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ORIGINAL ARTICLE

Long-term safety and efficacy of rIX-FP prophylaxis with extended dosing intervals up to 21 days in adults/adolescents with hemophilia B

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Abstract

Background: An international, multicenter extension study evaluated recombinant fusion protein linking recombinant coagulation factor IX (FIX) with recombinant human albumin (rIX-FP) in hemophilia B (FIX ≤ 2%) patients previously enrolled in a phase III study or who initiated rIX-FP prophylaxis following surgery.

Objectives: To investigate the long-term safety and efficacy of rIX-FP prophylaxis in adult previously treated patients (PTPs) with hemophilia B.

Methods: Male PTPs were treated with a 7- (35-50 IU/kg), 10- or 14-day regimen (50-75 IU/kg). Patients ≥18 years who were well-controlled on a 14-day regimen for ≥6 months could switch to a 21-day regimen (100 IU/kg).

Results: A total of 59 patients (aged 13-63 years) participated in the study. Following a single dose of 100 IU/kg rIX-FP, in patients eligible for the 21-day regimen, the mean terminal half-life was 143.2 hours. Mean steady-state FIX trough activity levels ranged from 22% with the 7-day regimen to 7.6% with the 21-day regimen. Median (Q1, Q3) annualized spontaneous bleeding rates were 0.00 (0.00, 1.67), 0.28 (0.00, 1.10), 0.37 (0.00, 1.68), and 0.00 (0.00, 0.45) for the 7-, 10-, 14-, and 21-day regimens, respectively. Comparable efficacy was demonstrated for both the 14- and 21-day regimens compared to the 7-day regimen. Overall, 96.5% of bleeding episodes were treated successfully with 1 to 2 rIX-FP infusions. No patients developed an inhibitor and treatment was well tolerated.

Conclusions: rIX-FP extended interval prophylaxis provides dosing flexibility and, in selected patients, a 21-day regimen may provide an alternative option to minimize treatment burden and individualize treatment.

KEYWORDS

clinical efficacy, clinical trial, coagulation factor IX, hemophilia B, pharmacokinetics, rIX-FP

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1 | INTRODUCTION

Hemophilia B patients are at an increased risk of bleeding because of a deficiency of factor IX (FIX). Prophylactic treatment with FIX replacement to prevent bleeding is the standard of care.[1] Prophylaxis in hemophilia is associated with improved patient outcomes, including reduced joint damage, the major long-term complication of untreated hemophilia.[2] Although prophylaxis is the gold standard for treating patients with severe hemophilia (≤1% factor activity),[1] it is not as widely used in hemophilia B patients as in hemophilia A patients.[3] This may be because hemophilia B is rarer than hemophilia A and therefore much of the evidence for prophylaxis comes from hemophilia A studies.[3]

Patients with mild/moderate FIX deficiency develop chronic arthropathy less frequently than those with a severe FIX deficiency[4]; therefore, the aim of prophylaxis in hemophilia is to maintain FIX trough levels well above 1% to reduce the frequency of breakthrough bleeding events and prevent joint damage.[5,6] A report by the World Federation of Hemophilia (WFH) suggests maintaining higher trough levels (e.g., 3%-5%), to convert patients from a severe phenotype to a mild-moderate phenotype, as the way forward for treating severe hemophilia patients.[5]

The half-life of FIX (18-36 hours) means patients require regular intravenous infusions (1-3 times per week) with standard-acting recombinant FIX (rFIX) or plasma-derived FIX replacement therapy[1,7,8] to maintain trough levels >1%. The frequency of infusions are a burden to patients and their caregivers and are known to be one of the main reasons for patients not adhering to their prophylaxis regimen.[9] The introduction of extended half-life (EHL) products in the past 2 years has made it possible for hemophilia B patients to extend dosing intervals while also maintaining higher FIX activity to minimize or even abolish the occurrence of spontaneous bleeding.[3] It is anticipated that extending dosing intervals with EHL products can provide a change in treatment behavior and help patients to achieve an optimal prophylaxis regimen; additional treatment options may improve adherence as well as improving quality of life by reducing the burden of treatment.[10] Previous studies have shown that the frequency of infusions can be reduced from 1 to 2 times per week to weekly or every 14 days in adults using EHL products that also provide excellent protection against bleeding.[8,11-14]

Recombinant fusion protein genetically linking human coagulation FIX with human albumin (rIX-FP; IDELVION®, CSL Behring) has an approximately five-fold longer half-life compared with conventional FIX replacement products.[11] In a global phase III study, the efficacy and safety of rIX-FP in prophylaxis was demonstrated in previously treated adult and adolescent patients (PTPs) with dosing intervals of 7, 10, and 14 days.[11] In this pivotal study, rIX-FP prophylaxis achieved mean steady-state trough FIX levels of 22% and 12% for 7- and 14-day regimens, respectively[15] and was highly effective in preventing bleeds; a median annualized spontaneous bleeding rate (AsBR) of 0.00 was observed with all dosing regimens.[11] In addition, the median annualized bleeding rate (ABR) was reduced by 91% when patients switched from on-demand to 7-day prophylaxis.[11]

Essentials

- Long-term safety and efficacy of rIX-FP was assessed in previously treated hemophilia B patients.
- Patients received rIX-FP prophylaxis with dosing intervals of 7, 10, 14 or 21 days.
- rIX-FP prophylaxis maintained very low bleeding rates with all regimens and was well tolerated.
- rIX-FP can be used to manage hemophilia B with flexible dosing intervals of up to 21 days.

Patients who participated in this pivotal phase III study could continue treatment in an extension study (NCT01496274), which aimed to evaluate the long-term safety and efficacy of rIX-FP. Here, we report the findings of this extension study in adult and adolescent PTPs (12-65 years) with prophylaxis dosing intervals of 7, 10, or 14 days, and also for the first time a dosing interval of 21 days. This extension study gave hemophilia B patients the flexibility to extend their dosing interval during the study if they were well-controlled on their preexisting regimen.

2 | METHODS

2.1 | Study conduct

The study was approved by the institutional review board/ethics committee at each participating center, registered at www.clinicaltrials.gov (NCT02053792), and performed in accordance with good clinical practice and local regulatory requirements. Written informed consent was obtained from all patients or their legal guardians and consent could be withdrawn at any time.

2.2 | Study design

This multicenter, open-label phase III extension study investigated the long-term safety and efficacy of rIX-FP for routine prophylaxis and on-demand treatment of bleeds. Hemophilia B PTPs (FIX ≤ 2% [n = 59]) who participated in a phase III pivotal study (NCT01496274)[11] or who underwent surgery with rIX-FP and continued with rIX-FP prophylaxis were enrolled in the study.

Treatment intervals and rIX-FP prophylaxis dose were determined at the investigators' discretion based on the dosing interval used in the pivotal study and/or investigators' and patients' preference. All patients could continue to use the same treatment interval that they received in the pivotal study or they could extend their dosing interval; intervals of 7 (35-50 IU/kg), 10 or 14 days (50-75 IU/kg) were used in the initial 6-month treatment period. From then on, dosing intervals could be changed at any 6-month follow-up visit during the study, at the investigators' discretion, based on assessment of the patient's

efficacy, safety, treatment compliance, and/or preference. During each 6 months of the treatment period, the regimen was not changed unless deemed necessary by the investigator for the patient's safety. In addition, patients ≥18 years old could extend their dosing interval to 21 days at a dose of 100 IU/kg if they were well-controlled (based on the investigators' discretion) on a 14-day regimen for at least 6 months of prophylaxis and had undergone a pharmacokinetic (PK) evaluation with a single dose of 100 IU/kg rIX-FP. The study was designed to allow all patients to achieve approximately 100 exposure days as required by the European Medicines Agency guidelines.[16]

2.3 | Trial objectives and outcome measures

The primary endpoint of the extension study was the total number of subjects who develop inhibitors against FIX during the study (approximately 4 years). All patients who received at least one dose of rIX-FP were assessed for the occurrence of inhibitors.

The secondary endpoint of the study was to evaluate the efficacy of rIX-FP to prevent bleeding episodes, assessed by a comparison of the ABR and AsBR in patients who were on a given regimen for at least 12 weeks, by treatment interval (once every 7, 10, 14, and 21 days). Steady-state trough FIX levels and total monthly consumption of rIX-FP in patients treated on the 21-day prophylaxis regimen were compared with patients on the 7-, 10-, and 14-day prophylaxis regimens. Safety was assessed by the frequency, severity, and relatedness of adverse events (AEs) to rIX-FP, as well as the incidence of antibodies against rIX-FP and Chinese hamster ovary (CHO) cell-derived proteins, and tolerability at injection sites.

Additional objectives of the study were to evaluate the PK parameters with a single dose of 100 IU/kg (21-day dose) and assess the hemostatic efficacy of rIX-FP for the prevention and treatment of bleeding episodes, as well as the overall safety of rIX-FP using repeated doses. The number of rIX-FP injections to achieve hemostasis in case of bleeding episodes were used to assess hemostatic efficacy.

2.4 | Analytical methods

2.4.1 | Safety assessments

The primary safety endpoint of the study was to determine the incidence of FIX inhibitors; inhibitors were titrated by the Bethesda method according to the Nijmegen modification and a titer of ≥0.6 Bethesda units was considered positive.[17] Antibodies to rIX-FP and CHO cell proteins were detected using direct binding enzyme-linked immunosorbent assays as previously described.[11]

2.4.2 | PK assessment

FIX activity was measured at a central laboratory using a validated one-stage clotting method with Pathromtin SL (Siemens Healthcare Diagnostics) as an activator agent, as previously described.[11] FIX activity levels were assessed for all prophylaxis regimens at intervals of 12, 18, 24, 30, and 36 months. Steady-state trough (FIX activity after repeated dosing) FIX activity was also calculated, and only FIX trough measurements collected before a fourth consecutive dose on the 7-day regimen, a third consecutive dose on the 10- and 14-day, and a second consecutive dose on the 21-day regimen, were included. If unscheduled doses of FIX product were administered (e.g., to treat a bleed), subsequent trough FIX measurements, occurring within 21 days for the 7- and 21-day regimens and 28 days for the 10- and 14-day regimens, were excluded because the washout period for rIX-FP is about 5 half-lives.

Patients switching to a prophylaxis interval of 21 days underwent a PK evaluation with a single injection of 100 IU/kg rIX-FP. Plasma FIX activity was measured before rIX-FP infusion and then at 30 minutes, and 72, 168, 336, and 504 hours after injection. PK parameters included area under the curve, terminal half-life, incremental recovery, and total body clearance normalized to body weight and were evaluated using collection times according to the International Society on Thrombosis and Hemostasis recommendations.[18,19]

2.4.3 | Efficacy assessments

The efficacy endpoints were assessed in all patients who received at least one dose of rIX-FP for prophylaxis. The ABR, AsBR, and annualized joint bleeding rate were calculated for each treatment interval (7, 10, 14, and 21 days). To demonstrate the efficacy of the 21-day prophylaxis regimen in patients ≥18 years, the difference in mean AsBRs between the 21-day regimen and the 7-day regimen were calculated in patients who were treated with both regimens for at least 12 weeks. The same analyses were conducted for the comparison of ABR and AsBR between the 21- vs 14-day (in patients ≥18 years) and 14- vs 7-day regimens (in patients ≥12 years). In this analysis, data for the 7- and 14-day regimens were combined from the extension study and the pivotal study. Treatment of minor and moderate bleeding episodes was considered successful if hemostasis was achieved with one or two injections.

3 | RESULTS

3.1 | Study population

Overall, 59 male PTPs (≥12 years) with hemophilia B from 29 sites in 12 countries were enrolled in the extension study and were treated with rIX-FP between February 2014 and June 2018. Fifty-four patients (91.5%) completed the study and five patients discontinued the study (reasons for discontinuation include: AE [n = 1]; withdrew consent to participate [n = 2], and at the physician's decision [n = 2]). Patient baseline demographics and characteristics are shown in Table 1. Patients were between 13 and 63 years of age; 52 patients were enrolled from the pivotal phase III study and a further seven

TABLE 1 Baseline demographics and patient characteristics

	n = 59
Age (y), mean (range)	36.1 (13-63)
12-17 y, n (%)	5 (8.5)
≥18 y, n (%)	54 (91.5)
BMI (kg/m^2), mean (SD)	
12-17 y	24.6 (6.33)
≥18 y	23.8 (4.11)
Race, n (%)	
White	45 (76.3)
Asian	12 (20.3)
Black	2 (3.4)
Geographic region	
Europe	32
Asia-Pacific	12
Middle East	11
North America	2
Africa	2
Ethnicity, n (%)	
Hispanic	0
Not Hispanic	59 (100)
Initial regimen, n (%)	
7 d	19 (32)
10 d	13 (22)
14 d	27 (46)

Abbreviations: BMI, body mass index; SD, standard deviation.

patients were enrolled following their participation in the surgical substudy with rIX-FP.[20]

During the study, patients were treated for a mean (standard deviation) of 35.9 (11.04) months, with a median (range) of 36.8 (7, 49) months.

3.2 | Prophylaxis dosing intervals

A summary of patient enrollment, and initial and final dosing regimens used in the extension study is shown in Figure 1. During the study, the majority of patients were able to be treated with an extended dosing interval of 10-, 14-, or 21-day prophylaxis. Overall, 37 patients maintained their prophylactic dosing interval during the extension study, 18 lengthened their infusion interval and four switched back to a shorter interval at the investigator's discretion to reduce bleeding rates. Eleven patients (19%) initially switched to the 21-day regimen and two of them switched back to a 14-day regimen because of the occurrence of breakthrough bleeding. The total mean monthly consumption of rIX-FP was 146.9 IU/kg/mo on the 21-day regimen, compared with 206.4 IU/kg/mo on a 7-day regimen and 158.0 IU/kg/mo on a 14-day regimen (Table 2).

3.3 | Safety of rIX-FP

During this extension study, there were 5595 prophylaxis infusions with a mean of 107 exposure days per patient across all regimens. No patient developed anti-FIX inhibitors during the study.

A total of 51 (86.4%) patients reported a total of 330 treatment-emergent AEs (TEAEs). The majority of TEAEs (97%) were mild-to-moderate in severity. The most frequently reported TEAEs were arthralgia (25 events in 19 [32.2%] patients), headache (12 events in 6 [10.2%] patients), nasopharyngitis (10 events in 7 [11.9%] patients), and gastroenteritis (6 events in 6 [10.2%] patients).

A total of 16 treatment-emergent serious AEs (SAEs) were observed in 10 (16.9%) patients; five mild, five moderate, and six severe. One patient on the 10-day regimen experienced a treatment-emergent SAE (intracranial hemorrhage) and subsequently died during the study; this was as a result of a motorcycle accident and therefore was assessed by the investigator as not related to rIX-FP. One SAE was considered to be related to treatment; one patient on the 7-day regimen experienced a SAE (arterial thrombosis) after undergoing knee replacement surgery, followed by persistent postoperative complications (an unsuccessful thrombectomy that resulted in transfemoral amputation). The patient's history of right knee replacement with prosthesis was considered a contributing factor to joint swelling and peripheral ischemia. No anaphylactic reactions were reported in any patient receiving rIX-FP, and no patient developed antibodies against rIX-FP or CHO cell proteins.

The safety profile of the 21-day regimen in patients ≥18 years was similar to the approved 14-day regimen because no related AEs or SAEs were observed with either regimen and the majority of TEAEs reported with both regimens were mild or moderate in severity (98.5% on the 14-day regimen and 96.6% on the 21-day regimen). No safety concerns associated with the 21-day regimen were identified in this study.

3.4 | PK analysis of rIX-FP

rIX-FP prophylaxis maintained high trough levels with all regimens (Table 2). Mean steady-state trough FIX activity was 22.0%, 19.8%, 13.6%, and 7.6% with 7-, 10-, 14-, and 21-day regimens, respectively. Before switching to a 21-day regimen, patients ≥18 years (n = 16), who were well-controlled on the 14-day regimen for at least 6 months and therefore eligible to extend their dosing interval, underwent PK analysis following a single intravenous dose of 100 IU/kg rIX-FP. One patient had 2 PK parameter estimates for all PK parameters and was counted separately for each measurement. The following PK parameters could be calculated based on in 10 PK assessments in 9 patients with sufficient data: mean (standard deviation) baseline-uncorrected half-life was 143.2 (37.36) hours, area under the curve$_{0-\infty}$ was 17 068 (3269.8) hours × IU/dL, clearance was 0.66 (0.101) mL/h/kg. Mean baseline corrected incremental recovery was 1.02 (0.128) (IU/dL)/(IU/kg) based on 17 PK assessments in 16 patients.

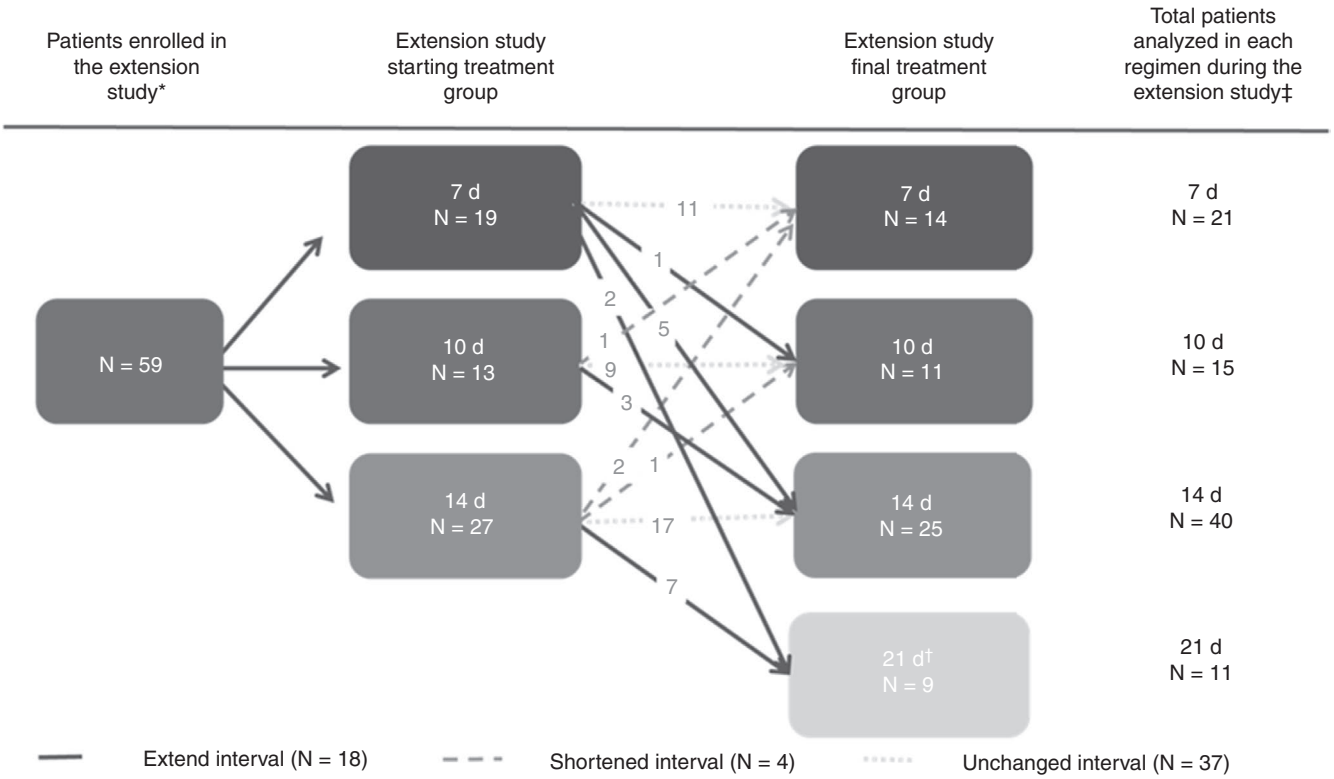

FIGURE 1 Study flow diagram demonstrating change in regimens. *Seven new patients were directly enrolled in the extension study following their participation in the surgical sub-study. †Only patients ≥18 years who were well-controlled on a 14-day regimen for at least 6 months could switch to a 21-day regimen. ‡The number of patients in each dosing regimen is the total number of patients that received that regimen for at least 12 weeks during the study. Patients could be assigned to multiple regimens during the study and could change dosing intervals at any 6-mo follow-up during the study, or at the investigators' discretion

TABLE 2 Summary of monthly consumption, steady-state FIX trough activity across rIX-FP dosing regimens

Regimen	7 d	10 d	14 d	21 d*
Dose, IU/kg/infusion				
Median (min, max)	49.7 (19, 90)	74.3 (38, 86)	74.9 (7, 106)	99.8 (85, 111)
Total consumption, IU/kg/mo				
Mean (SD)	206.4 (43.39)	212.3 (26.26)	158.0 (17.92)	146.9 (5.53)
Steady-state trough FIX, %				
N subjects (N measurements)	5 (17)	6 (7)	24 (50)	6 (16)
Mean (SD)	22.0 (8.4)	19.8 (16.0)	13.6 (6.4)	7.6 (2.3)
Median (min, max)	21.4 (12.7, 47.7)	12.8 (11.0, 55.6)	13.1 (3.2, 40.1)	7.7 (3.9, 11.0)

Abbreviation: SD, standard deviation.

*Only patients ≥ 18 y who were well controlled on a 14-d regimen could switch to a 21-d regimen.

3.5 | Efficacy of rIX-FP

The prophylactic efficacy of rIX-FP was maintained during long-term treatment, with low ABR, AsBR, and annualized joint bleeding rates observed with all dosing regimens (Table 3). The median AsBR was 0.00 for both of the 7- and 21-day regimens and 0.28 and 0.37 for the 10- and 14-day regimens, respectively. Consistent with data previously reported in the phase III trial, the bleeding rates in patients on a 14-day regimen were compared with patients on the 7-day regimen; the mean (95% confidence interval [CI]) difference in AsBR between the 14-day and the 7-day regimen was −0.84 (95% CI, −1.411 to −0.270) bleeding episodes/year/subject (Table 4). Furthermore, this study also demonstrated that bleeding rates in the 21-day regimen were comparable to the 7-day regimen in patients ≥18 years; the mean difference in AsBR was −0.45 (95% CI, −1.464 to 0.555) bleeding episodes/year/subject (Table 4).

During the study, 8/59 (13.6%) patients each developed a single target joint, defined as at least three spontaneous bleeds into a single

TABLE 3 Efficacy of rIX-FP across all prophylaxis regimens

Regimen*	7 d	10 d	14 d	21 d†
N subjects	22	17	41	11
Patients with zero spontaneous bleeds, n (%)	10 (46)	9 (53)	18 (44)	7 (64)
Bleeding rates‡	n = 21	n = 15	n = 40	n = 11
AsBR				
Median (Q1, Q3)	0.00 (0.00, 1.67)	0.28 (0.00, 1.10)	0.37 (0.00, 1.68)	0.00 (0.00, 0.45)
Mean (SD)	1.30 (1.96)	0.67 (0.98)	1.24 (2.26)	0.60 (1.41)
ABR				
Median (Q1, Q3)	1.33 (0.36, 4.17)	0.80 (0.26, 4.93)	0.92 (0.00, 2.94)	0.32 (0.00, 2.48)
Mean (SD)	2.50 (2.60)	2.06 (2.22)	2.33 (3.36)	1.19 (1.57)
AjBR				
Median (Q1, Q3)	0.80 (0.00, 2.34)	0.65 (0.00, 2.90)	0.13 (0.00, 2.34)	0.00 (0.00, 1.78)
Mean (SD)	1.79 (2.43)	1.48 (1.85)	1.63 (3.17)	0.93 (1.56)

Abbreviations: ABR, annualized bleed rate; AjBR, annualized joint bleed rate; AsBR, annualized spontaneous bleed rate; Q1, first quartile; Q3, third quartile; SD, standard deviation.

*Subjects could be assigned to multiple regimens during the study.

†Only patients ≥ 18 y who were well controlled on a 14-d regimen for at least 6 mo could switch to a 21-d regimen.

‡The number of patients in each dosing regimen is the total number of patients that received that regimen for at least 12 wk during the study.

joint within a consecutive 6-month period.[21] In six of seven patients with available data, the target joint developed in a joint with a history of hemophilic arthropathy. Three patients were on a 7-day regimen and five patients were on a 14-day regimen when the target joint developed; two patients were switched to a shorter dosing interval (one to 10 days and one to 7 days) to reduce bleeding episodes. At the investigators' discretion, no other dose adjustments were made in the additional three patients treated on the 14-day regimen, nor in those treated on a 7-day regimen. Target joints had resolved (less than two bleeds into the single joint within a consecutive 12-month period) in six patients at study completion. The other two patients remained on study for <12 months until study completion, following their target joint developing so the definition of target joint resolution could not be applied.

A total of 379 bleeding episodes were reported in 38 (64.4%) patients, of which there were 328 bleeds (87%) that required treatment with rIX-FP (including 164 spontaneous bleeds, 108 trauma induced bleeding episodes, and 56 unknown episodes). More than one-half of the bleeding episodes (n = 223/386 [57.8%]) were joint bleeds into index joints (ankles, knees, and elbows). Overall, 90.1% and 96.5% of these bleeding episodes were successfully treated with one or two rIX-FP infusions, respectively; the probability of success, defined as the probability of achieving hemostasis with one or two infusions, was 98.0% across all regimens.

4 | DISCUSSION

The long-term safety and efficacy of using rIX-FP prophylaxis in adult and adolescent PTPs has been confirmed in this extension study, in which patients were treated for up to 4 years. Data from this long-term study are consistent with data previously reported in the phase III trial,[11] and confirm that treatment with rIX-FP is safe and effective even at extended dosing intervals. These findings also support the shift of routine prophylaxis regimens to prolonged dosing intervals of up to 3 weeks in some patients who are well-controlled for at least 6 months on their current 14-day regimen, with a FIX trough level ≥5% and reported no bleeding events in the 2 months before switching.

rIX-FP provides favorable bleed prevention with low AsBRs across all regimens and a low FIX consumption demonstrated by an approximately 30% reduction in rIX-FP annual consumption between the 21-day regimen and the 7-day regimen; consistent with the reduced consumption previously demonstrated with prolonged dosing intervals of 14-days.[11] Although most patients who switched to extended dosing regimens had comparable bleeding rates with their prior regimen, some patients who extended their dosing interval may experience higher bleed rates as their trough levels reduce during the extended time between dosing. However, these patients, including two patients who developed a target joint, were able to switch back to a shorter dosing interval to maintain higher trough levels and reduce the frequency of bleeding. In addition, rIX-FP has demonstrated an excellent safety profile with no inhibitors reported and similar frequency and severity of AEs to previous regimens and studies.[11] Patients dosing every 21 days with rIX-FP showed comparable efficacy and safety to 7-day prophylaxis regimen in patients ≥18 years and should be considered as an option for selected patients who are well-controlled on their current 14-day regimen. In this subset of patients, the extension of treatment interval will also allow for the additional advantage of a lower factor consumption.

It has previously been demonstrated that rIX-FP has an improved pharmacokinetic profile and prolonged pharmacodynamic activity,

TABLE 4 Comparison of efficacy in prophylaxis between rIX-FP dosing regimens

	7 d/14 d comparison			7 d/21 d‡ comparison			14 d/21 d‡ comparison		
	7 d*	14 d*	Mean difference (95% CI§)	7 d*	21 d†	Mean difference (95% CI§)	14 d*	21 d†	Mean difference (95% CI§)
No. of patients	41	41		11	11		11	11	
AsBR, mean (SD)	0.49 (1.135)	1.33 (2.349)	−0.84 (−1.411, −0.270)	0.14 (0.477)	0.60 (1.408)	−0.45 (−1.464, 0.555)	0.23 (0.596)	0.60 (1.408)	−0.37 (−1.360, 0.628)
ABR, mean (SD)	1.12 (1.697)	2.19 (3.000)	−1.07 (−1.891, −0.258)	0.52 (0.780)	1.19 (1.572)	−0.66 (−1.662, 0.340)	0.44 (0.786)	1.19 (1.572)	−0.75 (−1.639, 0.146)

Abbreviations: ABR, annualized bleed rate; AsBR, annualized spontaneous bleed rate; CI, confidence interval; SD, standard deviation.

Note: Patients were included in this analysis if they were treated with both regimens for a duration of at least 12 wk.

*Data from the extension study were combined with those from the pivotal study; subjects were on a 7- or 14-d regimen for at least 12 wk.

†Subjects included in the analysis were on the 21-d regimen for at least 12 wk.

‡Only patients ≥18 y who were well-controlled on a 14-d regimen for at least 6 mo could switch to a 21-d regimen.

§The estimated rate was calculated assuming a Poisson distribution.

when compared with standard-acting rFIX.[22] Additionally, an indirect comparison of rIX-FP and rFIX recently demonstrated that rFIX has a significantly higher median ABR on a weekly dosing regimen (2.0), and patients experienced an average of 2.1 fewer spontaneous bleeds per year when treated with rIX-FP compared with rFIX,[23] indicating that rIX-FP offers more efficient bleed protection than rFIX when dosed weekly. Furthermore, a recent retrospective study assessing the real-world use of rIX-FP demonstrated that the majority of patients were able to reduce their infusion frequency from 2×/wk with standard-acting FIX to 1×/wk after switching to prophylaxis with rIX-FP.[24] After switching to rIX-FP, patients also experienced substantial reductions in bleeding rates and FIX consumption compared with treatment with their prior standard-acting product.

This study adds to the scientific evidence for the effective use of EHL-FIX therapies long-term. Another EHL-FIX, rFIXFc (Alprolix®, Biogen Idec), has also demonstrated long-term efficacy, with low ABRs when dosed every 1 to 2 weeks (median ABR for 7-day prophylaxis was 2.3).[12] The median AsBRs for 7-day prophylaxis and individualized prophylaxis (intervals of 8-16 days) with rFIXFc were 0.8 and 0.7, respectively,[12] higher than observed here with rIX-FP (AsBR of 0.00 with weekly prophylaxis and 0.37 with a 14-day regimen). However, in the study with rFIXFc, prophylactic regimens were adjusted to maintain a FIX trough level of 1%-3%, which is much lower than that achieved with rIX-FP.

Weekly administration of 40 IU/kg N9-GP (Refixia®, Novo Nordisk) has achieved a median AsBR of 0.00 in adults when used long term.[14] The low clearance of N9-GP may allow prolonged dosing intervals in adults, but intervals longer than 7 days have not been evaluated using N9-GP and the weekly regimen is the only one licensed to date.[3,14] Mean steady-state FIX trough levels with N9-GP 7-day prophylaxis have previously been reported as 27.3% in adults and adolescents,[25] and FIX activity levels with N9-GP have been shown to be six-fold greater than with rFIXFc in a recent head-to-head PK study.[26]

Following a single dose (50 IU/kg), N9-GP has a prolonged FIX activity in the body compared with rFIXFc, achieving an average half-life of 103.2 versus 84.9 hours, respectively.[26] Here, long-term evaluation of rIX-FP in patients ≥18 years who were eligible to switch to a 21-day regimen if they were well-controlled on a 14-day regimen for at least 6 months, demonstrated an extended half-life of 143.2 hours (100 IU/kg dose), and mean steady-state trough FIX activity levels were maintained at 22% in patients on a 7-day prophylaxis regimen, 14% with 14-day prophylaxis, and 7.6% with 21-day prophylaxis, all of which are well above the target 3%-5% as proposed by WFH.[1] The half-life of rIX-FP in patients undergoing PK assessment before switching to a 21-day regimen reported here is longer (143.2 hours) than previously reported in patients treated with a single dose of 50 IU/kg rIX-FP (101.7 hours).[11] In conjunction, the mean incremental recovery reported here (1.02 (IU/dL)/(IU/kg)) is lower than previously reported in patients treated with a single dose of 50 IU/kg rIX-FP (1.30 (IU/dL)/(IU/kg)).[11] We hypothesize that these differences between the doses may be due to a larger amount of rIX-FP distributing into the extravascular tissues (lower

incremental recovery) and increased collagen binding (increased half-life and lower clearance). The half-life reported here is based on a small (n = 10) sample of selected patients receiving a single 100 IU/kg rIX-FP dose who were eligible to switch to the 21-day regimen if they were well-controlled on the 14-day regimen for at least 6 months.

The possibility of using extended dosing intervals in some patients provides dosing flexibility for patients and physicians. This could improve adherence to prophylaxis as well as improving patient quality of life by reducing the treatment burden. While a trough level of 3%-5% has been recommended to reduce bleeding in patients with hemophilia B, there have been no prospective trials to demonstrate an optimal trough level to prevent bleeding in all patients. It has previously been shown that maintaining FIX activity trough levels >1% of normal significantly reduces the incidence of clinical bleeds.[27] It is, however, unclear whether subclinical bleeding may be occurring, causing progressive joint and tissue damage.[28] Higher trough levels of 15% have been proposed as an ideal target with the goal of eliminating joint bleeds.[29] Before the advent of long-acting FIX, trough levels of 5% to 15% were not practical because of the need for frequent dosing, but it is now possible to achieve these trough levels with fewer doses; in this study, the prolonged half-life of rIX-FP enables high FIX activity levels, consistent with a moderate or mild hemophilia phenotype, to be maintained with extended dosing intervals of up to 21 days. However, unlike other long-acting FIX products, rIX-FP dosing was not designed to maintain a specific trough level. In addition, the dosing regimens for rIX-FP, have been shown to maintain FIX activity >5% in the majority of patients in previous studies, consistent with a mild hemophilia phenotype,[15] offering additional bleed protection; here we show that even when dosing every 21 days in selected patients, it is still possible to maintain a mild hemophilia phenotype.

This study was designed to evaluate the long-term effects of rIX-FP and data can be used to help guide clinical decisions; however, we acknowledge that there were some limitations with the study design. This extension study included patients who were enrolled in the phase III study and also includes seven additional patients who were directly enrolled following their participation in the surgical substudy. In addition, patients who were <12 years of age were included and data will be reported separately. Patients <18 years of age were not eligible to receive the 21-day regimen and so the potential clinical benefits of extended dosing intervals in these patients cannot be evaluated. In addition, eight patients with a history of hemophilic arthropathy developed a target joint during the study. Despite target joints resolving in six patients, where it could be assessed within the time frame of the study, this remains a concern in some patients and shows that a minority of patients may still experience bleeding despite high trough levels. Additional data regarding the FIX activity level at the time of bleeding events in relation to the FIX dose were not recorded, and data on compliance or physical activity during bleeding episodes were not reported.

In conclusion, switching to the EHL product rIX-FP may provide dosing flexibility of up to 21 days with prophylaxis in adult patients; a new approach to the treatment of patients with hemophilia B. Extending dosing intervals up to 21 days might further revolutionize current hemophilia B treatment, enabling true treatment individualization taking into account patient conditions, lifestyle, and preferences. Dosing flexibility gives patients the opportunity to benefit from a combination of the multiple advantages of rIX-FP, such as reduced injection frequency and FIX consumption, minimization of the treatment burden, and attainment and maintenance of excellent prophylactic efficacy.

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CONFLICT OF INTEREST

E.S. received honoraria for speaking and/or for consulting from CSL Behring, Bayer, Baxalta/Shire, Pfizer, NovoNordisk, Roche, Sobi/Biogen Idec, Biotest, Kedrion, Octapharma, and Grifols and received unrestricted research grants from Pfizer; M.E.M. as acted as paid consultant for Bayer Healthcare, CSL Behring, Novo Nordisk, Pfizer, Kedrion, Sobi/Biogen, Baxalta/Shire, and Roche and as paid speaker for Bayer Healthcare, CSL Behring, Novo Nordisk, Sobi/Biogen, Baxalta/Shire, Roche, Biotest, and Octapharmal; A.N. received honoraria for speaking from CSL Behring, Bayer, Baxalta/Shire, Novonordisk, Chugai, and Bioverative and received research grant from Baxalta/Shire; W.S. and Y.L. are employees of CSL Behring; and A.L., B.P.P., and T.L. have nothing to disclose.

AUTHOR CONTRIBUTIONS

E. Santagostino, M. E. Mancuso, A. Lubetsky, T. Lissitchkov, B. Pan-Patesch, A. Nagao, I. Pabinger, A. Harroche, C. Negrier, J. Oldenburg, M. Buhrlen, W. Hassenpflug, M. von Depka Prondzinski, A. Tagliaferri, A. Tosetto, T. Matsushita, R. Shirayama, S. Higasa, M. Taki, K. Fukutake, K. Nogami, F. Abdul Karim, L. Mae Lepatan, J. Mahlangu, M. F. López Fernández, A. Santamaria, MT Román Álvarez, A. Shapiro, and E. Chang were all principal investigators for the trial; W. Seifert and Y. Li were responsible for the design of the trial protocol and authored the manuscript; Y. Li was responsible for statistical analysis; and all authors contributed equally to the interpretation of results and preparation and review of the manuscript.

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APPENDIX 1

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