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Pattern of use and clinical outcomes with rIX-FP in pediatric/adolescent patients with haemophilia B in Italy: Results from IDEAL real-world study

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Abstract

Objectives: To evaluate pattern of use and clinical outcomes in pediatric/adolescent patients enrolled in the IDEAL study.

Methods: This post-hoc analysis of IDEAL retrospective-prospective observational study focused on patients <18 years, 100% on prophylaxis during the entire observation period.

Results: Thirteen subjects (median age 10.0 years; 61.5% ≤ 11 years) were analyzed. The infusion frequency changed from 2/week in 84.6% ($N = 11$) of patients with previous rFIX, to less than 1/weekly in 76.9% ($N = 9$) with rIX-FP and the annualized number of infusions reduced of 57% ($p = .002$), from a mean ± SD of 95.1 ± 22.77 to 40.4 ± 6.79, respectively. Annualized mean consumption decreased of about 56% ($p = .001$), from 3748.4 ± 1155.40 IU/kg with previous rFIX, to 1656.8 ± 456.63 IU/kg of rIX-FP. Mean FIX trough level changed from 3.0% ± 1.98% to 10.92% ± 3.6%. Low mean Annualized Bleeding Rate was maintained across all prophylaxis regimens (0.8 ± 1.69 vs. 0.3 ± 0.89) and zero bleeding patients moved from 69.2% ($N = 9$) with previous rFIX to 84.6% ($N = 11$) with rIX-FP ($p = .63$). Two adverse events, none related to rIX-FP, occurred in two patients. No inhibitors development was reported.

Conclusions: The results in this pediatric/adolescent subgroup support rIX-FP prophylaxis may reduce infusion frequency, while providing high FIX trough levels, stable annualized bleeding rate and a good safety profile.

KEYWORDS

bleeding, haemophilia B, nonacog-alfa, observational, pediatric, prophylaxis, real-world, rIX-FP

Members of IDEAL Study Group are present in Appendix.

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Novelty statements

What is the new aspect of your work?
This post hoc-analysis evaluated the clinical outcome or rIX-FP prophylaxis within the subgroup of pediatric/adolescent population enrolled in a real-world retro-prospective observational study.

What is the central finding of your work?
The switch to prophylaxis with rIX-FP consistently reduced the number of infusion and drug consumption versus previous FIX, with higher trough levels and low ABR in the analyzed subgroup of haemophilia B pediatric/adolescent.

What is (or could be) the specific clinical relevance of your work?
Routine rIX-FP prophylaxis may reduce treatment burden and drug consumption versus previous FIX showing both good effectiveness and safety profile, not only in the general haemophilia B population but also within the pediatric/adolescent subgroup.

1 | INTRODUCTION

Haemophilia B (HB) is a rare, X-linked inherited bleeding disorder characterized by a deficiency of coagulation factor IX (FIX). Clinical manifestations include increased bleeding after surgeries and spontaneous or traumatic bleeding in the muscle or joint spaces of elbows, knees, and ankles and depend on severity of FIX deficiency.[1] If not properly managed, repeated bleeding can lead to progressive deterioration of joints and muscles, severe loss of function, muscle atrophy, pain, joint deformity, and contractures within the first one to two decades of life, traducing in chronic disease and lifelong disabilities.[1–4]

Prophylaxis with FIX replacement represents the established gold standard for children in most developed countries; for pediatric patients with severe haemophilia A or B, the WFH recommends early initiation of prophylaxis with clotting factor concentrates (standard or extended half-life FVIII/FIX) prior to the onset of joint disease and, ideally, before age 3, in order to prevent spontaneous and breakthrough bleeding including hemarthroses which can lead to joint disease.[1] Therapy with standard short half-life (SHL) FIX requires frequent (i.e., generally twice weekly) intravenous injections,[1,5] and, thus, is associated with a considerable treatment burden for both patients and caregivers, with a potential impact on long-term compliance.[6,7]

Recombinant fusion protein genetically linking human coagulation FIX with human albumin (rIX-FP albutrepenonacog alfa; IDELVION®, CSL Behring) has an approximately five-fold longer half-life and five-fold slower clearance compared with SHL FIX, allowing less frequent infusions, while maintaining a circulating FIX level high enough to minimize the occurrence of bleeding episodes.[5,8,9]

In the PROLONG-9FP clinical trial phase III with severe and moderately severe HB (FIX residual activity ≤2%) patients, rFIX-FP prophylaxis achieved median AsBR of 0.00 with 7-, 10- or 14-day dosing intervals in patients ≥12 years and 7-day dosing interval in children (<12 years). Patients ≥12 years maintained a mean trough of 20.0% and 12.4% FIX activity on prophylaxis with rIX-FP 40 IU/kg weekly and 75 IU/kg every 2 weeks, respectively, while pediatric patients maintained a trough level of 13.4 IU/dL with a mean rIX-FP weekly dose of 47 IU/kg.[10–12]

In addition, the PROLONG-9FP phase 3b extension study demonstrated that, in selected pediatric patients, adequate bleed protection can be achieved with 10- or 14-day rIX-FP regimens while maintaining safety.[13]

In the IDEAL observational study,[14] all age subjects switching from their previous SHL FIX product to prophylaxis with rIX-FP have been evaluated in a real-world setting. Dosage and infusion frequency adjustments as per physicians' decisions and their impact on clinical outcome, tolerability and immunogenicity of rIX-FP have been investigated. This real-world study demonstrates that patients receiving rIX-FP had a notably reduced treatment burden and drug consumption versus previous treatment, while showing increased protection, with higher factor levels, ABR equal to zero and no bleeds in 78% of patients.

This post-hoc analysis is aimed at evaluating pattern of use and clinical outcomes within the subgroup of pediatric/adolescent patients enrolled in the IDEAL study.

2 | MATERIALS AND METHODS

2.1 | Study design and patient population

The IDEAL study was a multicenter, non-interventional, retrospective-prospective study, conducted in 23 Italian Haemophilia Treating Centres (HTC) from October 2017 to February 2021 (Appendix S1).[14]

Male patients of any age, with moderate to severe HB (residual FIX activity ≤5%), who had been using rIX-FP for at least 6 months, were eligible for enrolment and were followed-up for 2 years. Patients with other inherited bleeding disorders and/or participating in any other clinical trial were excluded.

The retrospective phase collected data about the previous FIX (the 12-month period before the patients' switch to rIX-FP) and the following period from the first infusion with rIX-FP until enrolment. Patients were assigned to treatment regimens and doses according to current local practice. In case of a switch to another treatment, they were withdrawn from the study. In order to assess patient's adherence, information related

TABLE 1 Baseline clinical demographic characteristics.

	0–11 years (*N* = 8)	12–17 years (*N* = 5)	Overall (*N* = 13)
Age (years), mean ± SD	7.6 ± 1.77	13.4 ± 2.19	9.8 ± 3.46
Median (min–max)	7.5 (5.0–10.0)	12.0 (12.0–17.0)	10.0 (5.0–17.0)
Ethnicity			
Caucasian	7 (87.5%)	5 (100.0%)	12 (92.3%)
Black or African-American	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	1 (12.5%)	0 (0.0%)	1 (7.7%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)
Height (cm), mean ± SD	129.6 ± 8.02	159.4 ± 9.37	141.0 ± 17.18
Weight (kg), mean ± SD	31.9 ± 7.46	54.0 ± 13.75	40.4 ± 14.86
BMI (kg/m^2), mean ± SD	18.8 ± 2.84	21.3 ± 5.20	19.7 ± 3.91
Age at diagnosis			
Known	6 (75.0%)	3 (60.0%)	9 (69.2%)
Age at diagnosis (years) mean ± SD	0.2 ± 0.41	0.7 ± 0.58	0.3 ± 0.50
Median (min–max)	0.0 (0.0–1.0)	1.0 (0.0–1.0)	0.0 (0.0–1.0)
Diagnosis date unknown			
Prenatal	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neonate	2 (100.0%)	0 (0.0%)	2 (50.0%)
Toddler	0 (0.0%)	1 (50.0%)	1 (25.0%)
School age	0 (0.0%)	1 (50.0%)	1 (25.0%)
Adolescent	0 (0.0%)	0 (0.0%)	0 (0.0%)
Family history of haemophilia B			
Yes	4 (50.0%)	2 (40.0%)	5 (38.5%)
Unknown	2 (25.0%)	0 (0.0%)	2 (15.4%)
Genetic testing with mutation analysis			
Conducted	8 (100.0%)	3 (60.0%)	11 (84.6%)
Pathogenic variant			
Nonsense	2 (25.0%)	0 (0.0%)	2 (18.2%)
Missense	5 (62.5%)	2 (66.7%)	7 (63.6%)
Inversion	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deletion	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intron/exon	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nonstop mutation	1 (12.5%)	0 (0.0%)	1 (9.1%)
Not specified	0 (0.0%)	1 (33.3%)	1 (9.1%)
Disease severity			
Severe (FIX residual activity <1%)	7 (87.5%)	3 (60.0%)	10 (76.9%)
Moderate (FIX residual activity 1%–5%)	1 (12.5%)	2 (40.0%)	3 (23.1%)
If moderate, FIX residual activity mean ± SD	2.0 ± 0.0	3.7 ± 1.91	3.1 ± 1.65
Median (min–max)	2.0 (2.0–2.0)	3.7 (2.3–5.0)	2.3 (2.0–5.0)

to date, duration of each infusion, IU, reasons for infusion and site of bleeding, if any, were additionally collected by infusion diary filled by the patient or by his caregiver during the observational period. In addition, labels of the used vials were required to be stuck onto the diary.

The study was approved by the ethics committees at each participating center and performed in accordance with good clinical practice and local regulatory requirements. Written informed consent for minors was obtained from their legal guardians and informed assent from the patients aged 7 years. Consent could be withdrawn at any time.

2.2 | Trial objectives and outcome measures

The primary objective of this study was the assessment of dosage patterns and annual consumption of rIX-FP in real life. Endpoints included annual

TABLE 2 Summary of regimen profile, consumption, bleedings and FIX trough activity over time, by age class.

	0–11 years ($N = 8$)			12–17 years ($N = 5$)			Overall ($N = 13$)		
	Previous rFIX	Baseline rIX-FP	2YFUP rIX-FP	Previous rFIX	Baseline rIX-FP	2YFUP rIX-FP	Previous rFIX	Baseline rIX-FP	2YFUP rIX-FP
Frequency of infusion, *N* (%)									
Two times/week	7 (87.5%)	0 (0.0%)	0 (0.0%)	4 (80.0%)	0 (0.0%)	0 (0.0%)	11 (84.6%)	0 (0.0%)	0 (0.0%)
Once per week	0 (0.0%)	4 (50.0%)	3 (37.5%)	1 (20.0%)	2 (40.0%)	0 (0.0%)	1 (7.7%)	6 (46.2%)	3 (23.1%)
Every 8–10 days	1 (12.5%)	4 (50.0%)	5 (62.5%)	0 (0.0%)	3 (60.0%)	5 (100.0%)[a]	1 (7.7%)	7 (53.8%)	10 (76.9%)
Annual number of infusions, *N*									
Mean ± SD	95.9 ± 23.99	44.3 ± 8.38	42.4 ± 8.12	93.9 ± 23.34	42.8 ± 8.59	37.3 ± 1.82	95.1 ± 22.77	43.7 ± 8.14	40.4 ± 6.79
Median (min–max)	104.4 (36.5–104.4)	44.3 (36.5–52.2)	36.5 (36.5–52.2)	104.4 (52.2–104.4)	36.5 (36.5–52.2)	36.5 (36.5–40.6)	104.4 (36.5–104.4)	36.5 (36.5–52.2)	36.5 (36.5–52.2)
Prescribed dose									
IU/kg mean ± SD	38.2 ± 8.62	41.6 ± 10.47	44.1 ± 12.41	44.3 ± 21.67	39.0 ± 2.09	35.8 ± 5.12	40.5 ± 14.47	40.6 ± 8.19	40.9 ± 10.78
Median (min–max)	36.7 (29.4–53.6)	42.6 (29.4–61.2)	44.0 (22.0–61.5)	40.8 (27.0–80.0)	40.0 (36.4–40.8)	38.5 (27.8–40.5)	40.8 (27.0–80.0)	40.5 (29.4–61.2)	38.5 (22.0–61.5)
IU mean ± SD	1187.5 ± 258.77	1312.5 ± 395.28	1781.3 ± 725.03	2600.0 ± 1981.16	2100.0 ± 547.72	2300.0 ± 570.09	1730.8 ± 1363.44	1615.4 ± 591.74	1980.8 ± 695.68
Median (min–max)	1000.0 (1000.0–1500.0)	1375.0 (750.0–2000.0)	1750.0 (1000.0–3000.0)	2000.0 (1000.0–6000.0)	2000.0 (1500.0–3000.0)	2500.0 (1500.0–3000.0)	1500.0 (1000.0–6000.0)	1500.0 (750.0–3000.0)	2000.0 (1000.0–3000.0)
Annualized consumption									
IU/kg mean ± SD	3726.5 ± 1348.58	1778.2 ± 464.70	1754.2 ± 558.92	3783.5 ± 905.33	1699.2 ± 305.37	1501.0 ± 171.81	3748.4 ± 1155.40	1747.8 ± 398.31	1656.8 ± 456.63
IU mean ± SD	115 360.0 ± 41 001.28	55 655.2 ± 15 803.82	58 124.8 ± 16 609.57	208 560.0 ± 82 440.58	90 260.6 ± 21 811.27	84 596.9 ± 21 546.09	151 206.2 ± 73 982.22	68 964.9 ± 24 725.11	68 306.4 ± 22 256.66
Trough levels, %FIX activity									
	$N = 8$	$N = 5$	$N = 4$	$N = 5$	$N = 2$	$N = 1$	$N = 13$	$N = 7$	$N = 5$
Mean ± SD	3.5 ± 2.12	9.64 ± 2.7	11.48 ± 3.9	2.6 ± 2.01	6.35 ± 3.6	8.70 ± 0.0	3.0 ± 1.98	8.70 ± 3.1	10.9 2 ± 3.6
Median (min–max)	3.5 (0.9–6.0)	11.0 (5.5–12.0)	11.2 (7.0–16.5)	3.5 (0.9–6.0)	6.4 (3.8–8.9)	8.7	2.3 (0.8–6.0)	8.9 (3.8–12.0)	11.0 (7.0–16.5)
Zero bleeding patients, *N* (%)									
	5 (62.5%)	7 (87.5%)	7 (87.5%)	4 (80.0%)	5 (100%)	4 (80.0%)	9 (69.2%)	12 (92.3%)	11 (84.6%)
ABR									
Mean ± SD	1.1 ± 2.10	0.1 ± 0.37	0.4 ± 1.11	0.2 ± 0.45	0.0 ± 0.00	0.2 ± 0.46	0.8 ± 1.69	0.1 ± 0.29	0.3 ± 0.89
Median (min–max)	0.0 (0.0–6.0)	0.0 (0.0–1.1)	0.0 (0.0–3.1)	0.0 (0.0–1.0)	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.0 (0.0–6.0)	0.0 (0.0–1.1)	0.0 (0.0–3.1)
AjBR									
Mean ± SD	0.4 ± 0.74	0.1 ± 0.37	0.0 ± 0.00	0.2 ± 0.45	0.0 ± 0.00	0.0 ± 0.00	0.3 ± 0.63	0.1 ± 0.29	0.0 ± 0.00
Median (min–max)	0.0 (0.0–2.0)	0.0 (0.0–1.1)	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–2.0)	0.0 (0.0–1.1)	0.0 (0.0–0.0)

[a]For one patient frequency was every 9 days.

consumption of rIX-FP versus previous treatment, number of infusions and dosage per infusion required to prevent or resolve bleeding episodes in prophylaxis or on demand regimens (rIX-FP vs. previous treatment).

The secondary objectives were the assessment of annualized bleeding rate (ABR, calculated as the number of reported bleeding events divided by the number of months of observation and multiplied by 12) and site of bleeds, the assessment of joint status (target joints, chronic joint pain, Haemophilia Joint Health Score, HJHS Score), of hemostatic efficacy of rIX-FP in the treatment of non-surgical bleeding episodes and during prevention and treatment of perioperative bleeding episodes. In particular each bleeding event was collected within the infusional diary filled in by the patient and then confirmed after discussion with the treating physician.

Target joint (TJ) was defined as the occurrence of ≥3 spontaneous bleeds into a single joint within a consecutive 6-month period.[15] A joint was no longer considered as TJ when 2 or less bleeds happened into the joint within a consecutive 12-month period.

Physical activity was reported as sedentary in case of no activity performed at all, moderately active, in case 1–2 days/week were devoted to physical activity and vigorously active, in case 3 or more days/week.

Moreover, the tolerability/immunogenicity of rIX-FP was assessed by collecting incidence of inhibitors in the prospective observational period and type/incidence of severe adverse events, adverse drug reactions and special situation.

2.3 | Data analysis

Due to the observational nature of the study, no hypothesis testing was performed in relation to the primary objective and, therefore, no

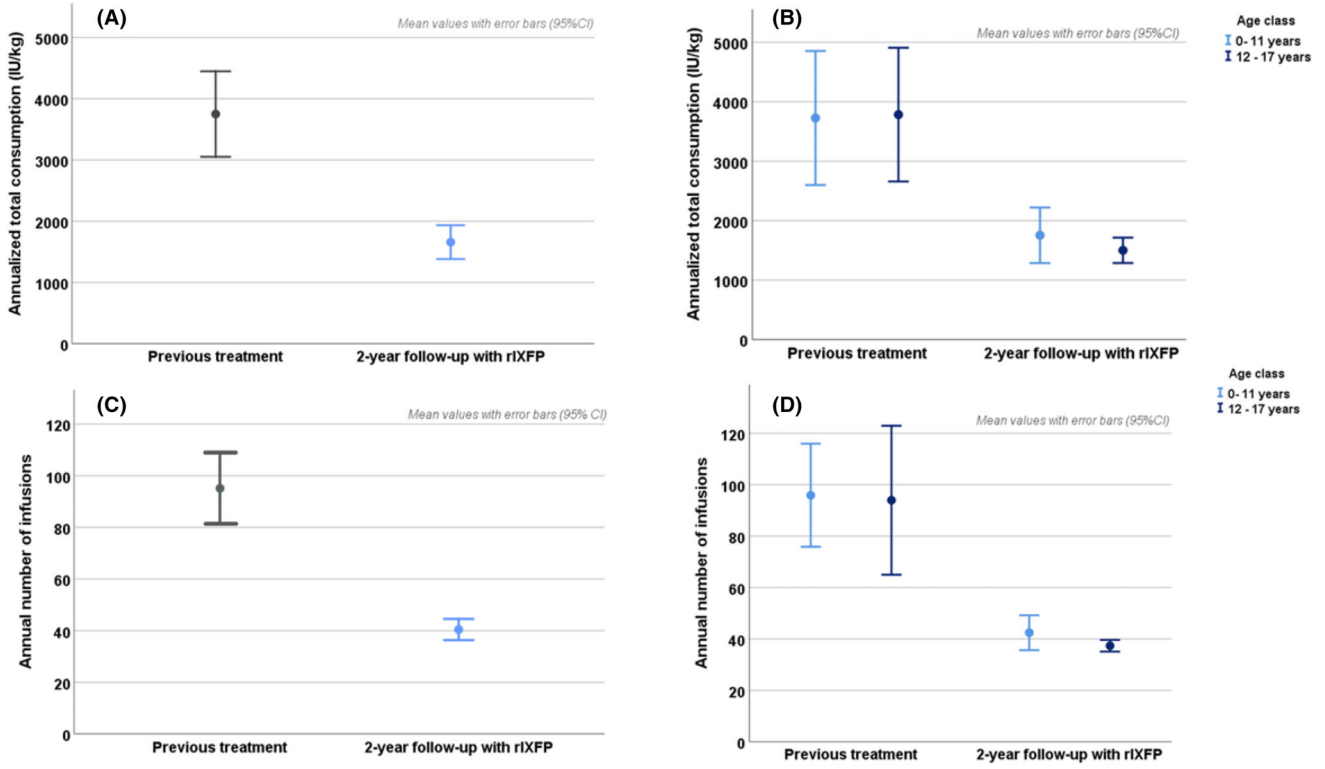

FIGURE 1 FIX annualized total consumption (IU/kg) and annual number of infusions, mean values with error bars—95% CI; previous treatment versus rIXFP; (A, C) all patients; (B, D) for age class.

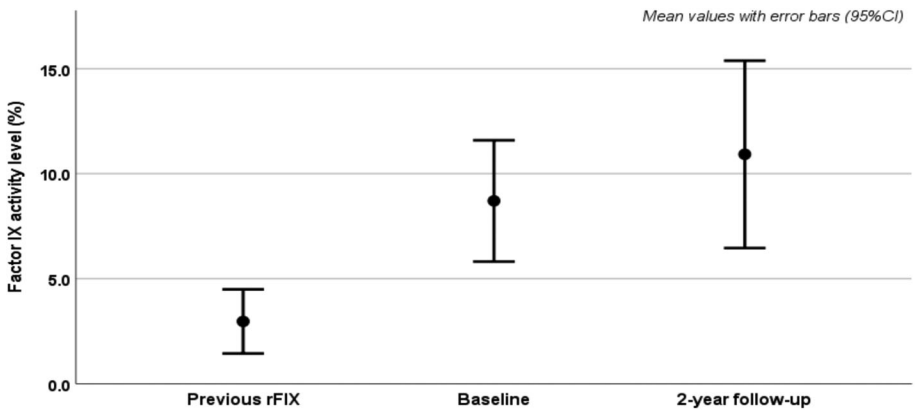

FIGURE 2 Factor IX activity level, overall population.

formal sample size calculation was computed a priori. As specified in the study protocol, data were presented only in a descriptive manner, with mean and standard deviation or median with range for continuous variables and count and percentage for categorical data. On an exploratory basis, the statistical significance of changes over time within group or any relationship between variables was assessed at univariate level (parametric or non-parametric test, as appropriate).

We present the results from a post-hoc analysis conducted on the pediatric/adolescent population involved in the study. The descriptive analyses have been conducted on all patients <18 years old at study entry, also divided in the two age classes (<12 and ≥12 years).

3 | RESULTS

3.1 | Study population

Overall, 15 minors with HB were enrolled in 9 out of 23 sites. All of them received at least one infusion of treatment after enrollment, therefore were included in the Safety Set (SS). The Full Analysis Set (FAS) included the 13 patients who completed the two-year observation period (*per protocol* population).

Age ranged from 5 to 17 years (median 10.0), with 61.5% of patients ($N = 8$) aged <12 years; the population was geographically distributed in all the Italian territory, 92.3% of them were Caucasian (Table 1). The overall median age at diagnosis was 0.0 years old (range: 0–1.0); severe haemophilia was recorded in 76.9% of the cases ($N = 10$), while within the "moderate" group (23.1%), the median FIX residual activity was 2.3% (range: 2.0%–5.0%) (see Table 1 for further details).

3.2 | Dosage regimen and annualized consumption

All the 13 patients <18 years had always been on prophylaxis with both previous rFIX and rIX-FP during the entire observation period. Dosage regimen and frequency are described in Table 2.

The frequency of infusion reduced from mainly every 2 times/week (84.6%, $N = 11$) with previous rFIX to less than once a week (every 9/10 days) in 76.9% ($N = 10$) of the cases at 2YFU, when no patient was infused less than once a week. In particular, within the 0–11 age class, 87.5% ($N = 7$) of the children received the previous rFIX two times per week, and 12.5% ($N = 19$) every 10 days, while at 2YFU with rIX-FP, 37.5% ($N = 3$) were treated every 7 days and 62.5% ($N = 5$) every 8–10 days. In the 12–17 age class, 80% ($N = 4$) of the patients were on twice/week prophylaxis regimen with the previous rFIX, while, at 2YFU with rIX-FP, 100% ($N = 5$) were treated every 9–10 days (see Table 2).

Adherence to the prescribed treatment throughout the 2-year observation period, evaluated in accordance to the infusion diary, was maintained in all age classes.

The annualized mean consumption decreased of about 56%, from 3748.4 ± 1155.40 IU/kg with previous rFIX, to 1656.8 ± 456.63 IU/kg with rIX-FP at 2YFU (Wilcoxon signed rank test: $p = .001$); the mean annual number of the infusion decreased of about 57.5% from 95.1

TABLE 3 Summary of bleeding episodes requiring treatment and short-term prophylaxis and hemostatic response to rIX-FP.

Patient with at least one bleeding	7
Number of bleedings	12
Total dose (IU), mean ± SD	2291.7 ± 1529.38
Median (min–max)	2000 (1000–6000)
Total dose (IU/kg), mean ± SD	51.4 ± 31.86
Median (min–max)	38.5 (22.0–113.2)
Total number of infusions, mean ± SD	1.4 ± 0.67
Median (min–max)	1.0 (1.0–3.0)
Hemostatic outcome	
Excellent	8 (66.7%)
Good	4 (33.3%)
Moderate	0 (0.0%)
Poor/no response	0 (0.0%)
Patients with at least one event requiring short term prophylaxis	7
Total number of events	12
Type of bleeding episode *N* (%)	
Major surgery	0 (0.0%)
Minor surgery	1 (8.3%)[a]
Invasive procedure	1 (8.3%)[b]
Other	10 (83.3%)[c]
Total dose (IU) pre- and post-surgery/procedure/event, mean ± SD	1958 ± 655.69
Median (min–max)	2000.0 (1000.0–3000.0)
Total number of infusions pre- and post-surgery/procedure/event, mean ± SD	1.3 ± 0.62
Median (min–max)	1.0 (1.0–3.0)
Hemostatic outcome	
Excellent	12 (100.0%)
Good	0 (0.0%)
Moderate	0 (0.0%)
Poor/no response	0 (0.0%)

Note: **Excellent**—pain relief and/or unequivocal improvement in objective signs of bleeding at approximately 24 h after the first infusion and no additional infusions required in order to achieve hemostasis; **Good**—definite pain relief and/or improvement in signs of bleeding at approximately 24 h after the first infusion, but required a second infusion in order to achieve hemostasis; **Moderate**—probable or slight beneficial effect at approximately 24 h after the first infusion and required more than 2 injections to achieve hemostasis; **Poor/no response**—no improvement or worsened at approximately 24 h after the first infusion and additional hemostatic intervention required with other FIX product or plasma to achieve hemostasis. Bleedings and short-term prophylaxis (additional infusions to prescribed prophylaxis to ensure more protection and prevent bleeds in case of surgery/invasive procedures or traumatic events) represents two distinct and independent features.

[a]Arteriovenous fistula closure.

[b]Gastroscopy.

[c]Pain in the right arm and shoulder, head injury after a fall, left ankle sprain, treatment of tooth abscess, additional infusion in view of the school trip, knee trauma post fall, minor trauma during bike (leg), minor trauma during sport activity at school (arm), minor trauma (sprain), minor trauma (sprain).

TABLE 4 Activity level over time, overall and by age class.

	0–11 years ($N = 8$)		12–17 years ($N = 5$)		Overall	
	Baseline	2-year FUP	Baseline	2-year FUP	Baseline	2YFU
Investigator's assessment on patient's physical activity						
Sedentary	2 (25.0%)	2 (25.0%)	0 (0.0%)	1 (20.0%)	2 (15.4%)	3 (23.1%)
Moderately active	5 (62.5%)	3 (37.5%)	5 (100.0%)	4 (80.0%)	10 (76.9%)	7 (53.8%)
Vigorously active	1 (12.5%)	3 (37.5%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	3 (23.1%)
Concordance in physical activity level performance between investigator and patient						
Agreement	7 (87.5%)	8 (100.0%)	5 (100.0%)	5 (100.0%)	12 (92.3%)	13 (100.0%)

± 22.77 to 40.4 ± 6.79 ($p = .002$, Wilcoxon signed ranks test) (Figure 1A,C).

As concerns the two age classes, the mean annualized total dose with previous rFIX reduced from 3726.5 ± 1348.58 IU/kg to 1754.2 ± 558.92 IU/kg in patients aged 0–11 years ($p = .012$ Wilcoxon signed ranks test) and from 3783.5 ± 905.33 to 1501.0 ± 171.81 in the ≥12 years group at the 2YFU ($p = .043$ Wilcoxon signed ranks test), with a decrease of 53% and 60%, respectively. Mean annual number of the infusion moved from 95.9 ± 23.99 to 42.4 ± 8.12 in patients aged 0–11 years, and from 93.9 ± 23.34 to 37.3 ± 1.82 in patients aged 12–17 years old (Figure 1B,D).

The prescribed mean dose of rIX-FP remained quite stable during the entire 2YFU period, with a mean value ranging from 40.6 ± 8.19 IU/kg at baseline to 40.9 ± 10.78 IU/kg, irrespective of the infusion frequency (further details in Table 2).

During the 2YFU 18 changes in dose or frequency occurred and the reasons reported were "weight change" (in 8 cases), PK adjustments (in 5 cases), "need for more protection" (in 3), and "other" (in 2, i.e., "clinical decision" and "good response to treatment").

3.3 | FIX trough levels

Due to the observational nature of the study, FIX trough levels measurements were available at 2YFU in 4 out 8 patients in 0–11 years subgroup and in only 1 out 5 patients in 12–17 years subgroup (see Table 2 for details). Mean FIX trough levels (Table 2 and Figure 2) changed from 3.0 ± 1.98 (0.8–6.0) with previous rFIX ($N = 13$) to 10.92 ± 3.6 (7.0–16.5) with rIX-FP at 2YFU ($N = 5$).

3.4 | ABR

No change in the mean was observed at the 2YFU with rIX-FP treatment: ABR remained low, 0.3 ± 0.89 compared to 0.8 ± 1.69 during the 12-month previous rFIX. AjBR was 0.0 ± 0.00, compared to 0.3 ± 0.63 with the previous FIX (Table 2). As regards the nature of the bleeds, in 5 cases within the infusional diary it was specified they were due to a trauma and, in particular 2 due to joint trauma.

The rate of subjects with zero bleedings was 69.2% ($N = 9$) during the last year of treatment with previous FIX and 84.6% ($N = 11$) at 2YFU with rIX-FP (Table 2) ($p = .63$ Related-Samples McNemar Change Test).

3.5 | Bleeding management

Overall, 7 patients experienced 12 bleedings during the 2YFU period (5 of them of traumatic nature); a mean of 1.4 infusions was required with a mean single dose/infusion of 35.38 ± 10.57 and a mean total dose of 51.4 ± 31.86 IU/kg (Table 3). The hemostatic outcome was judged excellent or good in 100% of cases ($N = 12$) (66.7% and 33.3%, respectively). Seven patients required 12 short-term prophylaxis due to 1 minor surgery (arteriovenous fistula closure), 1 invasive procedure (gastroscopy), 9 traumatic events and 1 tooth abscess. A mean total dose of rIX-FP of 1958 ± 655.69 IU was used with a mean number of infusions of 1.3 ± 0.62. Hemostatic outcome was defined as excellent in 100% of cases (Table 3).

3.6 | Joint status outcomes

Overall, no patients reported TJ, chronic joint pain or had prosthesis neither at baseline nor at 2YFU. The mean HJHS scores were 0.0 ± 0.00 and 0.5 ± 1.22, at baseline ($N = 7$) and at 2YFU ($N = 6$), respectively.

Comparisons with the previous treatment, apart from chronic joint pain, were not feasible since no data were available.

3.7 | Physical activity

Overall, moderate physical activity was reported in 76.9% ($N = 10$) of patients at baseline vs. 53.8% ($N = 8$) at 2YFU, vigorous physical activity in 7.7% ($N = 1$) and 23.1% ($N = 3$) while sedentary patients represented 15.4% ($N = 2$) and 23.1% ($N = 3$), respectively (Table 4).

3.8 | Safety

None of the assessments performed as per clinical practice detected the presence of inhibitors.

Out of 15 pediatric patients (SS), 2 (15.0%) reported 2 Treatment Emergent Adverse Events (TEAEs): 1 event, persistent vomiting, was classified as SAE (hospitalization). The second event, "haematuria" (not serious), led to temporary discontinuation of study drug. None of them was judged to be related to rIX-FP.

4 | DISCUSSION

Results from the IDEAL real-world study on 13 patients aged <18 years, support safety and effectiveness of rIX-FP prophylaxis in pediatric/adolescent population. Regardless of disease severity, initiation of rIX-FP resulted in excellent bleed control, reduced factor consumption, reduced frequency of infusions and maintained adherence. SHL FIX replacement products require frequent intravenous injections, creating a burden for both patients and caregivers, impacting long-term compliance.[7] Especially in the youngest children, difficult venous access may require central venous device with related risks of thrombosis and infections.[16] Moreover, adolescence is associated with the transition phase towards self-management and, therefore, represent a critical period with a high risk of lack of adherence to prophylaxis, healthcare, which might have serious consequences on daily activities and on quality of life.[17,18] rIX-FP, with its 5-fold extended half-life, allows to prolong the interval between two infusions and help to maintain high FIX levels and bleeds protection. Flexibility in posology regimen and tailored prophylaxis support a better adherence to the treatment; indeed, in clinical studies, the adherence to rIX-FP prophylaxis has been reported to be high, with a mean of 96% in patients ≥12 years along all prophylaxis regimen and 98% in pediatric patients under weekly prophylaxis.[19]

During this real-world observational study, rIX-FP prophylaxis was efficiently managed without requiring any central venous device, neither in our pediatric population. This finding is in accordance with PROLONG-9FP trial.

Moreover, it resulted that most patients, lengthened the dosing interval from twice a week to every 7 days when they started rIX-FP, and, in most cases, extended further dosing interval through the 2-years observational period. In particular, 100% ($N = 5$) of 12–17 years-old class received rIX-FP every 9–10 days at the end of follow-up period. Also, in the 0–11 age class ($N = 8$), the shift to longer intervals was done, even if more conservative: 62.5% were infused every 10 days at the end of the 2YFU, the remaining maintained weekly treatment, probably due to the clinician's choice to get more protection. Indeed, in the phase III extension study of the PROLONG-9FP trial, 24 children (1–11 years) with severe and moderately severe HB,[13] could extend their prophylaxis interval to every 10 or 14 days if well controlled. The patients, followed up for a mean period of 3 years, experienced a dosing interval >7 days in 66.7% of cases and, at the end of the study, 29.2% of the patients remained under a regimen every 10 or 14 days (12.5% and 16.7%, respectively).[13]

Mean single dose administered within the pediatric patients, in the extension study was 49 IU/kg for the 7-day regimen and 74 IU/kg for the 10- and 14-day regimen, versus 44 IU/kg prescribed in our patients aged <12 years. Irrespective of the infusion frequency, in our study the prescribed dose of rIX-FP remained quite stable during the entire 2YFU, and the annualized total dose significantly decreased (about 56%) compared to the previous treatment (Wilcoxon signed rank test: $p = .001$). Our results were consistent with a retrospective analysis of patients treated with rIX-FP in Germany,[20] where a reduction superior to 50% in weekly dosage from previous replacement therapy with nonacog-alfa was detected also for pediatric subpopulation. In particular, in patients aged >11 years, mean weekly dose of rIX-FP was 44.1 IU/kg/week, while mean weekly dose of nonacog alfa was 84.3 IU/kg/week. Within patients group aged 0–11 years, mean weekly dose of rIX-FP was 45.0 IU/kg/week and mean weekly dose of nonacog alfa 94.2 IU/kg/week.

Notably, the mean FIX through level reached in our study (i.e., 11%) was in accordance with the World Federation of Haemophilia guidelines that suggested to maintain at least of 3%–5%.[1]

Though infusion interval was increased, prophylaxis with rIX-FP was highly effective in bleeding prevention, as demonstrated by a low mean ABR and a 0.0 median ABR maintained across all the prophylaxis regimens. ABR reported in our study encompass also traumatic events (at least 42% of all events) and are aligned with phase III trials and real-world evidence published involving other FIX.[21–26]

The goal of zero bleeding events is currently considered the target of prophylaxis,[1] to avoid/delay permanent joint damage,[2,27–30] indeed, the rate of subjects with zero bleedings with rIX-FP at 2YFU was 84.6% ($N = 11$), compared to 69.2% ($N = 9$) of the previous treatment. Some spontaneous bleeds may occur despite high trough levels, since a certain heterogeneity in clinical bleeding phenotype has been observed in hemophilia patients with similar FVIII or FIX activity levels.[31] Due to the observational nature, trough levels measurement was not compulsory. Therefore, it was not possible to temporally correlate FIX levels with break through bleeds/traumatic bleeds occurred during our study. To be noted that the overall rate for all age patients reaching zero bleedings from the IDEAL study was 78%, same median ABR, 0.00. Out of 50 patients analyzed in the IDEAL study, 54% received the treatment every 8/10 days, 24% every 11/14 days and 6% every 15/21 days; notably, all the infusion regimens achieved mean FIX trough level >10%, in particular, every 8/10 days: 12.6 ± 5.5; every 11/14 days: 10.8 ± 3.8; every 15/21 days: 11.9.[14] As observed in the phase III PROLONG9-FP, a reduced number of infusions may have impacted in the treatment burden perceived both by patients and their caregivers, and may have led to an improvement to the quality of life.[32]

The HJHS scores were reported in a few samples, and comparison with the previous rFIX was not feasible, since no data were available neither for HJHS, nor for other articular parameters as target joints, or prosthesis.

Indeed, all the TJ reported at baseline (3 TJ in 2 patients) were no more present at 2YFU. This was consistent with PROLONG-9FP findings where all the TJ developed recovered at the end of the study.[33] No patients had chronic joint pain or prosthesis neither at baseline nor at 2YFU.

Though the 2YFU was impacted by COVID-19 pandemic restrictions and the % of sedentary patients raised, the improvement in the

prophylaxis coverage and of the articular status on physical activity may have allowed some patients to increase their physical activity.

Measures of hemostatic efficacy indicated that rIX-FP provided fast and complete control of bleeding episodes either due to surgical/invasive procedure or other events, with a success rate of defined as good/excellent of 100.0%. Almost all the bleeds were controlled with no additional infusions (median infusion number required of 1.0).

The main strength of this work is that this is the first real-world prospective observational study conducted on rIX-FP, that combines a long-term prospective observation (2-year follow-up) with retrospective data on rIX-FP treatment (6 month-therapy at least) and previous 12 months of other standard replacement therapies. The study helped to collect pattern of use and clinical outcome in terms of bleedings, joint status, and data concerning physical activity.

A limitation of the study could be represented by the low number of pediatric patients and the lack or partial data (i.e., trough level, or articular data for comparison with previous treatment). In the case of rare diseases, such as this one, where gathering many participants is challenging due to low prevalence, small sample studies may be the sole practical option.

Statistical analysis can still be valuable for various reasons, even if the goal is not to precisely estimate effect sizes or detect small effects. Small sample analysis can serve as an initial exploration, offering preliminary insights into potential trends or relationships in the data, which can subsequently guide further research with larger sample sizes, if necessary.

Despite these potential limitations, the results presented here are consistent with experience derived from rIX-FP PROLONG-9FP trial and suggest a potential benefit of switching from SHL replacement factors to rIX-FP for improved bleed control while achieving a lower treatment burden. In conclusion, the present post-hoc analysis focused on pediatric/adolescent subpopulation confirms the findings of the IDEAL study on general population[14] and is coherent with results from PROLONG-9FP trial with rIX-FP,[7,12] both in terms of effectiveness and safety profile.

In conclusion, rIX-FP prophylaxis resulted in reduced treatment burden and drug consumption when compared to the previous treatment, while showing higher FIX levels, ABR maintained low, with no bleeds at 2YFU in 84.6% ($N = 11$) of the patients.

AUTHOR CONTRIBUTIONS

All the authors were involved in patient management, data collection and manuscript review. Dr. Giancarlo Castaman was also involved in the study protocol design and data interpretation. All the members of the IDEAL Study Group were involved in the manuscript review. Between them, Dr. Annarita Tagliaferri and Dr. Antonio Coppola were member of the Study Steering Committee.

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CONFLICT OF INTEREST STATEMENT

C.B. has received honoraria for advisory board participation from Bayer, SOBI, Roche; R.D.C. has received honoraria for advisory board participation from Pfizer, Takeda, Bayer, CSL Behring, BioMarin, SOBI, Novo Nordisk; F.P. has received honoraria for advisory board participation from CSL Behring, BioMarin, Roche, Sanofi, SOBI and as speaker at educational meeting of Takeda and Spark; M.R.V. has received honoraria for advisory board participation from CSL Behring; A.C. has received honoraria for speaking and/or for consulting from Bayer, BioMarin, Novo Nordisk, SOBI, Takeda and Werfen; D.C. acted as consultant for Bayer, CSL Behring, Kedrion, Novo Nordisk, Pfizer, Roche; M.M. has received honoraria for advisory board participation from CSL Behring, Novo Nordisk, SOBI; C.S. has received honoraria for speaking or for advisory board participation from Roche, Novo Nordisk, Bayer, SOBI, Takeda, CSL Behring, BioMarin, Novartis, Amgen; R.C.S. acted as consultant for: Roche, CSL Behring, SOBI, Takeda, Pfizer, Bayer, Novo Nordisk; S.S. acted as consultant for CSL Behring, Takeda, Novo Nordisk, Bayer, Amgen, SOBI; A.T. has received honoraria for advisory board participation from Bayer, speaker fee by Novo Nordisk, expert opinion for BioMarin; A.T. has received honoraria for speaking from Sanofi, Werfen, Roche; E.Z. has received honoraria for advisory board participation from Bayer, BioMarin, Novo Nordisk; A.L. is a CSL Behring Employee; I.S. has received consulting fees from Horizon, Resonances Project (APDesign, Kansas State University), Hippocrates Research, Eyepharma, Hoya Holding N.V., DMG Italia; D.V. is a Hippocrates Research employee (CRO delegated for study conduction); G.C. has received fees as speaker at Company Satellite Symposia/Webinar during Scientific meetings for BioMarin, LFB, Kedrion, Takeda, Roche, Novo Nordisk, Pfizer, CSL Behring, SOBI, Werfen and other honoraria for participation in Advisory Boards of Bayer, BioMarin, CSL Behring, LFB, SOBI, Pfizer, Roche, Takeda. P.G., B.P., G.S., F.D., A.B., F.D., M.M., R.M., L.B., P.R., L.V. have no conflicting interests to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A: IDEAL STUDY GROUP

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