme, Pfizer.

Ethics/Ethical approval. Following IRB evaluation, the study was determined to be exempt from IRB oversight as it was secondary research using non-identifiable information for which informed consent is not required.

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