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ORIGINAL ARTICLE *Rare bleeding disorders*

Efficacy, safety and pharmacokinetics of a new high-purity factor X concentrate in subjects with hereditary factor X deficiency

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Introduction: Hereditary factor X (FX) deficiency is a rare bleeding disorder affecting 1:500 000 to 1:1 000 000 of individuals. Until recently, no specific replacement factor concentrate was available. **Aim:** The aim of this study was to assess safety and efficacy of a new, high-purity plasma-derived FX concentrate (pdFX) in subjects with hereditary FX deficiency. **Methods:** Subjects aged ≥12 years with moderate or severe FX deficiency (plasma FX activity <5 IU dL^{-1}) received 25 IU kg^{-1} pdFX as on-demand treatment or short-term prophylaxis for 6 months to 2 years. Subjects assessed pdFX efficacy for each bleed; at end-of-study, investigators assessed overall pdFX efficacy. Blood samples for pharmacokinetic analysis were obtained at baseline and ≥6 months. Safety was assessed by adverse events (AEs), inhibitor development and changes in laboratory parameters. **Results:** Sixteen enrolled subjects (six aged 12–17 years; 10 aged 18–58 years) received a total of 468 pdFX infusions. In the 187 analysed bleeds, pdFX efficacy was categorized as excellent, good, poor or unassessable in 90.9%, 7.5%, 1.1% and 0.5% of bleeds respectively; 83% of bleeds were treated with one infusion. For pdFX, mean (median; interquartile range) incremental recovery and half-life were 2.00 (2.12; 1.79–2.37) IU dL^{-1} per IU kg^{-1} and 29.4 (28.6; 25.8–33.1) h respectively. No serious AEs possibly related to pdFX or evidence of FX inhibitors were observed, and no hypersensitivity reactions or clinically significant trends were detected in laboratory parameters. **Conclusion:** These results demonstrate that a dose of 25 IU kg^{-1} pdFX is safe and efficacious for on-demand treatment and short-term prophylaxis in subjects with moderate or severe hereditary FX deficiency.

Keywords: clinical trial, clotting factor concentrate, efficacy, factor X deficiency, orphan drug, safety

Introduction

Hereditary factor X (FX) deficiency is a rare, autosomal recessive bleeding disorder of variable severity, with prevalence estimated at 1:500 000 to 1:1 000 000 of the general population [1–3]. Although bleeding tendency in patients with FX deficiency is variable, the disorder can result in the most severe symptoms among the rare bleeding disorders [3]. As in haemophilia A and B, patients with severe FX deficiency may present with bleeding into joints, muscles or mucous membranes [1,4]. However, unlike the X-linked disorders of haemophilia A and B, hereditary FX deficiency occurs equally in both sexes, with affected women often suffering from menorrhagia or postpartum haemorrhage [4].

Spontaneous and traumatic bleeds caused by FX deficiency are currently treated with fresh-frozen plasma (FFP), prothrombin-complex concentrates (PCCs) or a product containing both FIX and FX [5,6]. However, in situations requiring repeated and frequent dosing to maintain normal plasma FX levels

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(e.g. following a severe bleed or major surgery), the non-specificity of these treatments has raised concerns regarding volume overload, anaphylaxis and thrombosis [1,7,8]. Moreover, most products do not specify FX content, which can confound consistent dosing and result in variable elevations in plasma FX levels [2]. For these reasons, experts recommend use of single-factor concentrates, when available, for treatment of rare bleeding disorders [9].

A novel, high-purity, high-potency, plasma-derived FX concentrate (pdFX; Bio Products Laboratory, Elstree, UK) has been developed for replacement therapy in patients with hereditary FX deficiency. During manufacture, pdFX undergoes three separate and complementary virus elimination steps (solvent-detergent treatment, virus filtration and terminal heat treatment) and is available in lyophilized form with water for injection. On reconstitution, pdFX is formulated to contain plasma FX activity (FX:C) of 100 IU mL^{-1}, specific activity >100 IU mg^{-1} protein, <1 IU mL^{-1} each of FII and FIX and no added proteins; activated FXa and FIIa comprise <10 ppm by weight in the final product (data on file; Bio Products Laboratory).

Efficacy and safety of pdFX as replacement therapy have been demonstrated in subjects with mild-to-severe hereditary FX deficiency (plasma FX:C < 20 IU dL^{-1}) undergoing surgery [10]. Here, efficacy and safety of pdFX were investigated for the treatment of bleeding episodes in subjects aged ≥12 years with moderate or severe hereditary FX deficiency (basal plasma FX:C <5 IU dL^{-1}).

Materials and methods

Study design

This prospective, open-label, multicentre, non-randomized phase 3 study (ClinicalTrials.gov identifier, NCT00930176; EudraCT identifier, 2009-0111145-18) was conducted between February 2010 and October 2013 and performed in accordance with Good Clinical Practice Guidelines [11]. The protocol was approved by each centre's local or national independent ethics committee. All subjects provided written informed consent prior to enrolment.

Following screening, subjects underwent an on-demand treatment regimen for ≥6 months and until ≥1 bleed had been treated with pdFX, with study visits at baseline; months 1, 3 and 6; and at end-of-study. The study was extended for all subjects by study visits at 3-month increments (to a 24-month maximum participation for each subject) until 12 subjects with ≥12 assessable bleeds had received pdFX treatment. Full safety assessments were performed at end-of-study and, for subjects whose participation was extended beyond 6 months, at 9 months.

Considering that a dose of approximately 20–30 IU kg^{-1} is reported for PCC treatment of bleeds [3], a pdFX dose of 25 IU kg^{-1} (to the nearest 1 mL) was selected for treatment of bleeds, infused at a rate of ≤20 mL min^{-1}, and repeated as necessary until haemostasis was achieved. Based on the reported incremental recovery (IR) for PCCs [7], a 25 IU kg^{-1} dose of pdFX was expected to raise plasma FX:C to approximately 40 IU dL^{-1}, well above the established threshold of 10–20 IU dL^{-1} required for haemostasis [7] but without a concomitant rise in other coagulation factor levels. Except for the first infusion (administered at the hospital or local clinic during the baseline visit), bleeds were treated at home (by the study subject) or at the study site (by the investigator). To allow for the diversity of bleeding symptoms, the dose per infusion could be raised for any subject if 25 IU kg^{-1} proved insufficient to treat a bleed. Subjects could receive tranexamic acid to treat a bleed, but FX-containing products other than pdFX were prohibited.

Use of pdFX was also permitted as short-term preventative therapy (e.g. in anticipation of sporting activity or during joint rehabilitation following a bleed) and as perisurgical prophylaxis. Surgery results are reported elsewhere [10].

Pharmacokinetic (PK) assessments were performed in all patients at baseline and at 6 months or after ≥1 bleed had been treated with pdFX. At each PK assessment, blood samples were taken predose and at 0.25, 0.5, 1, 3, 6, 24, 48, 72, 96, 120 and 144 h post dose. Prior to each PK assessment, subjects had a minimum 7-day washout of any FX-containing product. To calculate IR (using the peak FX level within the first hour post dose) and half-life for pdFX, plasma samples taken at each PK assessment were assayed for FX:C. Changes in coagulation activation markers (thrombin-antithrombin complex [TAT], d-dimer and prothrombin fragments 1 and 2 [F1 + 2]) were measured predose and at 0.25, 0.5, 1, 3, 24, 48 and 72 h post dose at the PK visits. Haematology and clinical chemistry parameters and viral serology (hepatitis A, hepatitis B surface antigen, hepatitis C, human immunodeficiency virus and parvovirus B19) were measured at the baseline, 9-month and end-of-study visits.

Subjects

Subjects were eligible for enrolment if they were aged ≥12 years, had moderate or severe hereditary FX deficiency (defined as plasma FX:C <5 IU dL^{-1} [4]), and required replacement therapy (FFP, PCCs or FIX/X concentrate) for ≥1 spontaneous or menorrhagic bleeds in the past 12 months. Excluded subjects had a history of FX inhibitor development, were positive for FX inhibitors at screening or were thrombocytopaenic, had clinically significant renal or liver

disease or had another coagulopathy or known thrombophilia.

Efficacy assessments

Efficacy of pdFX was assessed in terms of bleeding episode treatment. Subjects evaluated the efficacy of the treatment of each bleed, and investigators evaluated treatment efficacy in subjects during visits to the investigational site. Investigators also assessed overall pdFX efficacy in all bleeds and prophylactic doses at each subject's study completion.

Bleeds were categorized as overt (extent and duration of bleeding is clinically obvious; e.g. epistaxis, tongue/gum bleeds, haematemesis, haematuria, rectal bleeding and external traumatic bleeding), covert (extent and duration of bleeding is difficult to assess; e.g. joint bleeds, muscle bleeds, intracranial haemorrhage, haematoma/bruising, melaena and internal traumatic bleeding) and menorrhagic (Table 1). Considering that bleeding is clearly visible in overt bleeds, efficacy assessment was based on the timeframe from first pdFX infusion to cessation of bleeding. However, because bleeding is not always visually observed in covert bleeds and the precise stop time may be unassessable, efficacy assessment was based on the number of pdFX infusions required and dosing timeframe. Because menorrhagia can vary significantly between individuals [12], assessment of efficacy was based on the number of pdFX infusions given during the perimenstrual period (i.e. the first dose administered ≤1 day prior to bleeding commencement) to maintain bleeding at a manageable level (i.e. no significant limitation to normal activities).

For each bleed, pdFX efficacy was assessed as excellent, good, poor or unassessable. A case narrative documenting the subject's medical and bleed history and relevant details about the bleed and its treatment was prepared for each bleeding episode. An independent data review committee (DRC) comprising three haemophilia experts reviewed each narrative to determine whether the bleed would be included in the efficacy assessment or as supportive data only (in cases of insufficient information and/or protocol deviations) and to characterize each bleed as major or minor.

Safety and laboratory assessments

Adverse events (AEs) were recorded in subject diaries. The following parameters were assessed at a central laboratory (Department of Haematology, Addenbrooke's Hospital, Cambridge, UK): plasma FX coagulant activity (FX:C; measured with a one-stage clotting assay); plasma FX antigen (FX:Ag; measured with Zymutest, HYPHEN BioMed, Neuville sur Oise, France); prothrombin time and activated partial thromboplastin time (APTT); coagulation activation markers; and FX inhibitors (assessed at 3-month intervals using time-dependent and time-independent APTT-based inhibitor screens and a Nijmegen-Bethesda assay). Coagulation activation marker values that were clearly spurious (e.g. a high result within an otherwise normal profile) or where the sample was haemolysed were excluded from analysis. Haematology and clinical chemistry parameters and viral serology were analysed by ACM Global, York, UK. In addition, the DRC examined PK parameters for each subject to assess possible development of inhibitors not detectable through the Bethesda assay.

Vital signs were assessed at every visit; additionally, at baseline, 6-month, and batch-change visits, vital signs and infusion-site reactions were assessed predose and post dose immediately prior to blood sample

Table 1. Rating scale for efficacy of pdFX (as assessed by subject).

Efficacy rating	Overt bleeds	Covert bleeds	Menorrhagic bleeds
Excellent	Bleeding stopped within 12 h after dosing with pdFX, with only 1 dose required	1 dose of pdFX was required or 2 doses of pdFX were required less than 48 h apart	1 dose of pdFX was required or 2 doses of pdFX were required less than 48 h apart
Good	Bleeding stopped within 24 h after the first dose of pdFX, with 1 or 2 doses required	3 doses of pdFX were required, with less than 48 h between the first and last dose	2 doses of pdFX were required, with more than 48 h between the first and the last dose
Poor	Bleeding stopped later than 24 h after the first dose of pdFX or more than 2 doses of pdFX were required or pdFX did not work at all	More than 3 doses of pdFX were required within any timeframe or pdFX did not work at all	More than 2 doses of pdFX were required or bleeding could not be kept at a manageable level
Unassessable	The patient did not take any pdFX for this bleed. or prior to taking pdFX for this bleed, the patient had taken a dose of fresh-frozen plasma, prothrombin complex concentrate or factor IX/X concentrate		

pdFX, factor X concentrate.

collection. Physical examinations were performed at baseline, 9-month and end-of-study visits.

Results

Subject population

Of 17 screened subjects, 16 were enrolled and received ≥1 pdFX dose. The median age of subjects was 20 years (range, 12–58), 6 subjects (37.5%) were ≤18 years of age and 10 (62.6%) were female. At baseline, 2 and 14 subjects were classified as having moderate (FX:C ≥1 but <5 IU dL^{-1}) and severe (FX:C <1 IU dL^{-1}) FX deficiency respectively (Table 2).

Prior to enrolment, subjects had experienced bleeding episodes attributed to spontaneous bleeding ($n = 14$), menorrhagia ($n = 7$), injury ($n = 6$) and unknown causes ($n = 4$). Previous treatments included replacement multifactor concentrates ($n = 15$), FFP ($n = 14$) and other blood products ($n = 12$). Among the seven enrolled subjects with a history of menorrhagia, previous menorrhagia treatments included blood transfusion ($n = 5$), hormonal contraceptives ($n = 5$) and iron ($n = 4$). Three subjects who had previously received hormonal contraceptive treatment continued this treatment during the study.

Of 16 enrolled subjects, 15 (93.8%) completed the study. Shortly after the 1-month study visit, one subject died from bilateral pneumonia complicated by a nosocomial infection, which was judged by the investigator as unrelated to pdFX. Thus, PK was analysed in 16 and 15 patients at the baseline and repeat PK assessments respectively. At the end of the study, 16 subjects had completed 6772 days in the study (mean, 13.9 subject-months).

Haemostatic efficacy

During the study, 16 subjects received 468 pdFX infusions. Of these, 242 were given to treat bleeds, 184 were given as a preventative measure (including 57 infusions given as routine prophylaxis to two subjects) and 42 were administered for PK assessments, batch-change assessments and as haemostatic coverage for surgical procedures. Overall, the mean number of infusions was 26.6 per subject (standard deviation [SD], 28.73; median, 17.5; range, 3–111), with a monthly mean of 2.1 (SD, 2.54; median, 1.1; range, 0.1–9.3) infusions/subject.

The 16 subjects experienced 228 bleeds (range, 1–59 per subject; 0–3.5 per subject/month) (Fig. 1). Of these, 20 bleeds did not require replacement therapy, 21 bleeds were not reviewed or were considered unassessable by the DRC (due to insufficient information and/or protocol violations) and the remaining 187 bleeds were judged by the DRC as able to be included for analysis. Of these, 16 (8.6%) were classified as overt, 110 (58.8%) as covert and 61 (32.6%) as menorrhagic, with 98 (52.4%) and 88 (47.1%) classified by the DRC as major and minor respectively (Table 3).

Of the 187 bleeds, 98.4% (95% confidence interval [excluding the one unassessable bleed], 96.2–99.9%) were considered by subjects to be a treatment success (characterized as a response of 'excellent' or 'good') (Table 4). In the 10 subjects who visited the investigational site for clinical assessment of their 42 bleeds,

Table 2. Demographic characteristics.

				Bleeding history*			
Subject number	Country	Age (years)	Sex	Joint	Muscle	Menorrhagia	Other†
Severe FX deficiency (plasma FX:C <1 IU dL^{-1})							
1	UK	35	M	Y	Y	NA	N
2	UK	32	F	Y	Y	Y	Y
3	UK	40	F	Y	N	Y	Y
4	Spain	58	F	Y	Y	N	N
5	Spain	22	M	Y	Y	NA	N
6	Spain	58	F	N	N	N	Y
7	Spain	20	M	N	N	NA	Y
8	USA	40	F	Y	Y	Y	N
9	USA	16	M	N	Y	NA	Y
10	Turkey	20	M	N	Y	NA	Y
11	Turkey	19	F	N	N	Y	Y
12	Turkey	14	F	Y	Y	N	Y
13	Turkey	17	F	N	N	Y	Y
14	Turkey	17	F	N	N	Y	N
Moderate FX deficiency (plasma FX:C ≥1 but <5 IU dL^{-1})							
15	Turkey	12	M	Y	N	NA	Y
16	Germany	14	F	Y	N	Y	Y

FX, factor X; FX:C, factor X activity; NA, not applicable.

*Includes all bleeds within the year prior to study entry and all significant bleeds in the subject's lifetime.

†Includes central nervous system, cut/wound, epistaxis, forehead, gastrointestinal, intracranial, intraperitoneal, mouth, mucosal (not menorrhagia), pelvic, rectal and unknown.

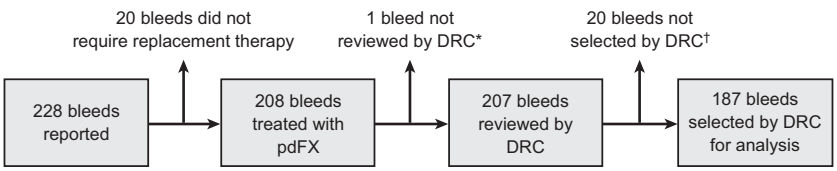

Fig. 1. Bleeding episodes reported, treated with pdFX, and analysed. DRC, data review committee; pdFX, factor X concentrate. *Bleed not reviewed by the DRC before database lock. †Excluded due to insufficient information and/or protocol deviations.

Table 3. Characteristics of bleeding episodes treated with pdFX and analysed (n = 187).

	Number (%) of bleeds
Bleed type	
Covert	110 (58.8)
Menorrhagic	61 (32.6)
Overt	16 (8.6)
Bleed location	
Mucosal	73 (39.0)
Joint	63 (33.7)
Muscle	26 (13.9)
Cut/wound	4 (2.1)
Other*	21 (11.2)
Bleed cause	
Spontaneous	79 (42.2)
Menorrhagia	61 (32.6)
Injury	47 (25.1)
Bleed severity†	
Major	98 (52.4)
Minor	88 (47.1)
Not evaluated	1 (0.5)

pdFX, factor X concentrate.
*Includes concussion, foot, forehead, hand, kidney, left forearm, lumbar area, right shoulder, subcutaneous and thumb.
†As assessed by the data review committee.

Table 4. Treatment success rate in bleeding episodes treated with pdFX and analysed.

	Number (%) of bleeds	
Treatment response per bleed	Subject assessment (n = 187)	Investigator assessment (n = 42)*
Treatment success†	184 (98.4)	41 (97.6)
Excellent	170 (90.9)	37 (88.1)
Good	14 (7.5)	4 (9.5)
Poor	2 (1.1)	1 (2.4)
Unassessable	1 (0.5)	0

pdFX, factor X concentrate.
*Investigators evaluated the efficacy of bleeds in 10 subjects who visited the investigational site for clinical bleed assessment.
†Defined as excellent or good response.

97.6% of bleeds were considered by the investigator to be a treatment success. Investigators rated overall pdFX efficacy in the 15 study completers to be excellent in 12 subjects (80%) and good in three subjects (20%).

A total of 155 bleeds (82.9%) were treated with one pdFX infusion, 28 (15.0%) with two infusions, three (1.6%) with three infusions and one (0.5%) with four infusions; a mean of 1.2 (SD, 0.47) infusions was given to treat a bleed. Each infusion had a mean dose of 25.3 (SD, 2.4) IU kg^{-1}, for a mean total dose of 30.4 (SD, 12.4; median, 25.0; interquartile range [IQR], 24.4–26.7) IU kg^{-1}. The standard pdFX dose of 25 IU kg^{-1} was maintained for 14 of the 16 subjects; the remaining two subjects used doses up to 30 and 33 IU kg^{-1} respectively. Tranexamic acid was used as an adjunct to pdFX treatment in seven (43.4%) subjects.

The mean cumulative dose of pdFX was 52 333 IU (range, 7818–221 229 IU) or 734 IU kg^{-1} (range, 124–2942 IU kg^{-1}) per subject, totalling 837 326 IU (11 741 IU kg^{-1}) administered to 16 subjects.

Because PK parameters observed at the baseline (n = 16) and repeat (n = 15) PK visits were equivalent (Fig. 2), parameters from each visit were combined (n = 31) to obtain summary PK values. The mean IR was 2.00 IU dL^{-1} per IU kg^{-1} (adjusted for dosing), and the mean half-life was 29.4 h. The median (IQR) IR and half-life values were 2.12 (1.79–2.37) IU dL^{-1} per IU kg^{-1} and 28.6 (25.75–33.10) h respectively.

Safety and tolerability

Of the 176 AEs observed in 16 subjects, headache was the most common, with 14 instances (8% of all AEs) occurring in eight subjects. Of these 14 instances, five subjects reported a single event during the study, two subjects reported two events, and one subject reported five events. Of the three subjects who reported >1 headache, each received ≥1 subsequent infusion of pdFX without recurrence of a headache event. All 14 headache events were mild and none was considered related to study drug. Only six AEs (3.4%) in two subjects were considered by the investigator as possibly related to pdFX. One subject reported two cases of fatigue, two cases of infusion-site erythema and one case of back pain; the other subject reported one case of predose infusion-site pain. All events were mild in severity, except for one case of moderate fatigue, and all subjects recovered without sequelae.

All inhibitor results were negative, no viral seroconversions were detected and no suspected hypersensitivity reactions to pdFX were observed. DRC review of the PK data found no indication of altered PK indicative of inhibitor development in any subject. In addition, no significant trends of abnormality were encountered during physical examination, nor were

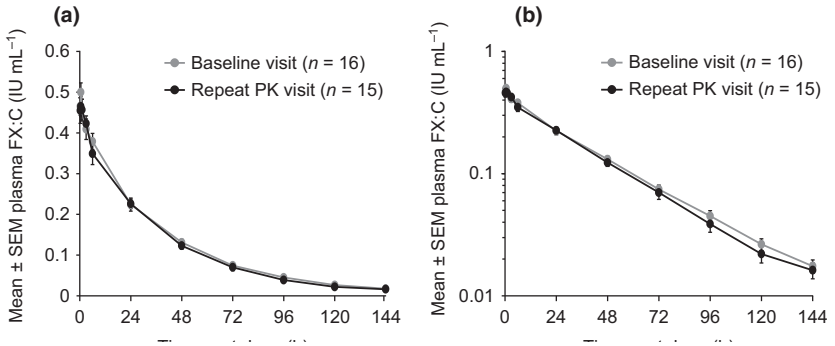

Fig. 2. Mean predose-adjusted plasma FX:C-clotting at baseline (PK1) and repeat (PK2) PK assessments on (a) linear and (b) semi-logarithmic scales. FX:C, factor X activity; PK, pharmacokinetic; SEM, standard error of the mean. Figure originally reported in Austin SK, Brindley C, Kavakli K, Norton M, Shapiro A. Pharmacokinetics of a high-purity, plasma-derived factor X concentrate in subjects with moderate or severe hereditary factor X deficiency. Haemophilia 2016. doi: 10.1111/hae.12894. Abbreviations used in the source figure legends have been expanded for clarity here.

clinically significant trends discovered in haematology parameters, clinical chemistry parameters or vital signs. Other than the two cases of mild erythema, no infusion-site reactions were reported following the 468 infusions.

Three subjects displayed significant elevations in markers indicative of coagulation activation from the predose value at ≥3 consecutive timepoints. However, the DRC did not consider any subject's results to be indicative of a possible thrombogenic effect of pdFX, and no clinical symptoms suggestive of thrombosis were seen in any subject.

Discussion

This was the first prospective, open-label, multicentre, non-randomized phase 3 study of the safety and efficacy of a new high-purity FX concentrate (pdFX) in subjects with moderate or severe hereditary FX deficiency. The majority (98.4%) of the 187 bleeding episodes treated with 25 IU kg^{-1} pdFX were considered a treatment success. Excluding one subject who died due to an unrelated AE, all subjects remained in the study and continued to receive pdFX until the study concluded.

Of the 6772 subject-days in study and 468 pdFX infusions administered, only six AEs in two subjects were considered by the investigator as possibly related to treatment, and no possibly related serious adverse reactions or hypersensitivity reactions were observed. In addition, no cases of viral seroconversion or FX inhibitor development were observed, and no clinically relevant trends in laboratory parameters were detected, except those related to coagulation activation (discussed below).

Because coagulation activation markers can be difficult to interpret, the independent DRC assessed whether observed elevations in these markers were of clinical significance. Three subjects had significant elevations in ≥1 marker, but no consistent elevation (i.e. no early, substantial or sustained elevation of all three markers) was observed. In addition, no subjects exhibited any clinical signs or symptoms of thrombosis, even though pdFX exposure was considerable in some subjects (one subject received 10 pdFX infusions at 24-hour intervals as secondary prophylaxis, and a second subject received approximately twice-weekly pdFX infusions to treat a bleed and as preventative therapy prior to regular physical activity). Therefore, the DRC concluded that none of the observed changes in coagulation activation markers following infusion was indicative of a possible thrombogenic effect of pdFX.

Due to the rarity of hereditary FX deficiency, this study was limited by small sample size. Since evaluation of pdFX prophylactic efficacy was not included in the study design, effectiveness of a routine prophylactic regimen was not systematically assessed and is therefore the subject of an ongoing clinical trial in a paediatric population [13].

In conclusion, pdFX is the first highly purified FX concentrate developed for patients with hereditary FX deficiency. PK analysis found pdFX to have a mean IR of 2.00 IU dL^{-1} per IU kg^{-1} and a half-life of approximately 29.4 h, and these results demonstrate that pdFX at a nominal dose of 25 IU kg^{-1} is safe and efficacious for on-demand treatment of bleeding episodes and short-term preventative therapy in subjects with moderate or severe hereditary FX deficiency.

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Author contributions

MN and AS contributed to the study concept and design. SKA, KK, MN and AS were involved in acquisition, analysis and interpretation of data. MN participated in the drafting of the manuscript. SKA, KK, MN, FP and AS were involved in critical revision of the manuscript for important intellectual content and gave approval of the manuscript for submission/publication.

Disclosures

SKA is an advisory board member for and has received educational support from Baxter, Bayer, Bio Products Laboratory, CSL Behring, Novo Nordisk, Pfizer, and SOBI. KK is an advisory board member for Baxalta, Bayer, Novo Nordisk, Pfizer and has received educational and investigational support from Baxalta, Bayer, Bio Products Laboratory, CSL-Behring, Novo Nordisk, Octapharma, and Pfizer. MN is an employee of Bio Products Laboratory. FP has received honoraria for participating as a speaker at satellite symposia and educational meetings organized by Alexion, Baxter, Bayer, Biotest, CSL Behring, Grifols, Novo Nordisk, and SOBI; she has received research grant funding from Alexion, Biotest, Kedrion, and Novo Nordisk and consulting fees from Bio Products Laboratory, Grifols, Kedrion, and LFB; and she is a member of the Ablynx scientific advisory board. AS is an advisory board member for Baxter BioScience, Biogen, and Novo Nordisk; a consultant for Baxter BioScience, Biogen, Kedrion Biopharma, Novo Nordisk, and ProMetic Life Sciences; a speaker's bureau participant for Biogen; a member of the International Network for Pediatric Hemophilia funded by Bayer Healthcare; a member of the Novo Nordisk Hemophilia Foundation funded by Novo Nordisk; and a contributor to clinical research protocols for Baxter BioScience, Bayer Healthcare, Biogen, CSL-Behring, Daiichi Sankyo, Kedrion Biopharma, Novo Nordisk, Octapharma, OPKO, ProMetic Life Sciences, PTC Therapeutics, and Selexys, with all grant/research funding and consultant fees associated with the above activities paid to the Indiana Hemophilia & Thrombosis Center.

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