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ORIGINAL ARTICLE

Real-world usage and effectiveness of recombinant factor VIII/factor IX Fc in hemophilia A/B: final data from the 24-month, prospective, noninterventional PREVENT study in Germany

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Abstract

Background: Real-world experience with efmoroctocog alfa (a recombinant factor [F] VIII Fc fusion protein [rFVIIIFc]) and eftrenonacog alfa (a recombinant factor IX Fc fusion protein [rFIXFc]) is needed to bridge evidence gaps.

Objectives: To describe rFVIIIFc/rFIXFc usage and effectiveness over a 24-month prospective period.

Methods: PREVENT (NCT03055611), a noninterventional study across 25 German hemophilia treatment centers, enrolled previously treated persons with hemophilia A and B (all ages/severities) on individualized rFVIIIFc/rFIXFc prophylaxis before/at enrollment. Primary endpoints included annualized bleeding rate (ABR), injection frequency (IF), and factor consumption (FC). Additionally, up to 12 months of retrospective FVIII/FIX data were collected. Physician and patient satisfaction, and safety outcomes were also assessed.

Results: Overall, 150 patients received ≥1 rFVIIIFc dose and 47 patients received ≥1 rFIXFc dose, with median prospective follow-up of 20.6 and 21.0 months, respectively. rFVIIIFc/rFIXFc demonstrated low median ABR (0.5/1.7), annualized IF (121.8/52.2 injections/y), and FC (4611.7/2423.9 IU/kg) in line with product labels. Compared with previous FVIII/FIX, there was a 56.0% reduction in ABR for rFVIIIFc (rate ratio, 0.44; 95% CI, 0.31-0.64), with no change for rFIXFc (rate ratio, 0.93; 95% CI, 0.66-1.31); rFVIIIFc/rFIXFc reduced annualized IF (rFVIIIFc, mean difference, −31.7; 95% CI, −40.3 to −23.1; rFIXFc, mean difference, −37.3; 95% CI, −46.9 to −27.8), while FC remained stable (rFVIIIFc, +374.1; 95% CI, +46.8 to +701.3; rFIXFc, +503.9; 95% CI, +95.4 to +912.4). Most physicians and patients were satisfied or highly satisfied with rFVIIIFc/rFIXFc. rFVIIIFc/rFIXFc were well tolerated, with no inhibitor development or treatment-related serious adverse events.

Some data reported in this article have been published previously at the 2019 Annual Meeting of the Society of Thrombosis and Haemostasis Research, the 2020 and 2021 International Society on Thrombosis and Haemostasis congresses, and the 2023 European Association for Haemophilia and Allied Disorders Congress.

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Conclusion: Real-world PREVENT data complement phase 3 trials and show that individualized rFVIIIFc/rFIXFc prophylaxis provided stable bleed protection with low IF and maintained FC. Compared with previous FVIII, ABR was considerably reduced with rFVIIIFc, with stable annualized FC. For rFIXFc, bleed protection was maintained vs previous FIX while reducing annualized IF.

KEYWORDS
hemophilia A, hemophilia B, recombinant fusion protein, rFVIIIFc, rFIXFc

Essentials

- PREVENT assessed recombinant factor (F)VIII Fc (rFVIIIFc)/recombinant factor FIX Fc (rFIXFc) use and effectiveness in Germany.
- rFVIIIFc/rFIXFc prophylaxis offered stable bleed protection and low factor use over ~21 months.
- rFVIIIFc improved bleed protection with stable factor use compared with previous FVIII.
- rFIXFc maintained bleed protection with fewer injections than previous FIX.

1 | INTRODUCTION

The standard of care for persons with hemophilia A (HA) or hemophilia B (HB), particularly those with severe disease or moderate disease with a severe phenotype, is regular prophylactic treatment with replacement factor (F)VIII or FIX, respectively [1]. The primary aim of long-term prophylaxis is to prevent recurrent joint bleeding, which constitutes up to 80% of all bleeding episodes, and subsequently mitigate the development of hemophilic arthropathy, which is a major cause of morbidity and reduced health-related quality of life [1–3].

The hemophilia community has set more ambitious treatment goals aiming to establish normal hemostasis as the new, higher standard of care [4]. Individualized prophylaxis with extended half-life (EHL) FVIII and FIX products, such as efmoroctocog alfa (a recombinant FVIII Fc fusion protein, herein rFVIIIFc) and eftrenonacog alfa (a recombinant factor IX Fc fusion protein, herein rFIXFc), can offer improved or intensified bleed protection with reduced treatment burden compared with standard half-life (SHL) products or similar alternatives [5,6].

Although the efficacy and safety of both rFVIIIFc and rFIXFc have been established across phase 3 pivotal and extension studies [7–14], more real-world evidence is needed to investigate factor usage and confirm their effectiveness in clinical practice. rFVIIIFc and rFIXFc are licensed for the treatment and prophylaxis of bleeding episodes in persons with HA or HB, respectively, and received reimbursement in Germany in June 2016 and December 2016 [15–18].

PREVENT (NCT03055611) was a 24-month prospective, noninterventional, phase 4 study, which aimed to provide further insights into the real-world experience with these products in persons with HA and HB across hemophilia treatment centers (HTCs) in Germany. Here, we report the final data from PREVENT.

2 | METHODS

2.1 | Study design and patients

PREVENT (NCT03055611) was a prospective, noninterventional, multicenter, phase 4 study conducted in Germany. The primary objective was to describe the real-world usage and effectiveness of rFVIIIFc/rFIXFc in persons with HA/HB over a 24-month (±6 months) prospective period (Figure 1). Additionally, retrospective data on previous SHL FVIII or FIX products, for up to 12 months, were collected for comparison. PREVENT adhered to the International Conference on Harmonization Guidelines for Good Clinical Practice and ethical principles in compliance with the Declaration of Helsinki [19,20].

Persons of all ages and with all severities of hemophilia who had previously been treated with an FVIII/FIX product were enrolled. Eligible patients were either on rFVIIIFc/rFIXFc prophylaxis before enrollment or prescribed rFVIIIFc/rFIXFc prophylaxis at study entry, irrespective of study participation. To minimize selection bias, a broad coverage of HTCs in Germany was invited to participate. Enrollment took place during routine clinic visits at participating HTCs. Subsequent on-study visits and the end-of-study visit (ie, the first patient visit occurring within the 18- to 30-month interval [24 ± 6 months] after enrollment) followed routine clinical care practice, including on-site visits, home visits, or phone calls. Protocol amendments allowed for delayed end-of-study visits beyond 30 months for sites impacted by COVID-19 (see Figure 1 footnotes for more details).

The period before the first rFVIIIFc/rFIXFc injection contributed to the 12-month retrospective period on previous FVIII/FIX products, while the period from enrollment to the last study visit contributed to the prospective period on rFVIIIFc/rFIXFc. The date of the first rFVIIIFc/rFIXFc injection, which could have occurred prior to study entry, was collected at the enrollment visit in order to determine the

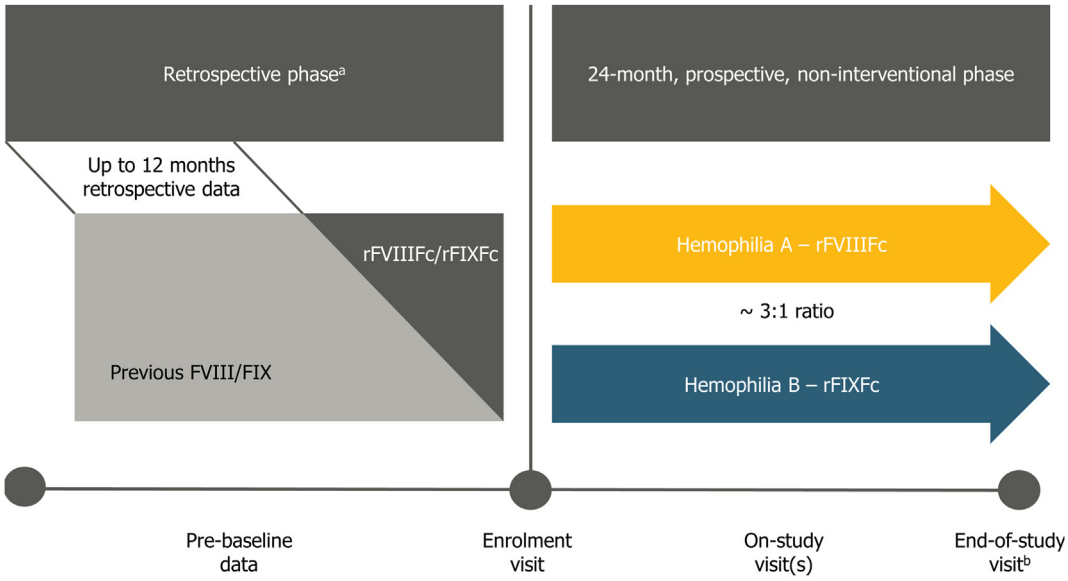

FIGURE 1 PREVENT study design. For patients on recombinant factor (F)VIII Fc (rFVIIIFc)/recombinant FIX Fc (rFIXFc) prophylaxis prior to enrollment, the 12 months before the treatment switch was considered the retrospective period on previous FVIII/FIX, with the prospective period beginning at enrollment visit. In cases where patients were prescribed rFVIIIFc/rFIXFc at inclusion, but initiated rFVIIIFc/rFIXFc after enrollment, the initial short period on FIX/FVIII treatment (typically a few days/weeks) contributed to the 12-month retrospective period. There were no limitations on prior/concomitant treatments during PREVENT. However, participation in an investigational medicinal product trial at any time during the 4 weeks before the first injection with rFVIIIFc/rFIXFc up to the enrollment visit was not permitted. Patients who discontinued prophylactic treatment with rFVIIIFc/rFIXFc during the study or enrolled in an investigational medicinal product trial were withdrawn from the study. [a]Retrospective data were collected for 12 months prior to the first rFVIIIFc/rFIXFc injection, including data on the prescribed and dispensed FVIII/FIX product. [b]The first patient visit performed in the 18- to 30-month (24 ± 6 months) interval after baseline was defined as the end-of-study visit. The patient was prematurely discontinued if no visit was available within this time interval. For sites affected by the COVID-19 outbreak (ie, a routine patient visit was cancelled/postponed), the end-of-study visit could be performed later than 30 months after baseline if necessary. However, the patient was prematurely discontinued if no visit was available before 30 months after the last patient's first visit in the study.

end of the retrospective period. rFVIIIFc/rFIXFc prophylaxis was prescribed according to the clinical judgment of the treating physician and in discussion with the patient. Dosing regimens were individualized in accordance with clinical practice and the relevant summary of product characteristics.

2.2 | Outcome measures and data collection

At enrollment, ≤12-month retrospective data on previous FVIII/FIX treatment (prescribed and dispensed), and data on patient characteristics, bleeding episodes, and target joints, defined as joints in which ≥3 spontaneous bleeding episodes occurred for 6 consecutive months during the retrospective period, were collected.

The following annualized primary endpoints were used to evaluate the real-world usage of rFVIIIFc/rFIXFc prophylaxis during the prospective period: annualized bleeding rate (ABR; assessed by local practice), annualized injection frequency (assessed by prescription), and annualized factor consumption (assessed by dispensed factor product) during the prospective period. Additionally, the proportion of patients experiencing 0 bleeding episodes (nonannualized analysis) at 6-month intervals was also evaluated to assess the primary objective.

Secondary endpoints included change in ABR, annualized injection frequency, and annualized factor consumption between the prospective and retrospective periods, prescribed prophylactic dose and dosing frequency (including treatment adjustments and reason for changes in prescribed dose and frequency), annualized joint bleeding rate (AJBR), annualized target joint bleeding rate (ATJBR), target joint resolution during the prospective period (defined as <3 bleeds, within a 12-month period, in the target joints identified at enrollment [potential new target joints were not evaluated]), and physician satisfaction with outcome of rFVIIIFc/rFIXFc treatment using a 5-point scale (highly dissatisfied, dissatisfied, neutral, satisfied, or highly satisfied). Patient-reported outcomes (PROs) included EuroQol-5 Dimensions-5 Levels (EQ-5D-5L), Hemophilia Activities List (HAL)/Pediatric Hemophilia Activities List (pedHAL; range, 0-100, with low scores indicating worse functional status), assessment of patient satisfaction with outcome of rFVIIIFc/rFIXFc treatment using the aforementioned 5-point scale and change from enrollment in PROs. Further details on PROs are provided in the Supplementary Methods. Physicians' justifications for initiating prophylactic rFVIIIFc/rFIXFc treatment are also reported.

Safety data, including serious adverse events (SAEs) during treatment with rFVIIIFc/rFIXFc from the first injection until the last study visit, non-SAEs leading to permanent discontinuation of

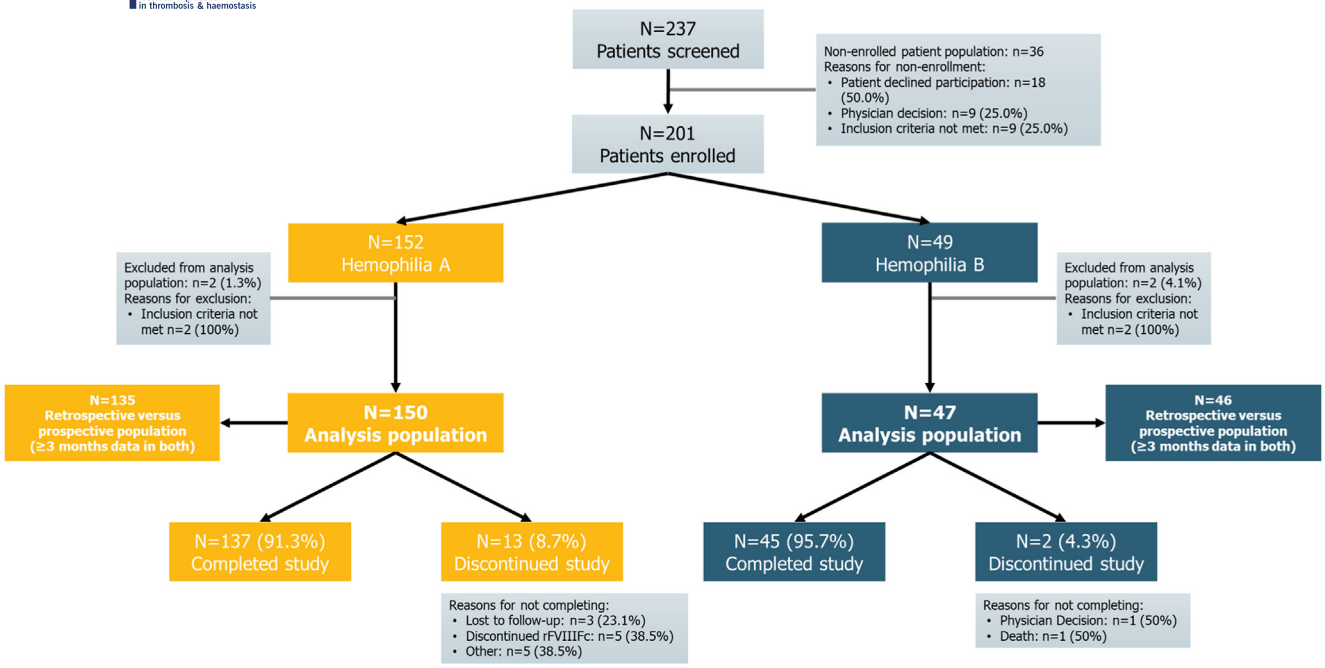

FIGURE 2 Disposition of patients in PREVENT. Patients in the retrospective vs prospective period population had ≥3 months of treatment data on prestudy factor (F)VIII/FIX and onstudy recombinant factor FVIII Fc (rFVIIIFc)/recombinant FIX Fc during the retrospective and prospective periods, respectively.

rFVIIIFc/rFIXFc, and inhibitor development (≥0.60 BU/mL), were collected during the prospective period.

Clinical data and PROs were collected from medical records, patient diaries, and patient reports at routine visits throughout the 24-month prospective period.

2.3 | Statistical analysis

Descriptive statistics were used to summarize all continuous variables, while categorical variables were presented in frequency tables.

Only patients with ≥3-month treatment duration with respective products (FVIII/FIX prior to switch or rFVIIIFc/rFIXFc after switch) from enrollment were included in the analyses of annualized endpoints. Prespecified subgroup analysis of primary endpoints by age category (<12 years and ≥12 years) was also performed.

Patient characteristics and effectiveness outcomes in patients with or without dose adjustments were assessed in a post hoc analysis to identify predictors of dose adjustments.

Model-based estimates for ABR, AJBR, and ATJBR were derived using negative binomial regression models (not included in the original predefined statistical analysis plan). Imputation of missing data was performed for PROs based on the scoring instructions of the respective questionnaires.

3 | RESULTS

From May 9, 2017, to January 15, 2020, PREVENT prospectively enrolled 201 persons with HA/HB across 25 HTCs in Germany (Supplementary Figure S1). The analysis population comprised 150 persons with HA and 47 persons with HB (who received ≥1 dose of rFVIIIFc/rFIXFc during the prospective period), of which 137 (91.3%) and 45 (95.7%), respectively, completed the study (Figure 2).

3.1 | Analysis population and duration of prospective follow-up

Of the 150 persons with HA, 149 were male and most had severe HA (88.0%), with a median age of 21.0 years. Among these patients, 43.3% (*n* = 65) were aged <18 years. All 47 persons with HB were male, and most (89.4%) had severe HB. Median age was 26.0 years, and 31.9% (*n* = 15) were aged <18 years (Table 1).

Among persons with HA, 57.4% (*n* = 78/136) were prescribed recombinant treatments for prophylaxis in the 12 months prior to switching to rFVIIIFc and 43.4% (*n* = 59/136) were prescribed plasma-derived treatments; among persons with HB, 54.3% (*n* = 25/46) were prescribed plasma-derived treatments and 47.8% (*n* = 22/46) were prescribed recombinant treatments for prophylaxis (including 3 patients on EHL products [recombinant FIX albumin fusion protein]) in the 12 months prior to switching to rFIXFc. Before enrollment, 85.3% (*n* = 128) and 74.5% (*n* = 35) of patients had already initiated rFVIIIFc and rFIXFc prophylaxis, respectively, with a median (range) duration of 8.6 (0.1-43.7) and 12.0 (0.1-33.4) months between rFVIIIFc/rFIXFc initiation and study enrollment. The median (range) duration of prospective follow-up on rFVIIIFc and rFIXFc prophylaxis during PREVENT was 20.6 (0.5-30.0) and 21.0 (3.9-29.7) months.

TABLE 1 Patient demographics and disease characteristics at enrollment.

Demographics and disease characteristics	Hemophilia A (*n* = 150)	Hemophilia B (*n* = 47)
Age (y), median (range)	21.0 (0-74)	26.0 (2-78)
Age category, *n* (%)		
<12 y	44 (29.3)	9 (19.1)
≥12 to <18 y	21 (14.0)	6 (12.8)
≥18 to <65 y	83 (55.3)	29 (61.7)
≥65 y	2 (1.3)	3 (6.4)
Sex,[a] *n* (%)		
Male	149 (99.3)	47 (100)
Female	1 (0.7)	0
Severity of hemophilia, *n* (%)		
Severe	132 (88.0)	42 (89.4)
Moderate	17 (11.3)	4 (8.5)
Mild	1 (0.7)	1 (2.1)
Relevant comorbidities, *n* (%)		
Yes	23 (15.3)	13 (27.7)
HIV	17 (11.3)	5 (10.6)
HCV	13 (8.7)	0
Liver disease	2 (1.3)	3 (6.4)
Renal disease	2 (1.3)	1 (2.1)
CV disease	3 (2.0)	1 (2.1)
Depression	1 (0.7)	0
Nonhemophilic acute or chronic medical conditions causing mobility/joint problems	4 (2.7)	4 (8.5)
No	127 (84.7)	34 (72.3)
History of inhibitors, *n* (%)		
Yes	24 (16.0)	2 (4.3)
Available positive inhibitor test (≥0.60 BU/mL)	17	2[b]
High titer inhibitors (≥5.0 BU/mL)[c]	9 (52.9)	1 (50.0)
Low titer inhibitors (≥0.60 to <5.0 BU/mL)	8 (47.1)[d]	1 (50.0)
No	126 (84.0)	45 (95.7)
Treatment status at enrollment, *n* (%)		
Initiating rFVIIIFc/rFIXFc prior to enrollment	128 (85.3)	35 (74.5)
Type of prophylactic FVIII/FIX prescribed 12 mo prior to initiating rFVIIIFc/rFIXFc[e,f,g]		
n	136	46
Missing	14	1
Recombinant	78 (57.4)	22 (47.8)
Plasma-derived	59 (43.4)	25 (54.3)
History of prophylaxis prior to rFVIIIFc/rFIXFc, *n* (%)		
n	132	41
Missing	18	6
Primary prophylaxis	57 (43.2)	19 (46.3)
Secondary prophylaxis	52 (39.4)	15 (36.6)
Tertiary prophylaxis	21 (15.9)	7 (17.1)
Not applicable	2 (1.5)	0
Patients with ≥1 target joint at enrollment,[h] *n* (%)	15/136 (11.0)	3/46 (6.5)

Percentage values may not sum to 100 due to rounding.

BU, Bethesda unit; CV, cardiovascular; FIX, factor IX; FVIII, factor VIII; HCV, hepatitis C virus; HIV, human immunodeficiency virus; rFIXFc, recombinant factor IX Fc fusion protein; rFVIIIFc, recombinant factor VIII Fc fusion protein.

[a]Sex as assigned at birth.

[b]Both patients tolerized prior to enrollment.

[c]All patients were tolerized prior to enrollment.

[d]All patients had inhibitor test results <0.60 BU/mL except 1 patient with a single result of 0.60 BU/mL during follow-up.

[e]A patient may have had several previous factor treatments prescribed within 12 months prior to first injection of rFVIIIFc/rFIXFc.

[f]Including 3 patients receiving recombinant FIX albumin fusion protein.

[g]Fourteen persons with hemophilia A and 5 persons with hemophilia B were treated on-demand with FVIII/FIX at any time in the 12 months prior to first injection of rFVIIIFc/rFIXFc.

[h]Target joints were defined as joints in which ≥3 spontaneous bleeding episodes occurred for 6 consecutive months during the 12-month retrospective period.

3.2 | ABR, annualized injection frequency, and annualized factor consumption

During the prospective period, median (IQR) ABR was 0.5 (0.0-1.7) and 1.7 (0.0-4.6) for rFVIIIFc and rFIXFc prophylaxis, respectively (Table 2, Figure 3 and Table 3, Figure 4). Corresponding values for

TABLE 2 Annualized bleeding rate, annualized injection frequency, and annualized factor consumption (dispensed) before and after the switch to recombinant factor (F)VIII Fc fusion protein in patients with a previous FVIII treatment duration of ≥3 months.[a]

Outcome measures	12-mo retrospective period on previous FVIII[b]	24-mo prospective period on rFVIIIFc[c]	Change
ABR			
n	135	135	135
Mean (95% CI)	3.6 (2.6 to 4.9)[d]	1.6 (1.2 to 2.1)[d]	Rate ratio, 0.44 (0.31 to 0.64)[e]
Median	1.0	0.5	0.0
IQR	0.0 to 3.0	0.0 to 1.7	−2.5 to +0.3
Annualized injection frequency (injections/y)			
n	135	135	135
Mean (95% CI)	162.3 (152.4 to 172.2)	130.6 (124.1 to 137.2)	Difference, −31.7 (−40.3 to −23.1)
Median	156.5	121.8	−26.1
IQR	130.4 to 182.6	104.4 to 156.5	−52.2 to 0.0
Range	52.2 to 365.3	52.2 to 365.3	−243.5 to +78.3
Annualized factor consumption (dispensed, IU/kg)[f]			
n	132	132	132
Mean (95% CI)	4326.9 (3920.9 to 4732.9)	4701.0 (4341.9 to 5060.0)	Difference, +374.1 (+46.8 to +701.3)
Median	4013.7	4570.0	+430.2
IQR	2651.5 to 5225.0	3393.4 to 5505.7	−522.9 to +1402.5
Range	385.9 to 13,481.4	789.8 to 14,381.7	−6607.1 to +5718.9

ABR, annualized bleeding rate; FVIII, factor VIII; rFVIIIFc, recombinant factor VIII Fc fusion protein.
[a]One-hundred thirty-five out of 150 (90.0%) patients had ≥3 months of treatment with previous FVIII.
[b]Calculated if the duration on previous factor treatment was ≥3 months to reduce potential misclassification; for patients initiated with rFVIIIFc before enrollment, only data under previous factor treatment within 12 months prior to first injection of rFVIIIFc were considered.
[c]Calculated if the duration of rFVIIIFc during the 24-month prospective period was ≥3 months to reduce potential misclassification.
[d]Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed period duration (in years) as an offset variable.
[e]Estimated using a repeated negative binomial model with treatment period (prospective vs retrospective) as a covariate.
[f]Missing data (n = 3).

prescribed annualized injection frequency were 121.8 (104.4-156.5) and 52.2 (52.2-63.6) injections/y (Table 2, Figure 3 and Table 3, Figure 4); corresponding values for dispensed annualized factor consumption were 4611.7 (3428.3-5591.2) and 2423.9 (1852.2-3490.7) international units per kilogram (IU/kg; Table 2, Figure 3 and Table 3, Figure 4).

When stratified by age group, average ABR and annualized injection frequency on rFVIIIFc were consistent between patients aged <12 years and those aged ≥12 years, while annualized factor consumption tended to be higher in patients aged <12 years than in those aged ≥12 years (Figure 3). For rFIXFc, patients aged <12 years had a similar average ABR and annualized injection frequency compared with those aged ≥12 years. However, patients aged <12 years had higher annualized factor consumption compared with those aged ≥12 years (Figure 4).

3.3 | Zero bleeding episodes

Throughout the prospective period, the proportion of patients experiencing 0 bleeding episodes was maintained at 6-month intervals up to month 18 (Figure 5). Limited data were available for patients up to month 24 due to missing observations.

3.4 | Change (prospective vs retrospective period) in ABR, annualized injection frequency, and annualized factor consumption

One-hundred thirty-five (90.0%) persons with HA and 46 (97.9%) persons with HB had ≥3 months of treatment data on prestudy FVIII/FIX and onstudy rFVIIIFc/rFIXFc during the retrospective and prospective periods, respectively. Median (range) treatment duration during the retrospective period was 12.0 (4.4-12.0) and 12.0 (9.4-12.0) months for HA and HB, respectively. Median (range) treatment duration during the prospective period was 20.7 (4.1-30.0) and 20.9 (3.9-29.7) months.

For rFVIIIFc, there was a 56.0% mean reduction in ABR (rate ratio, 0.44; 95% CI, 0.31-0.64) compared with previous SHL FVIII treatment. No change in ABR (rate ratio, 0.93; 95% CI, 0.66-1.31) was observed for rFIXFc when compared with previous FIX. Mean (95%

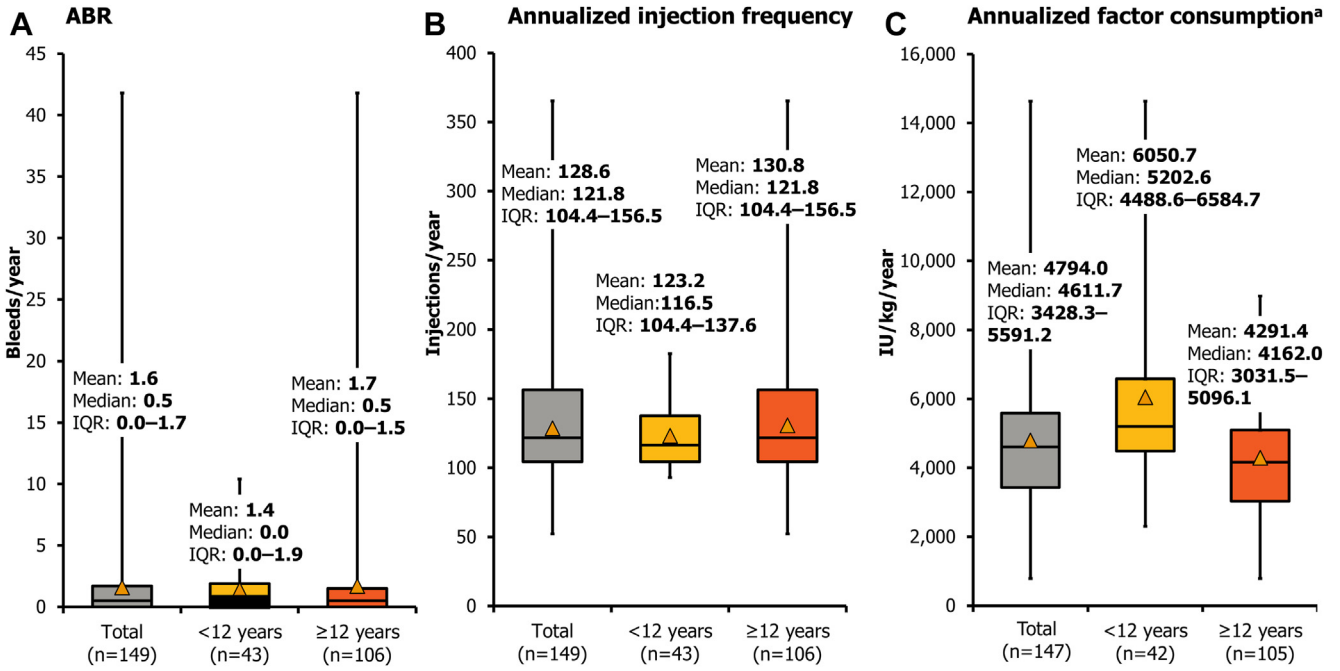

FIGURE 3 Annualized bleeding rate (ABR), annualized injection frequency, and annualized factor consumption for recombinant factor (F) VIII Fc fusion protein (rFVIIIFc) during the 24-month prospective period. Orange triangles represent means, box boundaries represent IQRs, and error bars represent ranges, with thick black lines indicating equal medians and quartiles. Patients with <3 months on recombinant FVIII Fc (n = 1) during the 24-month prospective period were excluded from analysis of annualized endpoints in order to reduce potential misclassification. [a]Missing data (total, n = 2; <12 years, n = 1; ≥12 years, n = 1).

CI) difference in annualized injection frequency for rFVIIIFc and rFIXFc was −31.7 (−40.3 to −23.1) and −37.3 (−46.9 to −27.8) injections/y, respectively, with a mean (95% CI) difference in annualized factor consumption of +374.1 (+46.8 to +701.3) and +503.9 (+95.4 to +912.4) IU/kg, respectively (Tables 2 and 3).

3.5 | Physician justification for initiating prophylactic rFVIIIFc/rFIXFc treatment

The most common clinical justification for initiating rFVIIIFc and rFIXFc prophylaxis was to "reduce injection frequency while maintaining protection from bleeds" in persons with HA (68.0%, n = 102/150) and HB (77.3%, n = 34/44), respectively.

Stratifying by clinical justification showed that patients who initiated rFVIIIFc prophylaxis to "improve protection from bleeds" (30.7%, n = 46/150) had the highest on-study mean ABR (Supplementary Table S1). This group also had a slightly higher annualized factor consumption, while annualized injection frequency was generally consistent regardless of the reason for initiating rFVIIIFc prophylaxis.

For rFIXFc, mean annualized endpoints were highest in the group initiating rFIXFc prophylaxis to "improve protection from bleeds" (22.7%, n = 10/44; Supplementary Table S2). All persons in this group had severe HB, and 3 patients had ≥1 target joint at enrollment. Median age was 26.5 years, with 40.0% of patients (n = 4) aged <12 years. At enrollment, 90.0% (n = 9/10) of patients were already receiving rFIXFc prophylaxis (n = 1 initiated rFIXFc at enrollment) and only 1 patient had prior on-demand treatment with previous FIX. Prestudy mean/median ABR on previous rFVIII/rFIX was 10.3/5.5, annualized injection frequency was 93.2/81.2 injections/y, and annualized factor consumption was 2498.2/1539.5 IU/kg. Change (prospective vs retrospective period) in mean/median ABR was −3.8/−2.6, change in annualized injection frequency was −17.4/−4.7 injections/y, and change in annualized factor consumption was +1366.1/+1923.6 IU/kg for these 10 patients.

3.6 | Real-world usage of rFVIIIFc/rFIXFc prophylaxis

Prescribed weekly dose at enrollment (see Supplementary Results and Supplementary Figures S2 and S3) was maintained during the prospective period for 72.7% and 55.3% of persons with HA and HB, respectively. Of the 150 persons with HA, 41 (27.3%) required adjustments to the weekly dose (IU/kg) prescribed at enrollment, of which 73.2% had 1 adjustment. Among persons with HB, 21 out of 47 patients had dose adjustments, with 52.4% requiring 1 adjustment. Most patients on rFVIIIFc (87.8%, n = 36/41) and rFIXFc (95.2%, n = 20/21) required at least 1 weekly dose increase (Supplementary Figures S4 and S5), while 8 (19.5%) and 10 (47.6%) patients required at least 1 weekly dose decrease, respectively. The most common reason for adjustment was to "improve protection from bleeds" for both rFVIIIFc and rFIXFc (Supplementary Figures S6 and S7).

TABLE 3 Annualized bleeding rate, annualized injection frequency, and annualized factor consumption (dispensed) before and after the switch to recombinant factor (F)IX Fc fusion protein in patients with a previous FIX treatment duration of ≥3 months.[a]

Outcome measures	12-mo retrospective period on previous FIX[b]	24-mo prospective period on rFIXFc[c]	Change
ABR			
n	46	46	46
Mean (95% CI)	3.2 (1.9 to 5.4)[d]	2.96 (2.0 to 4.4)[d]	Rate ratio, 0.93 (0.66 to 1.31)[e]
Median	1.0	1.8	+0.3
IQR	0.0 to 2.0	0.0 to 4.6	−1.0 to +2.2
Annualized injection frequency (injections/year)			
n	46	46	46
Mean (95% CI)	99.8 (90.9 to 108.7)	62.45 (56.0 to 68.9)	Difference, −37.3 (−46.9 to −27.8)
Median	104.4	52.2	−50.6
IQR	89.4 to 121.8	52.2 to 63.6	−52.2 to −6.9
Range	45.7 to 182.6	36.5 to 139.2	−104.4 to +29.8
Annualized factor consumption (dispensed, IU/kg)[f]			
n	42	42	42
Mean (95% CI)	2467.2 (2008.4 to 2926.0)	2971.1 (2418.6 to 3523.65)	Difference, +503.9 (+95.4 to +912.4)
Median	1969.8	2319.9	+261.0
IQR	1561.0 to 2916.0	1851.1 to 3240.3	−418.5 to +1390.1
Range	117.7 to 6613.5	877.0 to 9718.4	−2076.8 to +3436.0

ABR, annualized bleeding rate; FIX, factor IX; rFIXFc, recombinant factor IX Fc fusion protein.
[a]Forty-six out of 47 (97.9%) patients had ≥3 months of treatment with previous FIX.
[b]Calculated if the duration on previous factor treatment was ≥3 months to reduce potential misclassification; for patients initiated with rFIXFc before enrollment, only data under previous factor treatment within 12 months prior to first injection of rFIXFc were considered.
[c]Calculated if the duration of rFIXFc during the 24-month prospective period was ≥3 months to reduce potential misclassification.
[d]Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed period duration (in years) as an offset variable.
[e]Estimated using a repeated negative binomial model with treatment period (prospective vs retrospective) as a covariate.
[f]Missing data (*n* = 4).

In the post hoc analysis, patients who had at least 1 adjustment to their weekly prescribed rFVIIIFc dose (IU/kg; *n* = 41) during the prospective period were generally younger than those without dose adjustments (*n* = 109; Supplementary Table S3). A higher proportion of persons without dose adjustments (91.7%) had severe HA compared with those with dose adjustments (78.0%). Annualized endpoints during the retrospective period were similar between patients with or without rFVIIIFc dose adjustments.

For rFIXFc, persons with dose adjustments had a lower median (IQR) age of 18.0 (10.0-28.0) years compared with those without dose adjustments (30.5 [20.0-42.0] years; Supplementary Table S4). A higher proportion of persons in the group with no dose adjustments had severe HB (96.2%) compared with those with dose adjustments (81.0%). Persons with dose adjustments had a higher mean ABR during the retrospective period than those without dose adjustments. Mean ABR (0.7) was lowest for those patients who initiated rFIXFc at a dose lower than the product label (*n* = 8; comparison not shown). Annualized injection frequency was similar during the retrospective period, irrespective of whether there were dose adjustments during the prospective period. Retrospective annualized factor consumption was higher in persons with dose adjustments during the prospective period compared with those who did not have dose adjustments.

3.7 | Joint bleeding episodes and target joints

During the prospective period, median (IQR) AJBR on rFVIIIFc and rFIXFc was 0.0 (0.0-0.6) and 0.6 (0.0-1.8; Supplementary Figures S8 and S9), respectively. The corresponding estimated mean (95% CI) values were 1.02 (0.70-1.50) and 1.83 (1.14-2.95).

At enrollment, 20 target joints were identified in 15 out of 136 (11%) persons with HA and 4 were identified in 3 out of 46 (6.5%) persons with HB. Of the 20 target joints identified at enrollment, 15 (75.0%) were resolved in 86.7% (*n* = 13/15) of patients on rFVIIIFc, while 5 target joints in 2 patients remained unresolved. For rFIXFc, 3 (75.0%) target joints were resolved in 66.7% (*n* = 2/3) of patients, while 1 remained unresolved. Target joint resolution occurred during the first year of follow-up in 14 out of 15 and 1 out of 3 resolved target

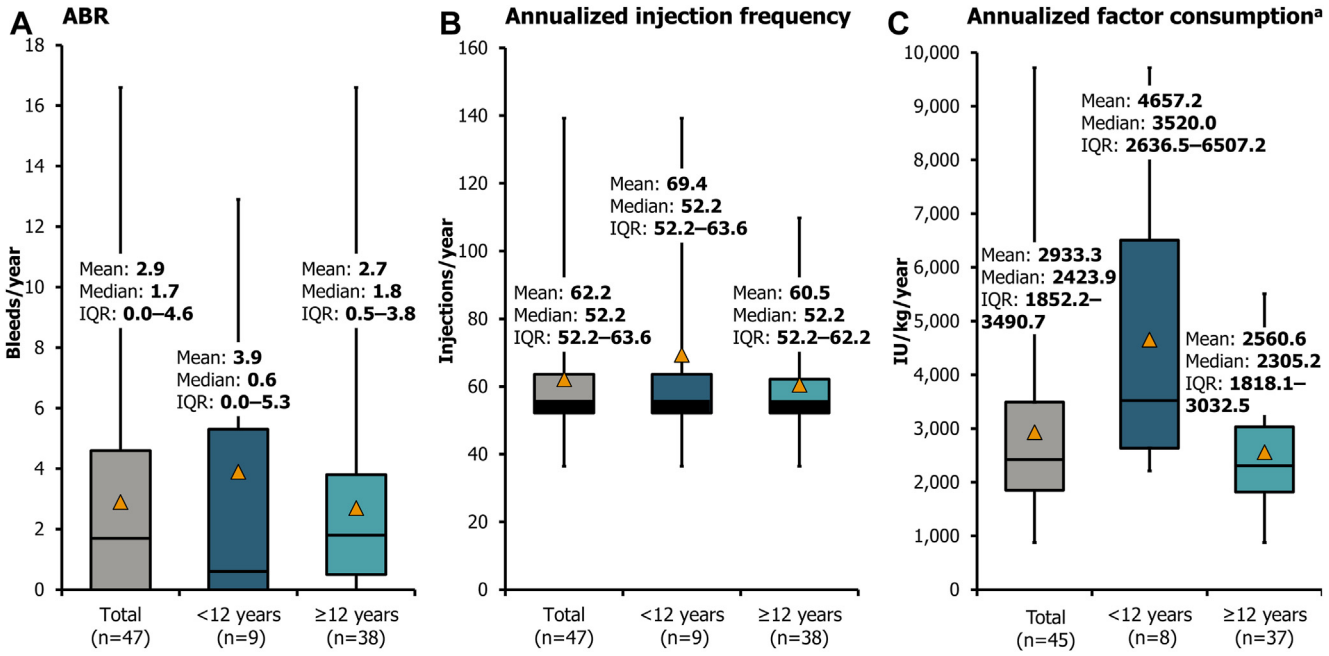

FIGURE 4 Annualized bleeding rate (ABR), annualized injection frequency, and annualized factor consumption for recombinant factor IX Fc fusion protein (rFIXFc) during the 24-month prospective period. Orange triangles represent means, box boundaries represent IQRs, and error bars represent ranges, with thick black lines indicating equal medians and quartiles. Patients with <3 months on rFIXFc (n = 0) during the 24-month prospective period were excluded from analysis of annualized endpoints in order to reduce potential misclassification. [a]Missing data (total, n = 2; <12 years, n = 1; ≥12 years, n = 1).

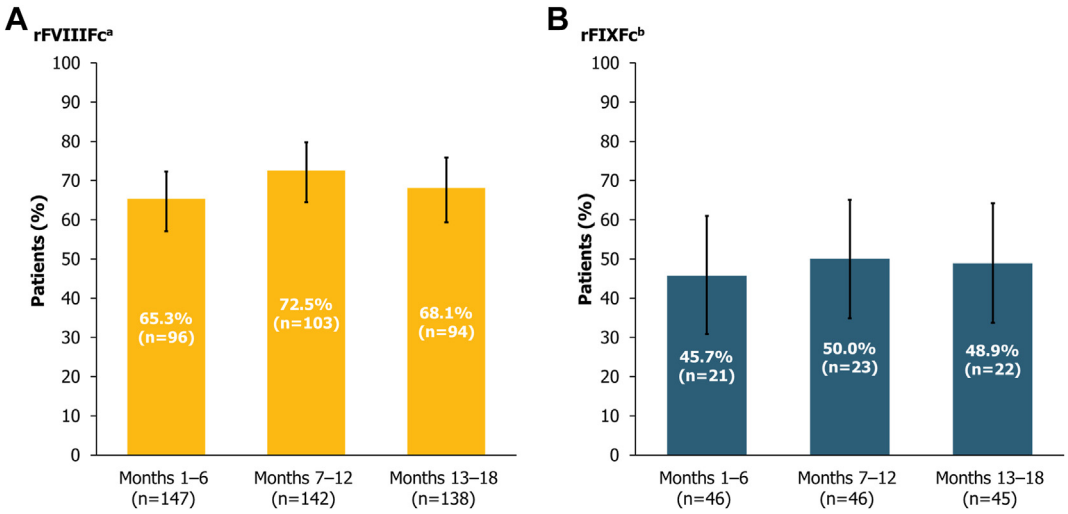

FIGURE 5 Zero bleeding episodes on recombinant factor (F)VIII Fc (rFVIIIFc)/recombinant FIX Fc (rFIXFc) across each 6-month interval of the prospective period up to Month 18. Error bars represent 95% CIs of the mean 0 bleeding episodes. [a]Missing data for Months 1 to 6 (n = 3), Months 7 to 12 (n = 8), Months 13 to 18 (n = 12). Limited data were available for Months 19 to 24 (n = 24) due to missing data (n = 126). [b]Missing data for Months 1 to 6 (n = 1), Months 7 to 12 (n = 1), Months 13 to 18 (n = 2). Limited data were available for Months 19 to 24 (n = 10) due to missing data (n = 37).

joints for rFVIIIFc and rFIXFc, respectively, and during the second year for the remaining resolved target joints.

Median (IQR) ATJBRs were 0.7 (0.0-1.2) and 2.7 (0.0-10.0) for rFVIIIFc and rFIXFc, respectively (Supplementary Figures S8 and S9), while the estimated mean (95% CI) ATJBRs were 4.02 (1.48-10.89) and 4.23 (0.85-21.11), respectively.

3.8 | Physician and patient satisfaction with rFVIIIFc/rFIXFc

Most physicians reported being "satisfied" or "highly satisfied" with rFVIIIFc (59.6% [n = 68/114] and 34.2% [n = 39/114], respectively) and rFIXFc (54.8% [n = 17/31] and 35.5% [n = 11/31], respectively) at

enrollment. This was maintained at each 6-month interval through Month 18 for rFVIIIFc (60.2% [*n* = 56/93] and 35.5% [*n* = 33/93]) and rFIXFc (67.9% [*n* = 19/28] and 21.4% [*n* = 6/28]) during the prospective period.

Similarly, most patients were also "satisfied" or "highly satisfied" with rFVIIIFc (44.7% [*n* = 38/85] and 50.6% [*n* = 43/85], respectively) and rFIXFc (51.9% [*n* = 14/27] and 40.7% [*n* = 11/27], respectively) at enrollment. These satisfaction rates were maintained with rFVIIIFc (42.6% [*n* = 26/61] and 52.5% [*n* = 32/61]) and rFIXFc (26.7% [*n* = 4/15] and 60.0% [*n* = 9/15]) across all time points through Month 18 during the prospective period. Mean physician and patient satisfaction score was 4 for rFVIIIFc and ranged from 4.0 to 4.6 for rFIXFc.

3.9 | PROs

EQ-5D-5L visual analog scale scores and index values for patients on rFVIIIFc or rFIXFc prophylaxis were high at baseline and remained stable up to Month 18 of the prospective period (Supplementary Figures S10–S13). Similarly, HAL or pedHAL total normalized scores were high and remained stable from baseline to Month 18 (Supplementary Figures S14 and S15).

3.10 | Safety

During the prospective period, 23 SAEs occurred in 17 (11.3%) patients on rFVIIIFc, and 19 SAEs occurred in 9 (19.1%) patients on rFIXFc; none of which were related to rFVIIIFc or rFIXFc treatment or resulted in permanent treatment discontinuation. Three SAEs (colon cancer, ileus paralytic, and septic shock) in 1 patient resulted in a fatal outcome, but these events were not considered to be related to rFIXFc treatment. No patients on rFVIIIFc or rFIXFc developed inhibitors during the prospective period, including patients who had inhibitors on previous FVIII products (all were tolerized prior to enrollment).

4 | DISCUSSION

Final data from PREVENT complement existing clinical data from phase 3 pivotal and extension studies and demonstrate the real-world usage and effectiveness of rFVIIIFc/rFIXFc prophylaxis across all ages and severities of hemophilia.

The primary annualized endpoints demonstrated that individualized prophylaxis with rFVIIIFc achieved a low median ABR, while weekly injection frequency (calculated from annualized injection frequency) and weekly factor consumption (calculated from annualized factor consumption) were in line with the product labels [17,18]. These findings were observed across the overall study population, with a median prospective follow-up of 20.6 months; similar trends were seen in patients receiving rFIXFc prophylaxis over a median follow-up of 21.0 months.

Subgroup data showed consistent low ABRs and stable annualized injection frequency observed across age groups (<12 years and ≥12 years) for rFVIIIFc and rFIXFc. However, patients aged <12 years on either rFVIIIFc or rFIXFc tended to have slightly higher annualized factor consumption. The range seen in annualized injection frequency and factor consumption may reflect the adoption of a more individualized approach to prophylaxis, which is an important component in the effective management of hemophilia [4].

Nonannualized analysis of bleeding episodes demonstrated that over half of the patients on rFVIIIFc and nearly half of the patients on rFIXFc prophylaxis had 0 bleeding episodes at each 6-month interval up to Month 18 of prospective follow-up.

Comparisons with previous SHL FVIII during the retrospective period revealed that the switch to rFVIIIFc led to a substantial reduction in the estimated mean ABR and annualized injection frequency while maintaining annualized factor consumption. These findings were generally consistent with the published literature, although comparisons are limited due to differences in study design and sample characteristics. Most of the published literature reports reduced factor consumption with rFVIIIFc vs previous SHL FVIII [21–25].

For rFIXFc, estimated mean ABR and annualized factor consumption remained stable with reduced annualized injection frequency compared with previous FIX. Real-world studies with rFIXFc have similarly shown reduced injection frequency and decreased factor consumption [25–27]. In our study, the maintained factor consumption with rFVIIIFc/rFIXFc prophylaxis may reflect the shift toward more individualized prophylaxis and prescribing practices in line with the product label [17,18].

Most physicians in this study indicated that the primary reason for initiating rFVIIIFc/rFIXFc prophylaxis was to improve treatment convenience while maintaining bleed protection. While these data were collected as part of the planned study design, this finding aligns with a European survey of 37 physicians who switched 133 persons with HA from SHL FVIII to rFVIIIFc and 25 physicians who switched 36 persons with HB from SHL FIX to rFIXFc [28]. The survey identified that reducing bleeding episodes and improving treatment adherence were 2 of the most significant factors influencing physician decision to switch to EHL therapy.

Patients receiving rFVIIIFc to "improve protection from bleeds" had the highest onstudy mean ABR and annualized factor consumption, compared with those receiving rFVIIIFc for other reasons, while the annualized injection frequency remained consistent across groups. In the HB cohort, patients receiving rFIXFc to "improve protection from bleeds" had the highest outcomes across annualized endpoints. Notably, the onstudy mean ABR was higher in this group than in those receiving rFIXFc to "reduce injection frequency while maintaining protection from bleeds." Compared with the overall study population, patients on rFIXFc to "improve protection from bleeds" exclusively comprised persons with severe HB and all persons with HB with target joints at enrollment, with a higher proportion of patients aged <12 years (40% vs 19%). These findings aligned with the higher prestudy mean/median ABR (10.3/5.5) reported in this group, compared with the overall study population (2.96/1.8). Further analysis showed that

this group also experienced a mean/median reduction in ABR of −3.8/−2.6 with rFIXFc compared with previous FIX treatment. As expected, for patients initiating rFIXFc to improve bleed protection, the reduction in injection frequency (mean, −17.4 injections/y; median, −4.7 injections/y) was not as considerable as for the overall study population (mean, −37.3 injections/y; median, −50.6 injections/y). However, there was a substantially higher annualized factor consumption (mean, +1366.1 IU/kg; median, +1923.6 IU/kg) compared with the overall study population (mean, +503.9 IU/kg; median, +261.0 IU/kg).

In the present study, most patients had already been receiving prophylactic rFVIIIFc/rFIXFc for a considerable duration of time before the study. During the 24-month prospective period, most patients on rFVIIIFc/rFIXFc prophylaxis did not require any adjustments to their prescribed dose at enrollment. Of note, post hoc analysis showed that these patients were older and comprised a more severe population than those who required dose adjustments. Additionally, previous on-demand treatment and target joints at baseline seemed to have no clear impact on the need for dose adjustments. Further, annualized endpoints were similar regardless of whether dose adjustments were needed or not, except for those on rFIXFc where ABRs and annualized factor consumption tended to be higher in patients requiring dose adjustments. Overall, these results indicate that the prescribed dose at enrollment were appropriate for maintaining bleed protection in most patients, especially in those with severe disease, and that patients with a higher disease burden may benefit from a stable prophylactic regimen without the need for further dose adjustments. Among patients who required at least 1 dose adjustment, the primary reason was to improve bleed protection, which is in line with the current objectives of prophylactic treatment in the hemophilia community. Notably, for patients on rFIXFc, the mean weekly prescribed dose at enrollment was slightly lower (43.8 IU/kg/wk) than the recommended dosage in the product label, but it was later increased to align with the label at the last prescribed dose (51.9 IU/kg/wk) [17]. Post hoc analysis revealed that the lower average dose at enrollment was due to 8 patients who initiated rFIXFc treatment at doses lower than recommended on the product label. Interestingly, ABRs for this group were below 3 per year during the retrospective period on previous FIX, suggesting that their prestudy prophylaxis provided optimal bleed protection.

The inclusion of physician and patient satisfaction scores is valuable as it provides insight into the real-world experience and ease of transitioning to rFVIIIFc/rFIXFc prophylaxis. High satisfaction levels indicated a positive acceptance of rFVIIIFc/rFIXFc treatment outcomes by the physicians and the studied hemophilia population.

Analysis of joint health outcomes indicated that median AJBR and ATJBR were low with rFVIIIFc/rFIXFc prophylaxis. Moreover, most target joints identified at enrollment were resolved during the prospective period.

EQ-5D-5L visual analog scale and index scores for patients on rFVIIIFc/rFIXFc prophylaxis remained stable during the prospective period, with no clear change from baseline at any 6-month time interval. Patient's perceived functional ability as measured by HAL and pedHAL were high during the prospective period. Overall, these results were consistent with a well-treated hemophilia population.

The safety profiles were consistent with the clinical trial and postmarketing experience with rFVIIIFc or rFIXFc [17,18]. Both products were well tolerated in all age groups and did not lead to inhibitor development or treatment-related SAEs during the prospective period.

The noninterventional and prospective study design of PREVENT is a strength that allows it to closely align with real-world clinical practice, accommodating individualized treatment and dosing flexibility across all age groups. Additionally, the study population is considered representative of the German hemophilia population due to the broad participation of HTCs involved in the study. This enhances the generalizability of the findings to the broader patient population. Although data on race and ethnicity were not collected, it is expected that the analyzed population would be a predominantly White population given that the study was only conducted in Germany; as such, it is unclear whether these results are applicable to a non-White population. An additional limitation of the present study was the lack of retrospective follow-up data to estimate annualized endpoints in some patients. This limitation may introduce a potential bias, as the complete data set was not available for all patients. Nevertheless, patients with data available from both the retrospective and prospective periods demonstrated outcomes similar to those of the overall study population. This provides reassurance that selection bias is unlikely to significantly impact the main effectiveness endpoints. Some PROs and the physician satisfaction questionnaire had missing data, which limited the conclusions that could have been drawn from these outcomes.

5 | CONCLUSION

Real-world data from PREVENT demonstrate the usage and effectiveness of rFVIIIFc and rFIXFc in persons with HA and HB across all ages and severities in Germany. Individualized prophylaxis with rFVIIIFc/rFIXFc provided good protection from bleeds with low injection frequencies and factor consumption over a median prospective follow-up of 20.6/21.0 months. Compared with the 12-month retrospective period on previous FVIII, there was a substantial reduction in mean ABR accompanied by stable annualized rFVIIIFc consumption. For persons with HB, bleed protection with rFIXFc prophylaxis was maintained compared with previous FIX, despite the reduction in annualized injection frequency.

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ETHICS STATEMENT

The PREVENT study protocol received approval from institutional review boards and/or ethics committees at participating institutions. Patients provided signed and dated informed consent before participating in the study. For pediatric patients, assent was obtained in line with local regulations, and informed consent was provided by the patient's legally acceptable representative before any study-related activities commenced. PREVENT adhered to the International Conference on Harmonization Guidelines for Good Clinical Practice and ethical principles in compliance with the Declaration of Helsinki. The study is registered with ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT03055611).

AUTHOR CONTRIBUTIONS

Substantial contributions to study conception or design: C.B., C.H., F.L., W.M., U.S., J.O., E.N., H.P., E.S., A.T.; substantial contributions to the acquisition, analysis, or interpretation of the data: C.B., C.H., F.L., W.M., U.S., J.O., E.N., H.P., E.S., A.T.; drafting the article or reviewing it critically for important intellectual content: C.B., C.H., F.L., W.M., U.S., J.O., E.N., H.P., E.S., A.T.; final approval of the version of the article to be published: C.B., C.H., F.L., W.M., U.S., J.O., E.N., H.P., E.S., A.T.

RELATIONSHIP DISCLOSURE

C.B.: consulting fees/research grants from Bayer, Biotest, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi, and Takeda. C.H.: consulting fees/research grants from Bayer, Biotest, Novo Nordisk, Pfizer, Roche, Sobi, and Takeda. F.L.: consulting fees/research grants from Ablynx, Alexion, Aspen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, CSL Behring, Daiichi Sankyo, Grifols, LEO Pharma, Novo Nordisk, Octapharma, Pfizer, Roche, Siemens, Sobi, Takeda, and Werfen. W.M.: consulting fees/research grants from Bayer, Biogen Idec, Biotest, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi, Takeda, and uniQure. U.S.: consulting fees/research grants from Bayer, CSL Behring, LEO Pharma, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi, and Takeda. J.O.: research funding from Bayer, Biotest, CSL Behring, Octapharma, Pfizer, Sobi, and Takeda, and consultancy, speakers bureau participation, honoraria, scientific advisory board participation, and/or support for travel expenses from Bayer, Biogen Idec, BioMarin, Biotest, Chugai, CSL Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Spark Therapeutics, Sobi, and Takeda. E.N.: employee of Sobi. H.P.: employee of Sobi. E.S.: employee of Sobi. A.T.: consulting fees/research grants from Alnylam, Bayer, Biogen Idec, Biotest, Boehringer Ingelheim, Chugai, CSL Behring, Daiichi Sankyo, LEO Pharma, Novo Nordisk, Octapharma, Pfizer, Portola, Roche, Sobi, and Takeda.

DATA AVAILABILITY

Sobi is committed to responsible and ethical sharing of data on participant level and summary data for medicines and indications approved by the European Medicines Agency and/or the US Food and Drug Administration while protecting individual participant integrity and complying with applicable legislation. Data access will be granted in response to qualified research requests. All requests are evaluated by a cross-functional panel of experts within Sobi, and a decision on sharing will be based on the scientific merit and feasibility of the research proposal, maintenance of personal integrity, and commitment to publication of the results. To request access to study data, a data sharing request form (available on www.sobi.com) should be sent to medical.info@sobi.com. Further information on Sobi's data sharing policy and process for requesting access can be found at https://www.sobi.com/en/policies.

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SUPPLEMENTARY MATERIAL

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