Received: 23 February 2024 | Revised: 17 May 2024 | Accepted: 9 June 2024

DOI: 10.1111/hae.15074

Haemophilia WFH WILEY

LETTER TO THE EDITOR

Real-world experience of rIX-FP prophylaxis at dosing intervals of 14 days or more in adult patients with haemophilia B in Italy – Results from IDEAL Part B

Recombinant factor IX-albumin fusion protein (rIX-FP, Albutrepenonacog alfa) is an extended half-life factor IX (FIX) with approximately 5-fold longer half-life compared to standard half-life (SHL) FIX and provides excellent bleeding prevention with a great flexibility in dosing intervals.[1] rIX-FP is approved for the treatment of persons with haemophilia B (PWHB) at dosing intervals of 7 days in <12 years, up to 14 days in ≥12 years and, in selected adults, up to 21 days.[2] However, available real-world evidence about prophylaxis regimen ≥14 days is limited. The observational study IDEAL (IDelvion in hEmophilia B: evaluAtion of posoLogic profile) described pattern of use and outcomes of rIX-FP prophylaxis in the clinical practice in moderate/severe PWHB (FIX ≤ 5%). The first phase (Part A) involved 23 Italian hemophilia treating centers (HTC) enrolling from October 2017 to February 2019 59 PWHB of all ages with a 2-year follow-up observation.[3] Herein, we present the subsequent phase of the study, Part B, specifically aimed at gathering real-world experience on adult PWHB on prophylaxis regimen with dosing intervals ≥14 days.

IDEAL Part B prospectively (1-year follow-up, 1YFU) collected, from April 2021 to December 2022, data about PWHB ≥18 years on dosing regimen ≥ 14 days at baseline, treated with rIX-FP ≥6 months, either previously involved in the Part A or not. The study was approved by the ethics committee at each participating centre and conducted in accordance with good clinical practice and local regulatory requirements. All patients provided written informed consent. Primary endpoints (EP) were infusion frequency, annualized number of infusions, FIX annualized consumption. Secondary EP included FIX trough levels (when measured), Annualized Bleeding Rate (ABR), rIX-FP haemostatic efficacy, presence of target joints (i.e., occurrence of ≥3 spontaneous bleeds into a single joint within a consecutive 6-month period[4]), chronic synovitis—assessed through physical examination (World Federation of Haemophilia, WFH, Orthopaedic Joint Score[5]) and, when available, ultrasound scanning according to the HEAD-US (Haemophilia Early Arthropathy Detection with Ultrasound[6]) protocol—chronic joint pain, physical activity, tolerability, and immunogenicity. Previous FIX data were retrospectively gathered (from Part A, or *de novo*, for new patients) and compared to rIX-FP at 1YFU. Patients were asked to fill in an infusion diary throughout the observational period including information on date, duration of each infusion, IU infused, reasons for infusion and site of bleeding, if any; each bleeding event reported in the patient diary was confirmed after discussion with the treating physician. According to physical activity, patients were considered as "sedentary" in case of no activity performed at all, "moderately active," if physical activity was practiced 1–2 days/week and "vigorously active," if 3 or more days/week. As specified in the study protocol, data are 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 groups or any relationship between variables was assessed at univariate level (parametric or nonparametric test, as appropriate).

Eight HTC enrolled 14 subjects (10 from the previous Part A) with a mean age of 46.3 ± 16.4 years, body mass index (BMI) of 26.5 ± 4.5 kg/m^2; severe haemophilia was recorded in 64.3% (n = 9) cases (Table 1). Patients were on rIX-FP prophylaxis since 39.1 ± 14.6 months, with frequency ≥ 14 days since 26.9 ± 19.5 months (four patients since the first rIX-FP regimen, 10 prolonged dosing intervals after first prescription); the mean prescribed dose was 43.7 ± 8.8 IU/Kg, and the infusion interval was in 92.8% (n = 13) every 14/15 days and 7.1% (n = 1) every 21 days (Table 1).

No patient dropped off the study. At 1YFU, all infusion frequencies remained stable apart from one case (temporary reduction from 14/15 days to once weekly, due to a major surgery concomitant to 1YFU), neither significant change in dose occurred. The 21-day dosing regimen, adopted in one severe PWHB, was maintained for the whole observation period. Before switching to rIX-FP, this patient was on prophylaxis regimen with rFIX 87.0 IU/Kg once weekly. A single FIX trough level (7.7%) was available during the 1YFU.

Previous FIX treatment was represented by SHL FIX in all cases, given in 4 out of 14 patients on demand and in 10 patients with prophylaxis regimens, 2–3/weekly (n = 6, 60%) or once weekly (n = 4, 40%). Compared data between 1YFU rIX-FP and previous FIX prophylaxis (n = 10) are summarized in Table 2. The single mean dose was 44.1 ± 16.3 IU/Kg with previous FIX, and 43.3 ± 10.0 IU/kg with rIX-FP at 1YFU. The annualized number of infusions decreased, at

TABLE 1 Patients demographic and clinical data ($n = 14$).

Age, years	
mean ± SD	46.3 ± 16.36
median (min, max)	44.0 (28.0–80.0)
BMI, cm/kg^2	
mean ± SD	26.5 ± 4.49
median (min, max)	26.2 (21.2–39.8)
Disease severity, *n* (%)	
Severe (FIX < 1%)	9 (64.3%)
Moderate (FIX 1%–5%)	5 (35.7%)
FIX residual activity in moderate PWH-B, (%)	
mean ± SD	2.6 ± .55
median (min, max)	3.0 (2.0–3.0)
rIX-FP treatment duration at baseline, (days)	
rIX-FP first prescription	
mean ± SD	1189.1 ± 443.58
median (min, max)	1378.5 (221.0–1602.0)
rIX-FP ≥ 14 days regimen	
mean ± SD	817.3 ± 594.28
median (min, max)	1032.5 (0.0–1506.0)
rIX-FP regimen at baseline (IU/kg)	
Overall patients ($n = 14$)	
mean ± SD	47.3 ± 8.78
median (min, max)	43.8 (26.3–56.3)
Every 14—15 days ($n = 13$)	
mean ± SD	42.8 ± 9.22
median (min, max)	45.5 (26.2–56.3)
Every 21 days ($n = 1$)	43.5

Abbreviations: BMI, body mass index; rIX-FP, recombinant factor IX-albumin fusion protein; SD, standard deviation.

1YFU, of 70%, from a mean of 93.6 ± 41 with the previous FIX to 27.4 ± 9 ($p = .005$) with rIX-FP, while mean FIX annualized consumption decreased of 67%, from 4020.8 ± 1826 IU/kg to 1339.1 ± 402 IU/kg ($p = .001$). Trough level mean values, calculated on all data available, were 4.4% ± 2.3 ($n = 7$) and 7.8% ± 4.1 ($n = 7$), for previous FIX and rIX-FP, respectively. Mean ABR remained low across all prophylaxis regimens (0.8 ± 1.20 with previous FIX vs. 0.6 ± 1.02 with rIX-FP at 1YFU). The percentage of subjects with zero bleeding (66.7%, $n = 6$), calculated on the number of patients always on prophylaxis and with available data ($n = 9$) for both retrospective and prospective part, remained unchanged compared to the previous FIX.

During the 1YFU, 5 out 14 subjects (35.7%) reported a total of seven bleeding episodes, two spontaneous gum bleeds and five traumatic bleeds (two joint, one subcutaneous, one muscle after intense physical activity and, one involving left arm, hemithorax, shoulder and leg) treated with a mean of 1.6 ± 1.7 infusions, with a mean dose for single infusion of 45.3 ± 5.4 IU/kg. The haemostatic outcome was rated good/excellent in 71.4% of cases ($n = 5$), moderate in the remaining two cases.

Chronic synovitis was present in 3 out 14 patients (21.4%) at baseline and in 2 out 13 (15.4%) at 1YFU. The third patient presenting synovitis at baseline underwent joint replacement during 1YFU and, therefore, was not evaluable at the end of the study. HEAD-US assessment was available, both at baseline and at 1YFU, in four cases (28.6%), in one with detection of synovitis. No target joints were reported neither at baseline nor at 1YFU, while chronic joint pain was present in 35.7% of patients ($n = 5$) with previous FIX and in 21.4% of patients ($n = 3$) at 1YFU with rIX-FP. When assessed, WFH Orthopaedic Joint score was 7.8 ± 15.0 ($n = 6$) at baseline, and 9.0 ± 9.7 ($n = 4$) at 1YFU.

At baseline, as regards to physical activity, 35.7% of patients were considered as "sedentary" ($n = 5$), 50% "moderately active" ($n = 7$) and 14.3% "vigorously active" ($n = 2$), while at 1YFU they were 50% ($n = 7$), 35.7% ($n = 5$) and 14.3% ($n = 2$), respectively.

Nine adverse events (including four COVID-19 infections) occurred in six patients, none related to rIX-FP, neither serious adverse events nor events leading to rIX-FP discontinuation occurred. No inhibitor development was reported.

Our findings are consistent with the phase III trial and extension phase IIIb study results showing that rIX-FP is safe and effective even at extended dosing intervals.[1,7] Indeed, rIX-FP pharmacokinetic profile allows a reduction in the infusion frequency and factor consumption, maintaining high level of protection at infusion intervals from 14 up to 21 days, often exceeding the minimum FIX trough levels of 3%–5% recommended by WFH guidelines.[5]

Mean ABR remained low, and the percentage of subjects with zero bleeding unchanged, despite a 70% reduction of the annual infusion number, compared with previous SHL FIX treatment. ABR reported in our study included mainly traumatic bleeds (71% of all events) and are aligned with phase III trials and real-world evidence published involving other FIX concentrates.[7,1,8,9] Due to the observational nature of the study, additional data regarding the FIX activity level at the time of bleeding events in relation to the FIX dose were not available.

A nonvigorous physical activity in most patients was likely affected by the age range of the subjects and the concomitance of COVID-19 pandemic. On the other hand, taking into account the patient physical activity level and lifestyle is relevant for defining the dosing intervals and personalizing prophylaxis regimens.[5]

Limitations of the study are represented by the low number of subjects and the lack or partial data due to the observational nature of the study (i.e., trough levels or assessment of joint status for comparison with previous treatment). However, in the case of rare diseases, such as haemophilia B, where gathering many participants is challenging due to low prevalence, small sample studies may be the sole practical option. In addition, recall bias could have affected the retrospective part.

In conclusion, the study results support the possibility, in patients ≥18 years, to extend rIX-FP dosing interval to 14 or more days (up to 21 days), reducing the burden of injection and FIX consumption, while maintaining high trough levels and excellent bleeding protection. Further data collection, however, is needed to achieve information about long-term outcomes, including joint health.

TABLE 2 previous FIX versus rIX-FP 1YFU (patients in prophylaxis also with previous FIX, $n = 10$).

	PREVIOUS FIX	rIX-FP 1YFU
Frequency of infusion, *n* (%)		
2/3 times/week	6 (60.0%)	0 (0.0%)
Once a week	4 (40.0%)	1 (10%)
Every 14–15 days	0 (0.0%)	8 (80%)
Every 21 days	0 (0.0%)	1[a] (10%)
Prescribed dose (IU/kg)		
mean ± SD median (min, max)	44.1 ± 16.31 43.5 (14.3–75.9)	43.32 ± 10.00 48.36 (26.3–65.6)
Annual number of infusions, *n*		
mean ± SD median (min, max)	93.6 ± 41.02 104.0 (52.0–156.0)	27.4 ± 9.04 26.1 (17.4–52.0)
Annualized total consumption, (UI/kg)		
mean ± SD Median (min, max)	4020.8 ± 1826.02 4030.6 (2234.6–7373.7)	1339.1 ± 401.50 1356.4 (686.1–2058.3)
Annualized bleeding rate, *n*		
mean ± SD median (min-max)	0.8 ± 1.20 0.0 (0.0–3.0)	0.6 ± 1.02 0.0 (0.0–3.0)
Zero bleedings, *n* (%) (data available for $n = 9$)	6 (66.7%)	6 (66.7%)
Annualized joint bleeding rate		
mean ± SD median (min-max)	0.8 ± 1.20 0.0 (0.0–3.0)	0.6 ± 1.02 0.0 (0.0–3.0)
FIX activity trough level, %		
mean ± SD median (min, max)	4.4 ± 2.31 3.5 (2.1–8.0)	7.8 ± 4.14 7.7 (2.7–14.0)

Abbreviations: FIX, factor IX; rIX-FP, recombinant factor IX-albumin fusion protein; SD, standard deviation.
[a]infusion interval was temporarily reduced to 1/week due to concomitant major surgery.

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.

ETHICS STATEMENT

The study was approved by the ethics committee at each participating centre and performed in accordance with good clinical practice and local regulatory requirements. Written informed consent was obtained from all patients and consent could be withdrawn at any time.

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REFERENCES

1. Mancuso ME, Lubetsky A, Pan-Petesch B, et al. Long-term safety and efficacy of rIX-FP prophylaxis with extended dosing intervals up to 21 days in adults/adolescents with hemophilia B. *J Thromb Haemost*. 2020;18(5):1065-1074. doi:10.1111/jth.14778
2. IDELVION Coagulation Factor IX [Recombinant], Albumin Fusion Protein (rIX-FP) Highlights of Prescribing Information. Marburg: CSL Behring GmbH; 2020. https://labeling.cslbehring.com/PI/US/Idelvion/EN/Idelvion-Prescribing-Information.pdf
3. Tagliaferri A, Molinari AC, Peyvandi F, et al. IDEAL study: a real-world assessment of pattern of use and clinical outcomes with recombinant coagulation factor IX albumin fusion protein (rIX-FP) in patients with haemophilia B in Italy. *Haemophilia*. 2023;29(1):135-144. doi:10.1111/hae.14689
4. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Subcommittee on factor VIII, factor IX and rare coagulation disorders of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost*. 2014;12(11):1935-1939. doi:10.1111/jth.12672
5. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia panelists and co-authors. *Haemophilia*. 2020;26(6):1-158. doi:10.1111/hae.14046
6. Martinoli C, Della Casa Alberighi O, Di Minno G, et al. Development and definition of a simplified scanning procedure and scoring method for haemophilia early arthropathy detection with ultrasound (HEAD-US). *Thromb Haemost*. 2013;109(6):1170-1179. doi:10.1160/TH12-11-0874
7. Santagostino E, Martinowitz U, Lissitchkov T, et al. Long acting recombinant coagulation factor IX albumin fusion protein (rIX-FP) in hemophilia B: results of a phase 3 trial. *Blood*. 2016;127:1761-1769.
8. Oldenburg J, Yan S, Maro G, Krishnarajah G, Tiede A. Assessing bleeding rates, related clinical impact and factor utilization in German hemophilia B patients treated with extended half-life rIX-FP compared to prior drug therapy. *Curr Med Res Opin*. 2020;36:9-15.
9. Hermans C, Marino R, Lambert C, et al. Real-world utilisation and bleed rates in patients with haemophilia B who switched to recombinant factor IX fusion protein (rIX-FP): a retrospective international analysis. *Adv Ther*. 2020;37:2988-2998.

SUPPORTING INFORMATION

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