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ORIGINAL ARTICLE

Rare bleeding disorders

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Prophylactic treatment of bleeding episodes in children <12 years with moderate to severe hereditary factor X deficiency (FXD): Efficacy and safety of a high-purity plasma-derived factor X (pdFX) concentrate

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Background: Hereditary factor X (FX) deficiency (FXD) affects 1:500 000-1:1 000 000 people worldwide. A novel, high-purity plasma-derived FX concentrate (pdFX) is available in the United States and European Union as replacement therapy for FXD, but data are scarce on pdFX use in children <12 years.

Aim: This prospective, open-label phase 3 study assessed the safety, efficacy and pharmacokinetics of pdFX in children <12 years with moderate/severe FXD.

Methods: Subjects aged <12 years with basal plasma FX activity (FX:C) <5 IU/dL received pdFX as prophylactic and on-demand treatment, with doses adjusted to maintain FX:C > 5 IU/dL. After ≥26 weeks and ≥50 exposure days, investigators rated pdFX efficacy for preventing/decreasing bleeds. Secondary endpoints included number and severity of bleeds, trough FX:C and incremental recovery. Safety parameters were adverse events (AEs), inhibitor development and changes in laboratory parameters.

Results: The study enrolled 9 subjects (0-5 years, n = 4; 6-11 years, n = 5) with severe (n = 8) or moderate (n = 1) FXD. At end of study, investigators rated pdFX efficacy excellent for all subjects. Ten bleeds occurred (n = 3 subjects; 6 major, 3 minor, 1 unassessed for severity). Trough FX:C levels remained >5 IU/dL for all subjects after the last dose adjustment study visit. Mean incremental recovery was significantly lower for younger vs older subjects (1.53 vs 1.91 IU/dL per IU/kg; $P = .001$). All AEs were unrelated to treatment; no inhibitor development or clinically significant changes in laboratory parameters were observed.

Conclusions: These results demonstrate the efficacy and safety of pdFX for treating children <12 years with moderate/severe hereditary FXD.

KEYWORDS

clotting factor concentrate, efficacy, factor X deficiency, paediatric, safety

1 | INTRODUCTION

Hereditary factor X (FX) deficiency (FXD) is a rare autosomal recessive bleeding disorder with an estimated prevalence of 1:500 000-1:1 000 000.[1] The bleeding patterns of FXD are broadly similar to those seen in haemophilia A and B: spontaneous joint and muscle bleeds are common, as are mucocutaneous bleeding (eg, nose, oral cavity and gastrointestinal tract), and there is a significant

risk of intracranial haemorrhage. Bleeding can also occur spontaneously, after minor trauma or during surgical interventions.[1-3] Unlike haemophilia A and B, however, FXD occurs equally among both sexes and affected women and girls also experience menorrhagia.[2] In general, FX activity (FX:C) levels of 10-20 IU/dL are regarded as sufficient to maintain haemostasis, but some individuals may experience significant bleeding despite having FX:C levels above 20 IU/dL.[4,5] Subjects with moderate FXD have levels of 1-5 IU/dL, and those with severe deficiency have levels <1 IU/dL.[2] As with other clotting factor disorders, the risk of bleeding increases with the severity of FX:C deficiency.[4]

Until recently, treatment options for factor replacement to treat bleeds in FXD were restricted to fresh-frozen plasma (FFP) and prothrombin-complex concentrates (PCCs), which contain factors II, VII and IX, as well as FX. However, because none of these treatments are specific for FX, they can lead to inconsistent dosing and variable elevations in plasma levels of both FX and other coagulation factors.[6] Treatment with FFP requires high-volume doses, which can cause volume overload and anaphylaxis, while PCC carries a risk of thrombosis due to accumulation of the other factors contained in the concentrate.[1,4,7] Single-factor concentrates are therefore recommended to treat rare bleeding disorders where only 1 factor is deficient, such as FXD.[8]

Plasma-derived factor X (pdFX) is a novel, high-purity, high-potency FX concentrate approved in the United States for on-demand treatment of hereditary FXD in adults and children (aged 12 years and above) and in the European Union for the prophylactic and/or on-demand treatment of hereditary FXD (marketed under the commercial name Coagadex® [Bio Products Laboratory, Elstree, UK]).[9,10] The safety and efficacy of pdFX as short-term prophylactic and on-demand treatment for subjects ≥12 years old with moderate and severe FXD has been established,[11-13] but data in children <12 years are limited to 3 children who received pdFX on a compassionate use basis. This study was therefore conducted to investigate the efficacy, safety and pharmacokinetics of pdFX in the prophylactic and on-demand treatment of moderate or severe hereditary FXD in children <12 years.

2 | MATERIALS AND METHODS

2.1 | Study design and subject population

This open-label, multicentre, non-randomized, phase 3 prospective study (ClinicalTrials.gov, NCT01721681; EudraCT, 2012-003093-98) was conducted between April 2015 and October 2016. The study was performed in accordance with the Declaration of Helsinki statement on ethical biomedical research and with the International Conference on Harmonisation Guidelines for Good Clinical Practice,[14] and the protocol was approved by a national independent ethics committee. The parents or legal guardians of all subjects provided written informed consent prior to enrolment of the subject in the study; when appropriate, the subjects also provided written assent to participate.

Following the initial screening visit, subjects underwent a prophylactic treatment regimen with pdFX (administered intravenously at a maximum rate of 3 mL/min). Subjects attended 5 scheduled visits to the study site: baseline (visit 1), 48 or 72 hours postdose (visit 2), days 9-28 (visit 3), days 29-42 (visit 4) and at end of study (visit 5). At visit 1, subjects received a bolus dose of 50 IU/kg pdFX, and incremental recovery (IR) was calculated according to plasma FX levels measured predose (trough) and at 30 minutes after the dose. Visit 1 was followed 48 or 72 hours later by visit 2, at which point a second dose was given under clinical supervision. At visit 5 (end of study; ≥50 exposure days and ≥26 weeks after visit 1), subjects received a 50 IU/kg bolus dose to again calculate 30-minute IR. During all visits, predose blood samples were collected to measure trough FX:C levels, and vital signs and adverse events (AEs) were checked. Subjects' weights were also checked regularly to determine whether their prophylactic dose (calculated as IU/kg) needed to be adjusted. Unscheduled visits were permitted to treat bleeds or to adjust the pdFX dose if trough FX:C fell below 5 IU/dL.

Between each visit, subjects received routine prophylactic infusions either at home, at a clinic local to the subject's home or at the study site. The recommended regimen was 40-50 IU/kg twice per week, but frequency and dose were adjusted through week 6 to maintain trough FX:C > 5 IU/dL. Thereafter, the dose regimen was to remain unchanged, unless adjustment was required to maintain trough FX:C > 5 IU/dL or to avoid breakthrough bleeding. Doses were limited to a maximum of 60 IU/kg, and subjects were required to space the doses at least 48 hours apart. Peak FX:C was recommended not to exceed 120 IU/dL.

A single dose of pdFX was administered to treat minor bleeds (25 IU/kg; bleeds that did not restrict the subject's day-to-day life, or normal bleeding after injury) or major bleeds (50 IU/kg; bleeds that restricted the subject's day-to-day life, required immediate medical attention, or excessive traumatic bleeding) and was repeated as often as necessary based on FX:C levels and clinical need. Doses were also permitted as preventative therapy prior to exercise or joint rehabilitation (40-50 IU/kg) or surgery. All major bleeds were to be treated under the supervision of a physician.

2.2 | Subjects

Up to 12 subjects were enrolled to obtain a minimum of 8 evaluable subjects. Children aged <12 years were enrolled if they had a diagnosis of moderate or severe hereditary FXD based on basal plasma FX:C < 5 IU/dL on the lowest recorded FX:C assessment. In addition, subjects were required to have either a history of severe bleeding or an *F10* gene mutation known to cause a severe bleeding phenotype. Subjects were excluded from the study if they had a history of FX inhibitor development, thrombocytopenia or clinically significant renal or liver disease. The study protocol required at least 4 subjects in each age group (0-5 and 6-11 years) and at least 4 with severe FXD. As some *F10* mutations have been associated with more severe bleeding phenotypes,[15] designation as severe or moderate FXD included bleeding phenotype and *F10* gene mutation in addition to plasma FX levels.

TABLE 1 Rating scale for investigator's overall assessment of pdFX efficacy in routine prophylaxis

Efficacy rating	Criteria
Excellent	No minor or major bleeds occurred during the study period or Lower frequency of bleeds than expected given subject's medical/treatment history
Good	Frequency of bleeds as expected given subject's medical/treatment history
Poor	Higher frequency of bleeds than expected given subject's medical/treatment history or pdFX did not work at all
Unassessable	Subject did not complete 6 weeks of treatment with pdFX or Subject developed inhibitors to pdFX or Failure to meet the minimum trough level due to non-compliance with the dosing regimen

pdFX, plasma-derived factor X.

2.3 | Study endpoints

The primary endpoint was the efficacy of prophylactic pdFX treatment in reducing or preventing bleeding over 26 weeks (6 months). Assessments were categorized as "excellent," "good," "poor" or "unassessable" and took into account the subject's risk of breakthrough bleeding (low/high risk), protocol compliance and attainment of trough FX:C levels ≥5 IU/dL (Table 1). Subjects at low risk for breakthrough bleeding were defined as those who received routine prophylaxis for ≥1 year prior to study entry, experienced ≤1 minor spontaneous bleeding episode (other than gum bleeds or bruising) requiring clinical assessment in the past year and experienced no major spontaneous bleeds in the past year; subjects at high risk for breakthrough bleeding were defined as those who did not meet criteria for low risk.

Secondary endpoints included the number of bleeds per month, total dose and number of infusions, mean dose per subject and mean monthly dose and number of infusions per subject. The secondary endpoints also included FX:C IR at baseline and end of study and trough FX:C levels at all scheduled and unscheduled study visits.

Safety endpoints were assessed at each visit beginning with the first treatment dose and included AEs and assessments of haematology, serum biochemistry, viral serology, FX inhibitor screen and Nijmegen-Bethesda assay, vital signs, physical examination, infusion site observations and number of exposure days. A follow-up visit or telephone interview was conducted 28 days after the final study visit to check for any new serious AEs.

2.4 | Statistical analyses

The primary and secondary endpoints were assessed using the per-protocol population, which was defined as all subjects who accumulated ≥50 exposure days and ≥26 weeks of treatment. Safety results

TABLE 2 Baseline demographic and clinical characteristics (per-protocol population)

Subject number	Age, y	Sex	Weight, kg	Severity of FX deficiency[a]	FX:C at diagnosis, IU/dL[b]	Lowest FX:C recorded, IU/dL[b]	Years since diagnosis
Age group: 0-5 y							
1	3.2	F	15.1	Severe	1	1	3.22
2	2.7	F	12.3	Severe	5	2	2.67
3	3.6	M	14.2	Severe	1	1	3.64
4	2.6	M	12.6	Moderate	2	2	2.54
Age group: 6-11 y							
5	10.2	F	18.7	Severe	4	4	10.23
6	8.5	M	35.2	Severe	1	1	8.55
7	11.3	M	46.3	Severe	1.7	2	11.00
8	11.9	F	41.5	Severe	2	1	11.88
9	11.8	F	46.4	Severe	1	1	11.66

FX, factor X; FX:C, FX activity.
[a]Based on basal FX activity, bleeding phenotype, and *F10* genotype.
[b]Values <1 were recorded as 1 for descriptive statistical analysis.

were summarized for the intent-to-treat/safety population, which included all subjects who received ≥1 dose of pdFX.

3 | RESULTS

3.1 | Subject population

Nine subjects completed 11 treatment cycles, including 2 subjects who had 50 exposure days but were withdrawn erroneously from the study prior to completing 26 weeks of treatment. These 2 subjects were re-screened and completed a second, per-protocol treatment cycle. Only these subjects' results from the per-protocol treatment cycle were included in per-protocol analyses; results from both treatment cycles were merged for analyses using the intent-to-treat/safety population. Tables 2 and 3 summarize subject demographics, baseline characteristics and bleed history by age group. Eight subjects had severe FXD, and 1 subject had moderate FXD. Prior to study entry, 3 subjects had received pdFX for compassionate use. All subjects had been exposed to FX replacement therapy at enrolment and were receiving routine prophylactic treatment during the year prior to study entry; 8 subjects had been treated with other replacement factor concentrates, 5 had been treated with FFP and 2 had been treated with other blood products. At study entry, all subjects were considered by the investigator to be at a low risk for bleeding, and no surgical interventions occurred during the study.

3.2 | Efficacy endpoints

In the per-protocol population, investigators rated the prophylactic efficacy of pdFX (primary endpoint) in all subjects as excellent.

Overall, 537 prophylactic infusions were administered in the per-protocol population (Table 4). A mean ± standard deviation (SD) total dose of 2302.4 ± 542.9 IU/kg was administered to each subject across 59.7 ± 5.1 prophylactic infusions (range, 47-65), resulting in a mean dose per subject per infusion of 38.8 IU/kg given every 3.1 ± 0.5 days (mean ± SD; range, 2-8 days). The mean prophylactic dose per subject per infusion was slightly higher for younger subjects than for older subjects (0-5 years, 40.1 IU/kg [range 32.7-46.2]; 6-11 years, 37.7 IU/kg [range 18.0-47.3]), but mean infusion intervals were similar between age groups (3.0 and 3.2 days, respectively). On a monthly basis, subjects received a mean ± SD of 9.3 ± 1.0 infusions per month and a total dose of 358 ± 79.8 IU/kg (range, 173-426 IU/kg) per month.

During the study, 10 bleeds (6 minor, 3 major and 1 without severity recorded) were reported in 3 (33.3%) subjects in the per-protocol population, with a mean ± SD of 0.53 ± 0.34 bleeds per subject per month. The location, cause and severity of these bleeds are summarized in Table 5. For 6 bleeds, duration was recorded and ranged from 10-90 minutes for 2 instances of spontaneous nosebleeds to 120-144 hours for 4 instances of menorrhagia. Of these 10 bleeds, 4 bleeds (3 major, 1 minor) in 2 subjects (both aged 6-11 years) were treated with pdFX. Each bleed was treated with a single infusion of

TABLE 3 Number of bleeds prior to study entry (per-protocol population)[a]

		Types of past bleeds			Cause of past bleeds				Location of past bleeds				
Subject number	Overall	Overt	Covert	Menorrhagic	Spontaneous	Injury	Menorrhagia	Surgery	Joint	Mucosal	Cut/wound	Muscle	Other[b]
1	2	1	1	-	2	-	-	-	-	-	-	-	2
2	2	2	-	-	1	1	-	-	-	-	1	-	1
3	1	1	-	-	1	-	-	-	-	-	-	-	1
4	7	3	4	-	5	1	-	1	2	-	2	2	1
5	2	1	1	-	2	-	-	-	-	-	-	-	2
6	1	1	-	-	1	-	-	-	-	-	1	-	-
7	1	-	1	-	1	-	-	-	-	-	-	-	1
8	3	-	1	2	1	-	2	-	-	2	-	-	1
9	2	1	1	-	2	-	-	-	-	-	-	-	2

pdFX, plasma-derived factor X.

[a]Includes all bleeds within 12 months prior to study entry and any severe or serious bleeds in the subject's lifetime prior to first pdFX treatment.

[b]Includes circumcision, umbilical stump bleed and cord bleed (1 bleed in 1 subject each); intracranial haemorrhage (1 bleed in each of 2 subjects); cord bleed and blood-streaked stool (2 bleeds in 1 subject); vomiting small amounts of blood and cord bleed (2 bleeds in 1 subject); and umbilical bleed and thigh haematoma and haematoma on back (2 bleeds in 1 subject).

TABLE 4 Prophylactic use of pdFX for each subject (per-protocol population)

Subject number	Planned dosing schedule	Total number of prophylactic infusions	Actual dosing interval, days, mean (range)	Actual dose per infusion, IU/kg, mean (range)	Number of bleeds
Age group: 0-5 y					
1	44.0 IU/kg every 3 days	60	3.0 (3-3)	43.23 (42.1-44.0)	1
2	38.6 IU/kg every 3 days	61	3.0 (3-3)	38.37 (38.0-38.6)	0
3	33.5 IU/kg every 3 days	60	3.1 (3-4)	32.69 (31.3-42.8)	0
4	47.6 IU/kg 2 times a week	58	3.1 (3-7)	46.25 (40.3-48.4)	0
Age group: 6-11 y					
5	50.8 IU/kg every 3 days	63	3.0 (2-4)	47.34 (40.1-50.1)	0
6	40.5 IU/kg 3 times a week	65	2.8 (2-7)	39.60 (38.0-40.5)	5
7	41.0 IU/kg every 3 days	61	3.0 (3-3)	39.45 (34.9-41.0)	0
8	43.4 IU/kg every 4 days	47	4.1 (4-8)	43.93 (43.4-44.6)	4
9	18.1 IU/kg every 3 days	62	3.0 (2-4)	18.00 (16.2-18.1)	0
All subjects		537	3.1 ± 0.5 (2-8)[a]	38.8 ± 9.0 (18.0-47.3)[a]	10

pdFX, plasma-derived factor X.
[a]Data are reported as mean ± standard deviation (range).

pdFX (mean ± SD dose of 35.3 ± 7.2 IU/kg; range, 24.6-40.5 IU/kg). In treating 2 of these major bleeds, both investigators and parents/guardians rated pdFX efficacy as excellent; the third major bleed was neither treated nor assessed at the investigational site, and an error was not assessed either by the subject's parent/guardian. However, the investigator assessed the overall efficacy of pdFX for this patient as excellent.

In the per-protocol population, mean trough FX:C increased from 7.9 IU/dL at screening to 11.1 IU/dL at visit 5 (range of mean trough FX:C, 6.1-12.3 IU/dL; Table 6). All subjects maintained trough FX:C levels >5 IU/dL after visit 4. The mean 30-minute IR for the baseline and end-of-study visits combined was 1.74 IU/dL per IU/kg (Figure 1). IR was significantly lower at each time point among subjects aged 0-5 years compared with subjects aged 6-11 years ($P < .05$) (Figure 1).

3.3 | Safety

Across 665 exposure days in the safety population, a total of 28 AEs were reported in 8 (88.9%) of the study subjects, none of which were considered related to pdFX treatment (Table 7). All reported AEs were of mild (26/28; 92.9%) or moderate (2/28; 7.1%) severity. One subject experienced 2 serious AEs (lower respiratory tract infection and influenza) requiring hospitalization; neither serious AE was considered related to pdFX treatment, and both resolved. No deaths or other serious AEs were reported during the study. No clinically significant changes were noted in vital signs, physical exams or laboratory measurements during the study, and no evidence of the FX inhibitor development was seen. Furthermore, no infusion site reactions were reported, regardless of administration route (central venous access device, n = 6; individual infusions, n = 3).

4 | DISCUSSION

Several studies have been published on the use of pdFX in subjects ≥12 years old with hereditary FXD.[11-13,16] However, data describing the use of FX-specific treatments in children <12 years old are scarce. Prior to the start of the current trial, 3 subjects had received pdFX as routine prophylaxis for 1-4 years on a compassionate use basis, but pharmacokinetic and efficacy data were not collected prospectively. Data published to date on use of other FX-containing products in children are minimal and inconclusive as to whether IR is affected by age.[7,17,18] In 1 study, routine prophylaxis with factor IX concentrate, which also includes some FX, in subjects with severe FXD (6 of whom were <20 years old) effectively controlled bleeding episodes.[19] However, as this was an evaluation of registry data, pharmacokinetic analyses were not included and potential variability in plasma levels of FX or other factors could not be assessed. The current trial was conducted to assess the efficacy and safety of pdFX in children <12 years when used prophylactically for 6 months and ≥50 exposure days.

Following 6 months of prophylactic treatment, investigators assessed the efficacy of pdFX in preventing or reducing bleeds as "excellent" for each of the 9 subjects, meaning that either the subject experienced no major or minor bleeds or that the frequency of bleeds was lower than expected given the subject's medical and treatment history. Of the 10 bleeds reported by 3 subjects, 3 were minor traumatic bleeds, 4 were menorrhagic bleeds and 3 were spontaneous nosebleeds, which are common in children even without bleeding disorders. One minor and 3 major bleeds in 2 subjects required treatment with pdFX, and in each case, the bleed was successfully treated with a single infusion. Of the 3 bleeds that were assessed for efficacy, pdFX treatment efficacy was rated as excellent. These results are consistent with a previous study conducted in subjects

TABLE 5 Characteristics of bleeding episodes (per-protocol population)

Subject number[a]	Severity	Location	Cause	Study day	Duration	Dose to treat bleed (IU/kg)	Subject's assessment	Investigator's assessment
1	Minor	Cut/wound	Injury	18	Unknown	ND	NA	NA
6[b]	Minor	Mucosal (nose bleed)	Injury	12	Unknown	ND	NA	NA
	Minor	Mucosal (nose bleed)	Injury	19	Unknown	ND	NA	NA
	Minor	Mucosal (nose bleed)	Spontaneous	68	NR	40.5	Excellent	NA
	Major	Mucosal (nose bleed)	Spontaneous	145	90 min	38.0	Excellent	Excellent
	Major	Mucosal (nose bleed)	Spontaneous	175	10 min	38.0	Excellent	Excellent
8[c]	Major	Mucosal	Menorrhagia	17	144 h	24.6[d]	NA	UA[e]
	NR	Mucosal	Menorrhagia	72	144 h	ND[d]	UA[e]	UA[e]
	Minor	Mucosal	Menorrhagia	117	120 h	ND[d]	UA[e]	UA[e]
	Minor	Mucosal	Menorrhagia	143	144 h	ND[d]	UA[e]	UA[e]

NA, not assessed; ND, not dosed; NR, not recorded; pdFX, plasma-derived factor X; UA, unassessable.

[a]No bleeding episodes occurred in subjects 2, 3, 4, 5, 7, or 9.

[b]All bleeding episodes reported for subject 6 were nosebleeds. The 2 self-assessed major bleeds occurred following exercise.

[c]Subject 8 commenced menstrual bleeding shortly before the study and so the bleed frequency inevitably changed from the prestudy period.

[d]Tranexamic acid was also administered.

[e]Site erroneously selected "Unassessable [pdFX given/not given another replacement factor given]" option on patient report form. Bleeds were treated at home and not assessed by the investigator site or subject; no other replacement factor was given.

TABLE 6 Trough FX:C levels (IU/dL) at all study visits, by age group

	0-5 y		6-11 y		All subjects	
Study visit	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Screening	7.8 (1.71)	6.0-10.0	8.0 (2.12)	6.0-11.0	7.9 (1.83)	6.0-11.0
1 (baseline)	6.5 (1.73)	5.0-8.0	5.8 (2.78)	2.0-9.0	6.1 (2.26)	2.0-9.0
2 (48/72 h)	11.0 (2.71)	7.0-13.0	13.4 (3.21)	10.0-17.0	12.3 (3.08)	7.0-17.0
3 (day 9-28)	9.5 (4.93)	4.0-15.0	8.8 (3.42)	5.0-14.0	9.1 (3.89)	4.0-15.0
4 (day 29-42)	10.5 (3.32)	8.0-15.0	10.6 (4.34)	7.0-17.0	10.6 (3.68)	7.0-17.0
End of study (≥26 weeks and 50 exposure days)	11.3 (1.71)	9.0-13.0	11.0 (1.87)	9.0-14.0	11.1 (1.69)	9.0-14.0

FX:C, factor X activity; SD, standard deviation.

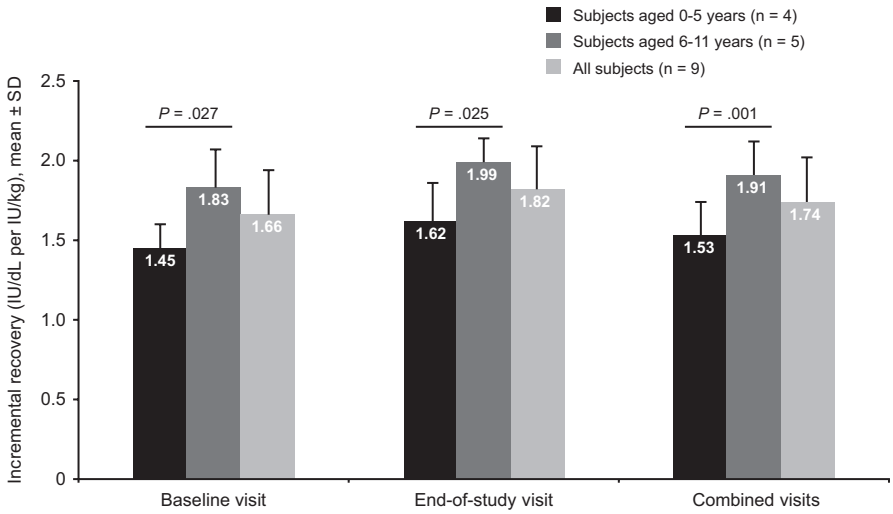

FIGURE 1 Incremental recovery (IU/dL per IU/kg) following bolus dosing at baseline and end-of-study visits (per-protocol population). SD, standard deviation.

aged ≥12 years in which pdFX successfully treated bleeds in 97% of subjects, and 83% of bleeds were treated with a single infusion.[12]

In pharmacokinetic analyses, trough FX:C levels were maintained at >5 IU/dL for all subjects after the dose adjustment period. Following a bolus dose of 50 IU/kg, the 30-minute IR remained consistent between the baseline and end-of-study visits (combined mean, 1.74 IU/dL per IU/kg for all subjects) but was significantly lower among younger subjects (1.53 IU/dL per IU/kg) compared with older subjects (1.91 IU/dL per IU/kg; $P = .001$). These differences in IR values are small but statistically significant and suggest that the pharmacokinetics of pdFX may differ for children <5 years old compared with older children.

Across 665 exposure days, no AEs occurred during this trial that were judged by investigators to be related to pdFX treatment. All reported AEs were mild or moderate in severity, and the 2 serious AEs that occurred in 1 subject (mild influenza and moderate lower respiratory tract infection) resolved.

Although the development of neutralizing antibodies (ie, inhibitors) is a relatively common complication of clotting factor therapies, particularly for haemophilia A and (to a lesser extent) haemophilia B,[20,21] inhibitors to FX have not been reported in hereditary FXD.[22,23] During extended prophylactic use of pdFX in subjects who had previously received treatment with other clotting factors—including 3 subjects who had received pdFX for compassionate use prior to study entry—no evidence was seen in this study population for the development of FX inhibitors. These data are consistent with previous pdFX studies in patients ≥12 years old with moderate to severe

TABLE 7 All reported AEs (safety population)

AE, n (%)	Subjects (N = 9)	Events (n = 28)
Any AE[a]	8 (88.9)	28 (100)
Nasopharyngitis	3 (33.3)	4 (14.3)
Pyrexia	3 (33.3)	4 (14.3)
Cough	3 (33.3)	3 (10.7)
Pain in extremity	2 (22.2)	3 (10.7)
Viral infection	2 (22.2)	2 (7.1)
Decreased appetite	1 (11.1)	2 (7.1)
Other[b]	5 (55.6)	10 (35.7)

AE, adverse event; pdFX, plasma-derived factor X.
[a]Includes any AE that appeared or worsened during the course of the study in any subject who received ≥1 dose of pdFX.
[b]Includes AEs of dysmenorrhoea, headache, temperature elevation, and vitiligo (each occurred once, each in a single subject) and anaemia, bacterial disease carrier, influenza, lethargy, lower respiratory tract infection, and rhinitis (each occurred once in the same subject).

FXD, who also showed no sign of inhibitor development.[12,13] In addition, no cases of FX inhibitor development have been reported in postmarketing safety surveillance.

Two limiting factors should be taken into account when interpreting the results of this study. First, not only is FXD a rare condition, but also this study focused on a relatively narrow age range. As a result, these results are limited by a small sample size (N = 9) and may or may not translate to patients' treatment responses in clinical practice. Caution should therefore be used when initiating a prophylactic treatment regimen with pdFX in children <12 years old—and particularly among children 0-5 years old—and patients should be monitored carefully for bleeds and to ensure that trough FX:C levels remain within the target range. In addition, studies have shown that inhibitors to clotting factors usually develop within the first 100 infusions,[24] but subjects in our study received a mean of 62 infusions. Although most subjects had previously received treatment with pdFX or other clotting factors, the total accumulated number of infusions for each subject is unknown. The development of inhibitors is primarily associated with treatment of haemophilia A and B and, although rare, with treatment of deficiencies in coagulation factors V, VII, XI and XIII.[20,21,23] No known reports exist on the development of alloantibodies following replacement therapy for hereditary FXD, and a previous study of prophylactic treatment for up to 2 years reported no development of inhibitors.[12] However, it remains possible that long-term exposure to pdFX may lead to inhibitor development in some patients, and all individuals with FXD who receive pdFX on a prophylactic basis should be monitored for inhibitors.

5 | CONCLUSIONS

In this study in children aged <12 years with moderate to severe hereditary FXD, pdFX given as routine prophylaxis for 6 months was rated excellent at reducing or preventing bleeding episodes. pdFX efficacy was also rated as excellent for on-demand treatment of both major and minor bleeds. Pharmacokinetic analysis demonstrated that at the range of doses and dosing intervals used in this study, trough levels were maintained above 5 IU/dL. However, 30-minute IR values were lower for children aged 0-5 years than for those aged 6-11 years, suggesting that the pharmacokinetics of pdFX may differ for the younger age group. Prophylactic dosing in children <12 years old should therefore be implemented cautiously and closely monitored to achieve the desired trough FX:C level. In summary, consistent with previous findings in subjects aged ≥12 years, these results demonstrate that pdFX was well tolerated, safe and effective among subjects <12 years old.

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DISCLOSURES

RL has received speakers' fees from Bio Products Laboratory and travel support and speakers' fees from Octapharma. JP has nothing to disclose. CA and MN are employees of Bio Products Laboratory.

AUTHOR CONTRIBUTIONS

MN and CA were responsible for the study concept and design. RL, CA, MN and JP helped in the acquisition, analysis and interpretation of data. MN and CA drafted the manuscript. RL, CA, MN and JP carried out the critical revision of the manuscript for important intellectual content. RL, CA, MN and JP were involved in the approval of the manuscript for submission/publication.

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