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Original Article

Post Hoc Analyses of A-SURE and PREVENT Confirm the Effectiveness of rFVIIIFc Prophylaxis Across All Ages, BMIs, Severities, and Inhibitor Histories

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ABSTRACT

Objective To assess the effectiveness of recombinant factor VIII Fc fusion protein (efmoroctocog alfa; referred to herein as rFVIIIFc) prophylaxis in people with hemophilia A (PwHA) stratified by age, body mass index (BMI), disease severity, and inhibitor history included in the A-SURE (NCT02976753) and PREVENT (NCT03055611) real-world studies.

Methods PwHA receiving at least one prescription of rFVIIIFc and ≥3 months of follow-up during the prospective periods were included. Post hoc analyses were performed for the overall analysis population and subgroups based on age, BMI, disease severity, and those with and without previous inhibitors. Effectiveness endpoints were annualized bleeding rate (ABR), annualized joint bleeding rate (AjBR), injection frequency, and factor consumption in the prospective period.

Results Overall, 333 PwHA were analyzed. ABRs and AjBRs, generally, were low across the different subgroups (range of medians, 0.0–0.6 for both ABRs and AjBRs, except for ABRs in PwHA aged ≥65 years). Injection frequencies (*n* injections/week) were comparable across subgroups (range of medians, 2.0–2.3), and factor consumption was generally similar (range of medians, 68.3–100.0 international units/kg/week), although with slightly higher factor consumption in pediatric PwHA and lower consumption in the overweight or obese BMI groups.

Conclusion These post hoc analyses support the effectiveness and, therefore, use of rFVIIIFc prophylaxis in PwHA across all ages, BMI categories, severities, and for those with a history of inhibitors.

Keywords hemophilia A, factor VIII, prospective studies

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Introduction

Hemophilia A accounts for approximately 80–85% of all hemophilia cases.[1] People with hemophilia A (PwHA) present with bleeding manifestations as a result of deficiency in factor VIII (FVIII), with the severity of the disease correlated to lower levels of FVIII; severe disease is defined as <1% of normal FVIII levels and nonsevere disease (mild or moderate hemophilia) as FVIII levels of 1–<40%.[1,2] Individuals with hemophilia each present with specific characteristics that require consideration when it comes to treatment management.[1]

Treatment considerations can change during a patient's lifetime, with joint deterioration likely to increase with age,[3] resulting in challenges associated with arthropathy.[4] A higher percentage of PwHA with ≥1 problem joint has been reported in adults when compared with children and adolescents.[3,5] Despite early treatment, bleeds can lead to progressive joint damage.[6,7] A systematic review noted that children and adolescents with hemophilia A tend to have a better quality of life compared with adults, although health-related quality of life (HRQoL) often declines as young individuals grow older.[8] Additionally, people with hemophilia (PwH) may encounter more challenges as they age, including comorbidities such as diabetes and cardiovascular disease, which are reported as more prevalent among older male adults compared with younger adults.[1,9]

The prevalence of overweight and obesity among PwH is generally comparable to that of the general population, as

observed in Europe and the United States.[10] Over recent decades, rates of overweight and obesity have risen globally, a trend expected to persist.[11] This global rise mirrors the increase observed in both children and adults with hemophilia between 2007 and 2016.[10]

Excess body weight can affect joint health both directly, by adding strain to weight-bearing joints,[12] and indirectly, by fostering an inflammatory microenvironment.[13] Joint pain and limited mobility might further contribute to a sedentary lifestyle, complicating weight management.[10] Research findings on the impact of body weight in PwH are mixed. For instance, a single-center study linked higher body mass index (BMI) to poorer ankle joint health,[14] while a post hoc analysis found no significant relationship between BMI and joint health deterioration.[15] When considering bleeding rates, BMI did not appear to significantly influence overall bleeding frequency in one study including PwHA;[16] a trend toward higher annualized bleeding rate (ABR) was observed in individuals of normal weight, compared with those who are overweight or obese.[16] Obese PwHA experienced a significantly higher number of bleeds requiring treatment compared with normal weight controls in another study.[17] This study and one other also showed there was no significant difference in joint bleeds observed between obese PwH and their healthy-weight hemophilia peers.[17,18]

People of all severities of hemophilia can experience bleeds, including subclinical bleeds, leading to progressive joint damage and pain.[7,19–23] Although patient-reported outcome measures related to HRQoL are observed to be better in those with mild disease when compared with moderate and severe disease,[20,24] a significant impact on HRQoL is still experienced in those with mild or moderate disease.[22,25] In Nordic countries, there is increased mortality and prevalence of comorbidities, along with higher use of medications for pain, depression, and anxiety, reported across all disease severities, including individuals with mild phenotypes (e.g., males with low factor usage and females, including carriers), compared with matched controls.[25,26]

Several treatment options are currently available for the management of hemophilia A, including factor and nonfactor replacement therapies. During FVIII replacement treatment, inhibitors can develop toward administered therapy,[2] which can increase treatment burden and bleeding rates, substantially impacting HRQoL for PwHA, even when they receive usual treatment.[27–29] Achieving tolerization to FVIII remains the proposed goal, as, independent of the prophylactic agent, bleeding situations will still require factor replacement;[30] immune tolerance induction is available to help eradicate inhibitors.[1,30]

Extended half-life (EHL) FVIII products allow maintenance of sufficiently high FVIII levels to provide protection from bleeds, while also addressing the challenges of prophylactic treatment.[1] Efmoroctocog alfa, a recombinant FVIII Fc fusion protein referred to as rFVIIIFc herein, is an EHL FVIII product that provides higher factor levels, enhancing bleed protection and allowing longer dosing intervals compared with standard half-life (SHL) products.[31–33] The efficacy and safety of rFVIIIFc have been thoroughly established through Phase 3 clinical trials involving individuals of all ages with severe hemophilia A. These trials include A-LONG (NCT01181128),[34] Kids A-LONG (NCT01458106),[35] PUPs A-LONG (NCT02234323),[36] and ASPIRE (NCT01454739).[37] However, it is important to note that individuals with nonsevere hemophilia or a history of inhibitors were not included in these clinical studies.

The A-SURE (NCT02976753) and PREVENT (NCT03055611) studies were performed to provide prospective real-world experience as to the effectiveness and usage of rFVIIIFc in clinical practice in Europe,[33,38] resulting in a large and robust pool of data, of which 333 PwHA were analyzed. The A-SURE study utilized a matched control group to compare the effectiveness of rFVIIIFc prophylaxis with SHL FVIII prophylaxis and demonstrated that rFVIIIFc provided improved bleed protection, lower factor consumption, and fewer injections.[33] The PREVENT study demonstrated that rFVIIIFc prophylaxis provides improved bleed protection, with reduced injection frequency and stable factor consumption compared with previous treatment.[38] These studies support the previously presented pharmacokinetic simulation data evaluating prophylaxis with rFVIIIFc compared with a rFVIII.[32]

We investigated the real-world effectiveness of rFVIIIFc prophylaxis in subgroups of PwHA with different characteristics, as described earlier, to provide real-world experience relevant to these individual subgroups and to support decision-making in clinical practice. The extensive real-world data collected by the A-SURE and PREVENT studies were utilized to provide data for subgroups that are of clinical relevance but may not always be available in clinical studies. We report the post hoc analyses of a pooled population of PwHA who received rFVIIIFc to assess the effectiveness of rFVIIIFc prophylaxis stratified by age, BMI, disease severity, or inhibitor history.

Methods

Study Design

A-SURE (NCT02976753) was a 24-month, prospective, observational study across nine European countries, which aimed to evaluate the real-world effectiveness of prophylaxis with rFVIIIFc in PwHA compared with a matched group receiving prophylaxis with SHL FVIII products,[33] and PREVENT (NCT03055611) was a 24-month prospective, observational study conducted in Germany, which aimed to assess the real-world usage and effectiveness of rFVIIIFc prophylaxis in PwHA.[38] The design of these studies has been previously described,[33,38] with PwHA prescribed rFVIIIFc treatment according to standard clinical practice in both studies.

The objective of the post hoc analyses reported here was to assess the effectiveness of rFVIIIFc prophylaxis in PwHA in a real-world setting stratified by age, BMI, disease severity, or inhibitor history, using final prospective data from the A-SURE and PREVENT studies.

Population and Outcome Measures

All PwHA from A-SURE and PREVENT receiving at least one prescription of rFVIIIFc and with ≥3 months follow-up during the prospective periods were pooled and included in the post hoc effectiveness analyses. Analyses were performed in the pooled analysis population, overall and in distinct subpopulations, with subgroups chosen to analyze the effect of age, BMI, disease

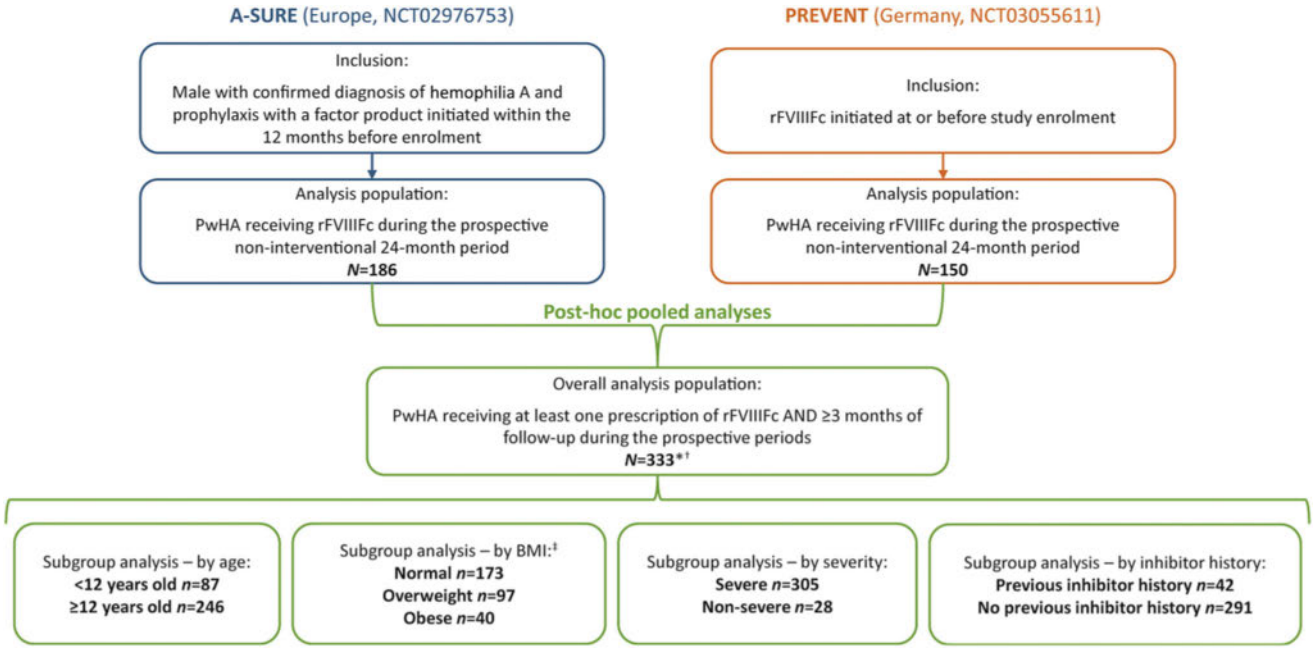

Fig. 1 Post hoc analyses design. *Three PwHA (*n* = 2, A-SURE; *n* = 1, PREVENT) had <3 months of follow-up during the prospective periods and were excluded from the analyses. †*n* = 318 PwHA with available BMI data. ‡Due to the small sample size, data from the underweight group were not analyzed further. BMI, body mass index; PwHA, people with hemophilia A; rFVIIIFc, recombinant factor VIII Fc fusion protein.

severity, and inhibitor history on the effectiveness of rFVIIIFc prophylaxis (Fig. 1).

For the overall analysis, population and all subgroups, demographics, baseline characteristics, and length of prospective follow-up were assessed. The effectiveness endpoints of ABR, annualized joint bleeding rate (AjBR), injection frequency (*n* injections/week), and factor consumption (international unit [IU]/kg/week) in the prospective period were analyzed for the overall analysis population and all subgroups.

For analysis by age, PwHA were grouped into those <12 years of age (pediatric) and those ≥12 years of age (adolescent/adult), with additional analyses performed for the endpoint of ABR across five age subgroups: <6, 6 to 11, 12 to 17, 18 to 64, and ≥65 years. The BMI subgroup analyzed PwHA with available BMI data grouped into predefined categories by baseline BMI (**Supplementary Table S1**). PwHA with severe hemophilia (FVIII levels <1%) and nonsevere hemophilia, consisting of those with mild or moderate hemophilia (FVIII levels 1–<40%), were analyzed separately. In the inhibitor history subgroup analysis, previously treated PwHA were grouped into those with a documented history of inhibitors who subsequently tested negative before switching to rFVIIIFc, and those with no prior history of inhibitors. In this subgroup, rFVIIIFc exposure days and inhibitor outcomes were also analyzed.

Statistical Analyses

Descriptive statistics were used to summarize data. Data analysis was based on available data from the A-SURE and PREVENT studies, and no imputation of missing data was performed.

Results

Population Characteristics and Effectiveness—Overall Analysis Population

The overall analysis population included 333 PwHA who received at least one prescription of rFVIIIFc and had ≥3 months of follow-up during the prospective periods in the A-SURE[33] (*n* = 184) or the PREVENT[38] (*n* = 149) studies (Fig. 1). Mean (standard deviation [SD]) age was 26.3 (18.3) years, with 26.1% of PwHA <12 years old, 15.0% ≥12 to <18 years old, 55.9% ≥18 to <65 years old, and 3.0% ≥65 years old. Most PwHA had severe hemophilia (305/333, 91.6%), and the most used prior treatment was SHL FVIII (265/269, 98.5%; Table 1). The median (interquartile range [IQR]) duration of prospective follow-up for the overall population was 20.9 (19.1–24.0) months, with 21.4 (19.4–24.3) months reported for the A-SURE study analysis population (*n* = 184) and 20.6 (19.0–22.6) months reported for the PREVENT study analysis population (*n* = 149).

Median (IQR) ABR and AjBR of 0.5 (0.0–1.6) and 0.0 (0.0–0.8) were observed, respectively. Median (IQR) injection frequency (*n* injections/week) was 2.1 (2.0–2.6), with median (IQR) factor consumption of 80.0 (60.6–102.9) IU/kg/week (**Supplementary Table S2**).

Analysis by Age

The analysis included 87/333 (26.1%) PwHA <12 years old and 246/333 (73.9%) PwHA ≥12 years old at enrolment; the age distribution was similar between A-SURE and PREVENT (Table 1). Mean (SD) age was 6.6 (3.4) years and 33.3 (16.2) years in the <12 years and ≥12 years groups, respectively

Table 1 Demographic and baseline characteristics of the overall analysis population from A-SURE and PREVENT.

	A-SURE (*n* = 184)	PREVENT (*n* = 149)	Overall analysis population (*n* = 333)
Age[a] (y)			
Mean (SD)	27.9 (18.6)	24.4 (17.7)	26.3 (18.3)
Median (min, max)	23.5 (3, 76)	21.0 (0, 74)	22.0 (0, 76)
Age category (y), *n* (%)			
<12	44 (23.9)	43 (28.9)	87 (26.1)
≥12–<18	29 (15.8)	21 (14.1)	50 (15.0)
≥18–<65	103 (56.0)	83 (55.7)	186 (55.9)
≥65	8 (4.3)	2 (1.3)	10 (3.0)
Body weight (kg)	*n* = 182[b]	*n* = 143[c]	*n* = 325[d]
Median (IQR)	69.0 (54.0–81.0)	73.0 (36.0–84.0)	70.0 (47.0–82.0)
BMI category	*n* = 181	*n* = 137	*n* = 318
Underweight	6 (3.3)	2 (1.5)	8 (2.5%)
Normal	104 (57.5)	69 (50.4)	173 (54.4%)
Overweight	45 (24.9)	52 (38.0)	97 (30.5%)
Obese	26 (14.4)	14 (10.2)	40 (12.6%)
Missing	3	12	15
Severity of hemophilia, *n* (%)			
Severe	174 (94.6)	131 (87.9)	305 (91.6)
Moderate	6 (3.3)	17 (11.4)	23 (6.9)
Mild	4 (2.2)	1 (0.7)	5 (1.5)
History of inhibitors, *n* (%)			
Yes	18 (9.8)	24 (16.1)	42 (12.6)
No	166 (90.2)	125 (83.9)	291 (87.4)
Type of prior product, *n* (%)	*n* = 133	*n* = 136	*n* = 269
SHL FVIII	131 (98.5)	134 (98.5)	265 (98.5)
EHL FVIII	2 (1.5)	2 (1.5)	4 (1.5)
Missing	51	13	64

Abbreviations: BMI, body mass index; EHL, extended half-life; FVIII, factor VIII; IQR, interquartile range; SD, standard deviation; SHL, standard half-life.
[a]Age at enrolment.
[b]Data missing for *n* = 2.
[c]Data missing for *n* = 6.
[d]Data missing for *n* = 8.

(**Supplementary Table S3**). The median (IQR) prospective follow-up for PwHA <12 years (*n* = 87) was 20.6 (19.1–22.4) months and 21.1 (19.1–24.0) months for those in the ≥12 years group (*n* = 246).

Median ABR and AjBR were comparable between the age groups <12 years and ≥12 years, ranging from 0.0 to 0.6 (**Fig. 2A, B**). When these age groups were split further (at 6, 12, 18 and 65 years), the range of the median ABR remained between 0.0 and 0.6 across all groups except for the ≥65 years subgroup (**Supplementary Fig. S1**). Median (IQR) injection frequency (*n* injections/week) was similar in both age groups (**Fig. 2C**), with the median (IQR) factor consumption (IU/kg/week) for PwHA <12 years slightly higher, compared with PwHA ≥12 years (**Fig. 2D**).

Analysis by BMI

Among the 318 PwHA with available data, 8/318 (2.5%) PwHA were underweight, 173/318 (54.4%) had normal weight, 97/318 (30.5%) were overweight, and 40/318 (12.6%) were obese (**Table 1**). Mean (SD) age was 19.6 (11.9) years, 22.5 (16.7) years, 33.6 (18.6) years, and 29.2 (19.3) years in those in the underweight, normal, overweight, and obese groups, respectively (**Supplementary Table S4**).

The effectiveness analysis included PwHA from the normal BMI group, overweight group, and obese group. Due to the small sample size, data from the underweight group (*n* = 8) were not analyzed. Of the overall analysis population, 15 PwHA (4.5%) had no BMI data and were excluded from the effectiveness analysis. The median (IQR) prospective follow-up was 21.0 (19.3–24.0) months, 21.0 (19.3–24.4) and 20.0 (18.9–22.6) in those in the normal (*n* = 173), overweight (*n* = 97), and obese (*n* = 40) groups, respectively.

Median (IQR) ABR and AjBR results were generally low across all BMI groups analyzed. However, a higher variability of bleeds and joint bleeds across obese PwHA resulted in slightly higher ABR and AjBR for this group (**Fig. 3A, B**). Median (IQR) injection frequency (*n* injections/week) was comparable between all three groups (**Fig. 3C**), and median (IQR) factor consumption (IU/kg/week) was lower for the overweight group and obese group, compared with the normal BMI group (**Fig. 3D**).

Analysis by Hemophilia Severity

Of the 333 PwHA in the severity subgroup, there were 305/333 (91.6%) people with severe hemophilia A and 28/333 (8.4%) with nonsevere hemophilia A; 23 with moderate hemophilia and five with mild hemophilia (**Table 1**). Mean (SD) age was 26.7 (18.3) years and 22.3 (17.3) years for those with severe hemophilia A and nonsevere hemophilia A, respectively (**Supplementary Table S5**). The median (IQR) prospective follow-up for people with severe hemophilia A (*n* = 305) was 21.0 (19.1–24.0) months, and 20.2 (19.2–22.6) months for those with nonsevere hemophilia A (*n* = 28).

The range of median ABRs and AjBRs was between 0.0 and 0.6 for both severe and nonsevere hemophilia A, with slightly higher ABR noted for people with severe hemophilia (**Fig. 4A, B**). The median (IQR) injection frequency (*n* injections/week) and factor consumption (IU/kg/week) were similar in people with severe and nonsevere hemophilia A (**Fig. 4C, D**).

Analysis by Inhibitor History

The inhibitor history subgroup included 42/333 (12.6%) PwHA with previous inhibitors and 291/333 (87.4%) without previous inhibitors (**Table 1**). Mean (SD) age was 18.3 (11.1) years and 27.5 (18.8) years in those with previous inhibitors and without previous inhibitors, respectively (**Supplementary Table S6**).

The 42 patients with previous inhibitors had more exposure days on rFVIIIFc in total for both retrospective and prospective periods, compared with the 291 patients without (**Supplementary Table S6**). The median (IQR) prospective follow-up for PwHA

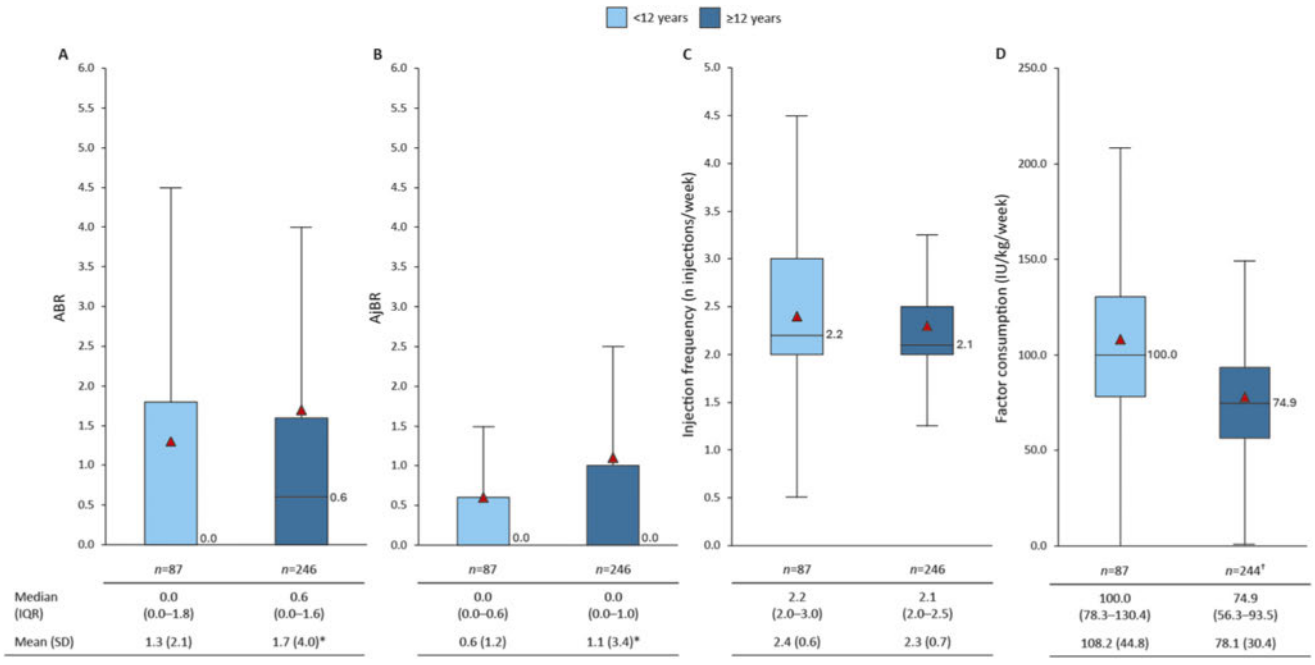

Fig. 2 Analyses of (**A**) ABR, (**B**) AjBR, (**C**) injection frequency of rFVIIIFc (*n* injections/week), and (**D**) factor consumption of rFVIIIFc (IU/kg/week) in PwHA aged <12 and ≥12 years. Box plots showing interquartile data range as box boundaries (length of whiskers showing 1.5 times IQR truncated at zero, where applicable), median data (horizontal lines and data labels), and arithmetic means (triangles). *The sample mean of 246 patients was heavily impacted by one extreme value of 42. †Data missing for *n* = 2. ABR, annualized bleeding rate; AjBR, annualized joint bleeding rate; IQR, interquartile range; IU, international unit; PwHA, people with hemophilia A; rFVIIIFc, recombinant FVIII Fc fusion protein; SD, standard deviation.

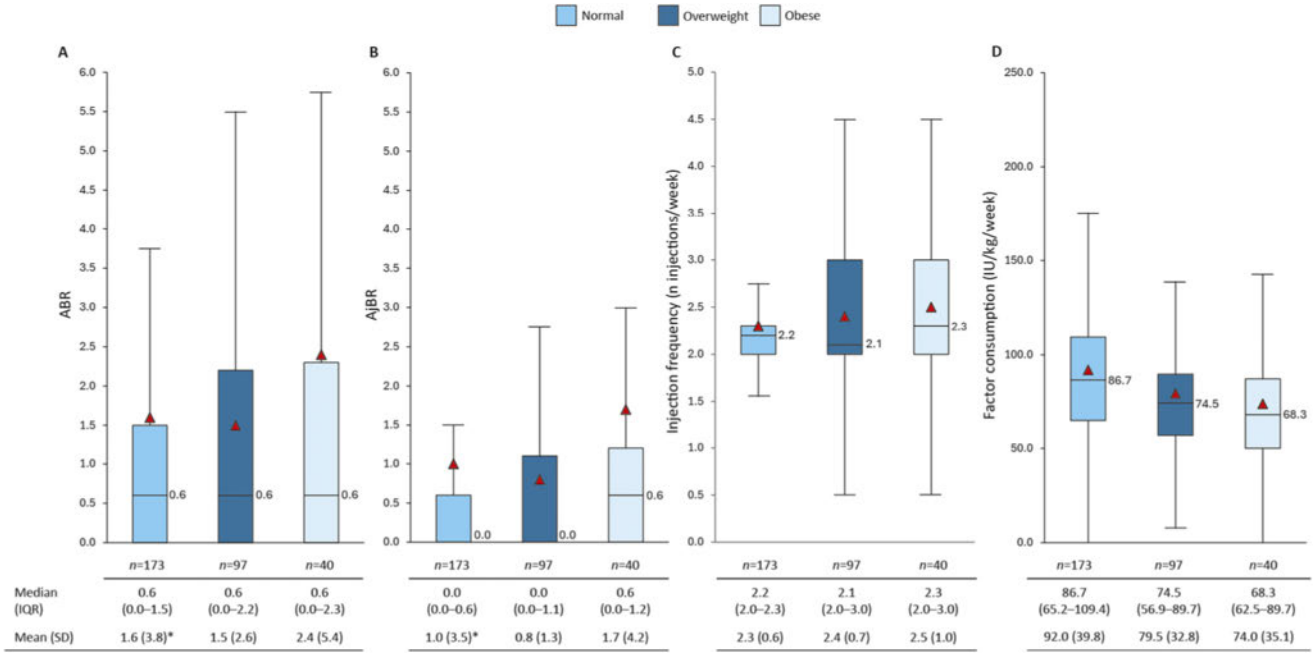

Fig. 3 Analyses of (**A**) ABR, (**B**) AjBR, (**C**) injection frequency of rFVIIIFc (*n* injections/week), and (**D**) factor consumption of rFVIIIFc (IU/kg/week) in PwHA by BMI group: normal, overweight, and obese. Box plots showing interquartile data range as box boundaries (length of whiskers showing 1.5 times IQR truncated at zero, where applicable), median data (horizontal lines and data labels), and arithmetic means (triangles). *The sample mean of 173 patients was heavily impacted by one extreme value of 42. ABR, annualized bleed rate; AjBR, annualized joint bleed rate; BMI, body mass index; IQR, interquartile range; IU, international unit; PwHA, people with hemophilia A; rFVIIIFc, recombinant FVIII Fc fusion protein; SD, standard deviation.

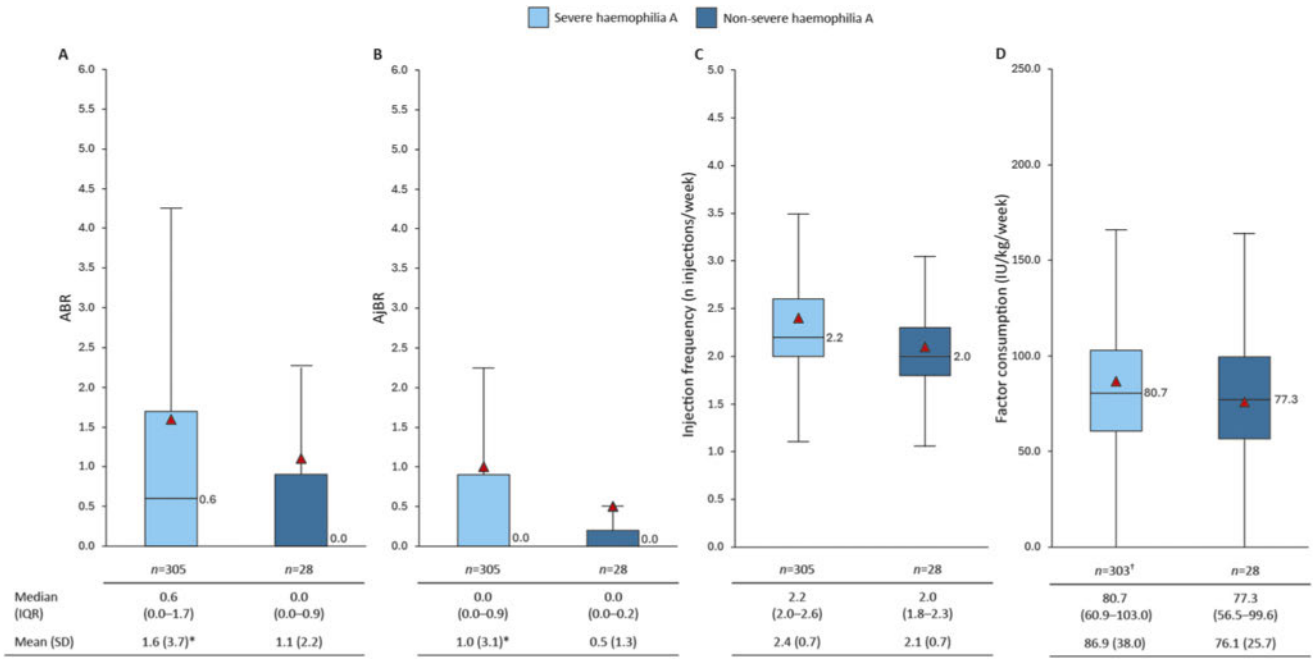

Fig. 4 Analyses of (**A**) ABR, (**B**) AjBR, (**C**) injection frequency of rFVIIIFc (*n* injections/week), and (**D**) factor consumption of rFVIIIFc (IU/kg/week) in people with severe and nonsevere hemophilia A. Box plots showing interquartile data range as box boundaries (length of whiskers showing 1.5 times IQR truncated at zero, where applicable), median data (horizontal lines and data labels), and arithmetic means (triangles). *The sample mean of 305 patients was heavily impacted by one extreme value of 42. †Data missing for *n* = 2. ABR, annualized bleeding rate; AjBR, annualized joint bleeding rate; IQR, interquartile range; IU, international unit; rFVIIIFc, recombinant FVIII Fc fusion protein; SD, standard deviation.

with previous inhibitors (*n* = 42) was similar to that without previous inhibitors (*n* = 291), with 21.0 (19.6–23.5) months and 20.9 (19.1–24.0) months of follow-up, respectively.

Median (IQR) ABR and AjBR for PwHA with previous inhibitors receiving rFVIIIFc were comparable to those without previous inhibitors (**Fig. 5A, B**). The median (IQR) injection frequency (*n* injections/week) and factor consumption (IU/kg/week) were similar in both groups analyzed (**Fig. 5C, D**). During prospective follow-up on rFVIIIFc prophylaxis, no inhibitors were reported in either the subgroup of PwHA with previous inhibitors (0/42, exact binomial 95% confidence interval [CI]: 0–8.4%) or without previous inhibitors (0/291, exact binomial 95% CI: 0–1.3%).

Discussion

This study investigated the effectiveness of rFVIIIFc prophylaxis in PwHA in subgroups stratified by age, BMI, disease severity, and presence of previous inhibitors utilizing real-world data from the A-SURE and PREVENT studies. These results provide data that may support clinical decision-making for different PwHA population groups.

rFVIIIFc is approved in PwHA of all ages,[31] and its efficacy and safety have been demonstrated in clinical trials in adolescents/adults and in children.[34–36] In the current post hoc analyses on real-world data, results stratified for the different age subgroups highlighted similar ABR and AjBR in those <12 and ≥12 years old. Low ABRs and AjBRs were observed in both adolescent/adult and pediatric PwHA. This is consistent with the interim results reported for the A-MORE study, an ongoing 48-month observational, prospective study evaluating joint health in PwHA receiving rFVIIIFc prophylaxis.[39,40]

With regard to factor usage, our analysis reported low injection frequencies and factor consumption in both age subgroups (<12 and ≥12 years). Similar injection frequencies (*n* injections/week) were observed in both age subgroups in our analysis, with slightly higher factor consumption (IU/kg) among PwHA <12 when compared with those aged ≥12 years. These results are generally consistent with the interim results of the A-MORE study,[39,40] a multicenter observational study from Canada[41] and an Irish real-world experience in pediatric PwHA.[42]

It has been acknowledged that there is limited rFVIIIFc data in older PwHA; a post hoc analysis of the A-LONG/ASPIRE clinical studies has been performed and reported that results for the analyzed population of ≥50 years receiving rFVIIIFc prophylaxis were aligned with those from the overall study populations, with low ABR and AjBR.[43] The ABR results for PwHA in the subgroup including adults and older individuals (18–64 years) in the current study were consistent with those for younger PwHA (<18 years), with median ABR of ≤0.6. Although the median (IQR) ABR remained low for all stratified subgroups, a slightly higher ABR was reported for PwHA aged ≥65 years, which may be due to suboptimal treatment earlier in life in this group. These data are based on a small number of PwHA and, therefore, any uncertainty concerning these data should be considered when generalizing these results to other PwHA aged ≥65 years. To prevent bleeding, which may lead to joint damage and disease, primary

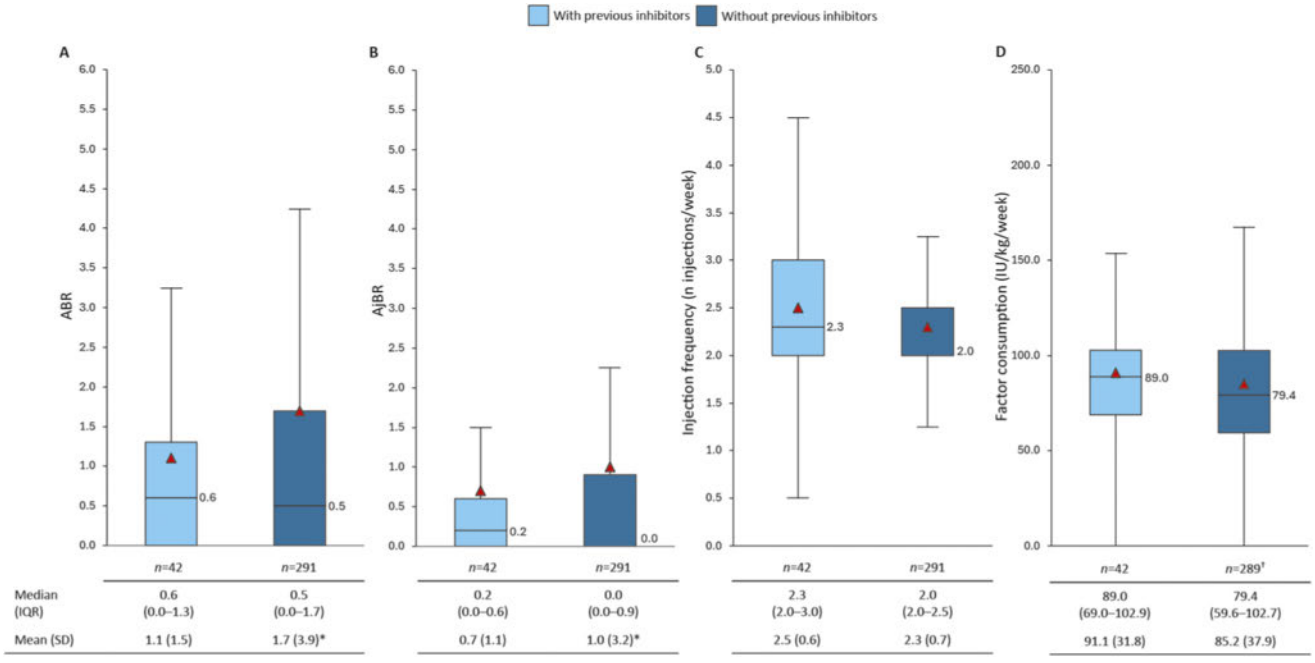

Fig. 5 Analyses of (**A**) ABR, (**B**) AjBR, (**C**) injection frequency of rFVIIIFc (*n* injections/week), and (**D**) factor consumption of rFVIIIFc (IU/kg/week) in PwHA with or without previous inhibitors. Box plots showing interquartile data range as box boundaries (length of whiskers showing 1.5 times IQR truncated at zero, where applicable), median data (horizontal lines and data labels), and arithmetic means (triangles). *The sample mean of 291 patients was heavily impacted by one extreme value of 42. †Data missing for *n* = 2. ABR, annualized bleed rate; AjBR, annualized joint bleed rate; IQR, interquartile range; IU, international unit; PwHA, people with hemophilia A; rFVIIIFc, recombinant FVIII Fc fusion protein; SD, standard deviation.

prophylaxis is recommended immediately or shortly after the first recognized bleed (joint/muscle) in those with severe hemophilia.[44] A database analysis of children with severe hemophilia A reported prophylaxis initiation at a median of 13.1 months in those born between 2010 and 2019, with 62% of children with zero joint bleeds prior to initiation.[45] A delayed start to prophylaxis has been associated with an increased risk of joint damage.[7]

The data resulting from the BMI subgroup analysis support the use of rFVIIIFc in PwHA in all BMI categories analyzed. Missing BMI data led to the exclusion of 15 PwHA from the BMI subgroup effectiveness analysis; due to the small sample size (*n* = 8), data for the underweight BMI group were not analyzed. The slightly higher median ABRs and AjBRs in the obese group, and the observed lower median rFVIIIFc consumption (IU/kg/week) in PwHA in both overweight and obese groups compared with the normal BMI group, may suggest that dosing is not appropriately adjusted in PwHA with a higher BMI.

Median ABRs and AjBRs of ≤0.6 were observed, and both injection frequencies and factor consumptions were similar between the severity subgroups. Observations related to ABR and injection frequency data are consistent with those reported in a systematic literature review on the real-world evidence of rFVIIIFc prophylaxis in PwHA in Europe.[46]

Recent literature has highlighted current challenges that exist for people with nonsevere hemophilia, including those relating to disease management and the role of prophylaxis.[47] PwH who have a milder phenotype, PwH with low factor consumption, and women including carriers use more pain, anxiety, and depression medication and have higher comorbidity burden and mortality, compared with the general population.[25,26] It has been suggested that prophylaxis has the potential to improve treatment outcomes with fewer bleeds and the prevention of damage to joints in this population.[48] In our analysis of pooled real-world data, the nonsevere subgroup had a median (IQR) ABR of 0.0 (0.0–0.9) and median (IQR) AjBR of 0.0 (0.0–0.2); this bleed protection combined with the limited burden provided by the reported low injection frequency may suggest that these data support the use of prophylaxis in all PwHA with a predisposed bleeding phenotype independent of their severity status. Physicians have reported switching PwHA with mild, moderate, or severe disease from SHL FVIII to rFVIIIFc, for reasons including fewer injections and to support the individual's convenience and lifestyle.[49]

PwHA with a history of inhibitors have been excluded from previous rFVIIIFc clinical trials (A-LONG, Kids A-LONG and ASPIRE), with no development of inhibitors reported in these study populations of previously treated people with severe hemophilia A.[34,35,37] Inhibitor development was reported in 31.1% of previously untreated people with severe hemophilia A in a Phase 3 trial evaluating the efficacy and safety of rFVIIIFc; this was considered in the expected range for this group.[36] The real-world data presented here demonstrate that the effectiveness of rFVIIIFc was comparable between PwHA with a history of inhibitors and those without previous inhibitors. In addition,

PwHA having previously experienced inhibitors were able to tolerate subsequent treatment with rFVIIIFc with no development of inhibitors during the follow-up period. The lack of inhibitor development reported in this study is consistent with findings from 12 real-world experience studies on treatment with rFVIIIFc, of which only one reported low-titer inhibitor development in a previously untreated patient.[46]

These post hoc analyses did not aim to address questions around safety, as safety data for rFVIIIFc have been previously reported in the A-SURE and PREVENT primary manuscripts[33,38] and found to be consistent with the established safety profile, including in patients with previous inhibitors, where no inhibitor recurrence was observed.

As the A-SURE and PREVENT studies were conducted in European countries, the study population may not be considered representative of PwHA globally. Moreover, since individuals with nonsevere hemophilia included in the A-SURE and PREVENT studies were required to be receiving regular prophylaxis to participate, this subgroup may not fully represent the broader population of people with mild or moderate hemophilia. However, these PwHA may be representative of those with nonsevere hemophilia, who present with a severe bleeding phenotype. An additional limitation was the exclusion of 15/333 (4.5%) PwHA in the BMI subgroup effectiveness analysis due to missing BMI data; as there was a limited number of excluded patients, no exploration of the impact of missing BMI data was performed. A limited number of PwHA were included in several subcategories, for example, the underweight BMI group (n = 8) or elderly PwHA (aged ≥65 years; n = 12). Results of the analysis of PwHA aged ≥65 years are not generalizable to these PwHA subgroups, and further data are needed to confirm the effectiveness of rFVIIIFc in underweight or elderly PwHA.

Generally, low ABRs and AjBRs were observed across the different subgroups investigated. Injection frequencies were comparable across subgroups, and factor consumption was generally similar, except for slightly higher factor consumption observed in PwHA <12 years of age and lower consumption (IU/kg) for those in the overweight or obese BMI groups. The results from the subgroups are in line with those reported for the overall analysis population. These post hoc analyses support the real-world effectiveness and, therefore, use of rFVIIIFc prophylaxis in PwHA across all ages, BMI categories, severities, and for those who have had inhibitors previously, providing additional information on rFVIIIFc effectiveness in population subgroups beyond the overall data available.

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Statements and Additional Information

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Data Availability Statement 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 U.S. Food and Drug Administration, while protecting individual participant integrity and compliance 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.

Contributors' Statement J.O., A.T., J.A., M.T.Á.R., C.B., P.A.H., and F.P.: resources and writing—review and editing. E.B.: conceptualization, investigation, methodology, resources, visualization, and writing—original draft, review, and editing. E.N.: conceptualization, formal analysis, investigation, methodology, resources, visualization, and writing—original draft, review, and editing. S.L.: conceptualization, funding acquisition, investigation, methodology, resources, supervision, visualization, and writing—original draft, review, and editing.

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Ethical Approval This post hoc analysis was based on data from previously published clinical trials, A-SURE and PREVENT (ClinicalTrials.gov identifiers: NCT02976753 and NCT03055611, respectively). Both studies were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice (https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf) and ethical principles that comply with the Declaration of Helsinki (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/). Study protocols were approved by the authorities and the ethics committees of the institutions involved. Signed informed consent was obtained from patients or patient guardians prior to participation in the clinical trials. Further consent was not required.

Clinical Trial Registration number (trial ID): NCT02976753; NCT03055611, Trial registry: ClinicalTrials.gov (http://www.clinicaltrials.gov/), Type of Study: Prospective.

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