



Continuous Infusion of Factor VIII and von Willebrand Factor in Surgery: Trials with pdFVIII LFB or pdVWF LFB in Patients with Bleeding Disorders

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Abstract

Background A plasma-derived factor VIII product (pdFVIII; Factane 100 or 200 IU/mL) and a plasma-derived von Willebrand factor product (pdVWF; Wilfactin 100 IU/mL) are approved for replacement therapy by intravenous bolus injections in hemophilia A (HA) and von Willebrand disease (VWD), respectively. However, in situations requiring intensive treatment, continuous infusion (CI) may be desirable to better control target plasma factor levels. **Aim** To evaluate the perioperative hemostatic efficacy and safety of these concentrates administered by CI.

Methods Three phase III trials were conducted. Adults with HA (FVIII:C < 1%) (studies 1 and 2) or VWD (VWF:RCo < 20%) (Study 3) received a preoperative bolus followed by CI of undiluted concentrate for at least 6 days. Bolus doses and CI rates were based on individual recovery and clearance, respectively. The initial infusion rate had to be higher for 48 hours for HA and 24 hours for VWD patients to anticipate potential fluctuations of factor concentrations during major surgery. Target levels of FVIII:C in HA and VWF:RCo in VWD were 80 and 70 IU/dL, respectively. Efficacy was assessed using a global hemostatic efficacy score.

Results Studies 1, 2, and 3 included 12, 4, and 6 patients, respectively. Efficacy outcomes were excellent/good in all 22 major surgeries including 18 orthopedic procedures. Most daily measured FVIII and VWF levels (92%) were on target. No safety concerns, thrombotic events, or inhibitors were identified.

Conclusion pdFVIII and pdVWF administered by CI represent an effective and safe alternative to bolus injections in patients with severe HA or VWD undergoing surgery.

Keywords

- ▶ coagulation factor
- ▶ hemophilia A
- ▶ von Willebrand disease
- ▶ surgical procedures

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Introduction

Hemophilia A (HA) and von Willebrand disease (VWD) could be associated with excessive bleeding during major surgeries especially during orthopedic surgeries.^{1,2} As in HA, a low factor VIII (FVIII) level is an important determinant for joint bleeding in VWD. Arthropathy caused by recurrent joint bleeding episodes therefore occurs in both diseases. Van Galen et al presented outcomes after joint bleeds in VWD and HA and showed that orthopedic surgical procedures are required in approximately one in five patients in both diseases.³ Perioperative prophylactic treatment with FVIII or von Willebrand factor (VWF) is required in these patients to correct the underlying coagulation abnormalities and minimize the bleeding risk.^{4–6} Replacement therapy of the lacking protein is classically administered by a bolus injection regimen consisting of an initial dose followed by subsequent intermittent administration to maintain adequate factor levels. This type of regimen may not be an optimal approach to manage hemostasis since it may be associated with low trough levels and therefore an increased risk of harmful bleeding. Replacement of blood coagulation factors by continuous infusion (CI) was previously reported to represent an appropriate option to prevent large variations of coagulation factor levels in the bloodstream, either low trough levels or unnecessary high peaks.^{7,8} Advantages are likely the improvement of the protection from excessive bleeding, and easier monitoring. Efficacy and safety of CI remain deeply investigated for management of patients with severe HA^{9–20} and VWD^{21–23} undergoing major surgery. Causes influencing CI rates are the product, its adsorption in the infusion system, its dilution, the type of surgery, and the inter-patient pharmacokinetic (PK) variability.¹⁴ This article aims to present the results from three phase III clinical trials assessing CI as a modality of administration within the surgery indication of Factane and Wilfactin/Willfact (LFB, Les Ulis, France) in patients with HA and VWD, respectively. Factane is a human plasma-derived FVIII (pdFVIII) product and Wilfactin/Willfact, a human plasma-derived VWF (pdVWF) almost devoid of FVIII.

Methods

pdFVIII and pdVWF Products

The therapeutic proteins are extracted from plasma using plasma fractionation techniques. Both products are purified by chromatography, treated by solvent/detergent to inactivate enveloped viruses, nanofiltered to eliminate nonenveloped viruses (filters with pore sizes of 35 and 15 nm for the FVIII concentrate and 35 nm for the VWF concentrate). A dry-heat treatment at 80°C for 72 hours is added for the VWF concentrate as a third dedicated viral removal/inactivation step. Each product administered by bolus injection was successfully used in the perioperative prevention and treatment of bleeding during surgery in adults with severe disease.^{24,25}

Compatibility Studies

The compatibility of products with the CI equipment (pdFVIII 100 IU/mL and pdFVIII 200 IU/mL recently manufactured with

a smaller reconstitution volume, and pdVWF) was based upon assays either performed with a syringe pump or with an ambulatory infusion pump including bag and tubing sets. These compatibility studies were performed using standardized protocols by the manufacturer. In vitro stability studies were also evaluated under real conditions within hospital organization to guarantee the pharmaceutical quality of the preparations. Details of the protocols are provided in the ► **Supplementary Material** (available in the online version).^{26,27}

Study Designs

Three prospective, open-label, phase III studies were conducted between 2005 and 2013 in accordance with Good Clinical Practice²⁸ and ethical principles outlined in the Declaration of Helsinki.²⁹ The use of CI of pdFVIII concentrated at 100 IU/mL (Study 1) and at a higher concentration of 200 IU/mL (Study 2) was investigated at a single center in Poland in patients with HA. Then, to extend the knowledge of this mode of administration in a context of VWD, Study 3 was initiated with pdVWF in France and Poland. Clinical investigations for CI adhered to current guidelines in force for FVIII products or were adapted for VWF products.^{30,31} Ethics and national authorities' approvals, and written informed consent were obtained prior to enrolment. Studies were registered in EudraCT (numbers 2010–023666–46 for the most recent study with pdFVIII and 2007–004116–32 for pdVWF). The studies consisted of (1) a presurgery PK evaluation, (2) a surgical period with factor replacement by CI for at least 6 days (144 hours), and (3) a safety observation period following the CI.

Patient Population

Enrolled patients were adults (≥ 18 years) who had to undergo elective major surgical procedures requiring at least 6 days of treatment. In Study 1 and Study 2, patients with severe HA (baseline FVIII coagulant activity [FVIII:C] levels < 1 IU/dL) could be enrolled if they had ≥ 150 exposure days to FVIII. In Study 3, patients with VWD should have inherited severe VWF deficiency (type 1, 2, or 3) with baseline VWF ristocetin cofactor (VWF:RCo) levels < 20 IU/dL. In all cases, present or past inhibitor against FVIII or VWF was also an exclusion criterion. Patients should not be included in case of problematic venous access.

Preoperative Pharmacokinetic Study

Each patient underwent a presurgery PK evaluation to determine their individual incremental recovery and the estimate of clearance for calculations of the loading dose and the initial infusion rate, respectively. PK endpoints were assessed after a single dose of 50 IU/kg of pdFVIII in HA patients or 60 IU/kg of pdVWF in VWD patients. Blood samples were withdrawn over a period of 48 hours (Studies 1 and 2) or 9 hours (Study 3) as detailed in the ► **Supplementary Material** (available in the online version).

Continuous Infusion Protocol and Maintenance of Factors Levels

A preoperative loading dose of factor concentrate was administered by bolus injection on the day of the surgical

procedure (D0). This bolus dose was calculated to raise a peak plasma levels between 80 and 120 IU/dL of FVIII:C for HA and at least 100 IU/dL of VWF:RCo for VWD patients according to the formula: $dose (IU) = body\ weight (kg) \times desired\ increase\ in\ factor\ level (IU/dL) / individual\ incremental\ recovery\ at\ 15\ minutes (IU/dL\ per\ IU/kg)$. CI was initiated immediately at the end of the bolus.

In the postoperative period, the target factor levels of FVIII:C and VWF:RCo were respectively between 80 and 120 IU/dL for HA and at least 70 IU/dL for VWD patients for the first week, and thereafter between 30 and 80 IU/dL for HA and at least 50 IU/dL for VWD patients. To achieve these levels, the infusion rate was based on the formula: $rate\ of\ infusion (IU/kg/h) = individual\ clearance (mL/h/kg) \times desired\ factor\ level (IU/mL)$. A multiplying coefficient was applied to baseline clearance during the first 48 hours in studies 1 and 2 (2.5 for H0–H12, 2 for H12–H24, and 1.5 for H24–H48) and during the first 24 hours (from 2.0 to 1.5) in Study 3, to take into account an anticipated increased factor consumption due to postsurgical hemodynamic disturbances caused by blood loss and the nature and volume of expansion fluids infused.³² Circulating factor levels were measured at 6, 12, and 24 hours and then every 24 hours until 144 hours after the start of the CI. If needed, additional bolus doses could be also administered to reach quickly the desired level. All steps relative to the CI protocol for a specific patient are detailed in the **►Supplementary Material** (available in the online version).

The lyophilized product was reconstituted with the provided sterile water once a day without further dilution. Products were filled under laminar air flow conditions in the pump reservoir which was either a syringe or an infusion bag which was connected to a giving set and an infusion pump. Minor amounts of unfractionated heparin previously diluted in saline (5 IU/mL) were added to pdFVIII before the transfer in the delivery system to prevent local thrombophlebitis.³³

Because some VWD patients have a secondary FVIII deficiency, a bolus dose of 60 IU/kg of pdVWF was administered 12 to 24 hours before surgery to start the increase of endogenous FVIII and correct the FVIII:C level at the time of surgery. The target FVIII:C levels were ≥ 50 IU/dL before surgery and thereafter.

Efficacy Endpoints

The primary outcome was the global hemostatic efficacy assessment score merging intraoperative and postoperative assessments: on day 0 by the surgeon and on day 7 by the investigator. An additional assessment on the day of drain tube removal (or day 2 if no drain) was performed by the surgeon in studies 1 and 2.

Each assessment was scored on a 4-point scale (excellent, good, moderate, none). The treatment was considered as a "success" if the patient obtained an excellent or good score in the successive hemostasis assessments. Prior to each surgical procedure, the surgeon provided an estimate of the average and maximum expected blood loss during surgery for a person with a normal hemostasis under the same conditions,

allowing comparison of actual to predicted blood loss. Other endpoints included the occurrence of bleeding complications, packed red blood cell units transfused, requirement of second surgical intervention, factor plasma levels, and product consumption (dosage, infusion rates, and number of additional bolus injections).

Safety Endpoints

Safety was evaluated through reports of adverse events analyzed according to their relationship with either the study drug or the method of administration. Special attention was given to possible thromboembolic events and allergic/anaphylactic-type reactions. A daily examination of infusion site for signs of redness, pain, or swelling was performed. Vital signs, physical examination, and laboratory parameters including hematology and blood chemistry were monitored at study visits. Inhibitors to FVIII:C or to VWF:RCo were measured regularly during the study in the central laboratory by assays based on the Nijmegen modification of the Bethesda assay.³⁴

Statistical Methods

Exposure, efficacy, and safety parameters were summarized using descriptive statistics. The number and percentage together with the exact two-sided 95% Clopper–Pearson confidence interval were calculated for the primary endpoint. PK variables were reported as descriptive statistics.

Results

Compatibility Studies

Compatibility studies showed that either FVIII (**►Supplementary Fig. S1** [available in the online version]) or VWF (**►Supplementary Figs. S2 and S3** [available in the online version]) retain at least 90% of baseline potency for at least 24 hours whatever the tested conditions. Both reconstituted products were stable for 3 days in ambulatory pumps. FVIII activity was not impacted by the presence of heparin, composition of container, product potency, or low rate of infusion. There was no evolution in the multimeric composition (≥ 10 -mers and ≥ 15 -mers) for pdVWF product (**►Supplementary Fig. S4** [available in the online version]). No microbial contamination was observed.

Demographics and Baseline Characteristics

A total of 12, 4, and 6 patients were included in studies 1, 2, and 3, respectively. Baseline characteristics of the patients are summarized in **►Table 1**. Age ranged from 28 to 75 years, and weight from 49 to 100 kg body weight. Basal FVIII:C levels in the VWD patients ranged from 2 to 18 IU/dL.

Preoperative Pharmacokinetic Study

All patients completed a preoperative PK study. The FVIII concentration–time profiles of pdFVIII 100 IU/mL (Study 1) and pdFVIII 200 IU/mL (Study 2) were similar (**►Supplementary Fig. S5** [available in the online version]). An abbreviated curve of VWF plasma decay over 9 hours after injection of 60 IU/kg of pdVWF yielded informative data in

Table 1 Demographics and baseline characteristics of treated patients

Parameters	Study 1	Study 2	Study 3
Hemophilia A, <i>N</i>	12	4	–
Von Willebrand disease, <i>N</i>	–	–	6
Type 1, <i>N</i>	–	–	2
Type 2, <i>N</i>	–	–	0
Type 3, <i>N</i>	–	–	4
VWF:RCo (IU/dL) in Type 1	–	–	13 (11–15)
VWF:RCo (IU/dL) in Type 3	–	–	Undetectable
FVIII:C (IU/dL)	<1 (<1 to <1)	<1 (<1 to <1)	7.5 (2–18)
Sex (male/female)	12/0	4/0	3/3
Age (y)	37.0 (28–67)	39.0 (37–43)	49.5 (32–75)
Weight (kg)	64.0 (54.0–90.0)	82.5 (70.0–98.0)	80.4 (49.0–100.0)
Body mass index (kg/m ²)	21.6 (18.7–27.8)	27.4 (24.5–29.1)	27.7 (21.2–32.3)

Abbreviations: FVIII:C, factor VIII coagulant activity; *N*, number of patients; VWF:RCo, von Willebrand factor ristocetin cofactor.

Note: Data are given as median (min–max).

the preoperative context (► **Supplementary Fig. S6** [available in the online version]). From each study, the following were found: mean incremental recovery measured 15 minutes after the end of injection was: for pdFVIII 1.9 ± 0.4 and 2.3 ± 0.4 IU/dL per IU/kg in studies 1 and 2, respectively, and for pdVWF 2.2 ± 0.5 IU/dL per IU/kg (Study 3). FVIII clearance was 2.42 ± 0.6 and 2.40 ± 1.2 mL/h/kg in studies 1 and 2, respectively. In Study 3, estimate of VWF clearance was comparable regardless of the method used, noncompartmental or compartmental analysis, with mean values of 4.7 ± 1.2 and 5.0 ± 1.1 mL/h/kg, respectively. Other PK parameters are shown in ► **Supplementary Table S1** (pdFVIII) and ► **Supplementary Table S2** (pdVWF) (available in the online version). A large inter-individual variability was evidenced considering the coefficient of variation of approximately 20%.

Efficacy

A total of 22 major elective surgical procedures were performed. In line with the total absence or severe deficiency of FVIII, most (18 of 22) were orthopedic procedures, including 4 hip or knee prosthesis revisions with high risk of bleeding complications. The success rate of the treatment was 100% as all assessments were rated as excellent or good, either at the early stage of CI by the surgeon or later by the hematologist ► **Supplementary Table S3** [available in the online version]. Details for each surgical procedure are presented in ► **Table 2**. Perioperative blood loss was within predicted ranges in all except in two patients who underwent a total knee replacement. For the first patient with HA (patient 14), the investigator reported that the joint was more destroyed and the surgery more complicated than initially expected, and thus the predicted intraoperative blood loss volume had been underestimated. For the second patient with VWD (patient 20), a tourniquet was used during the intervention and excessive bleeding occurred in the immediate postoperative period; the investigator considered that the actual volume of blood was in line with the individual surgical conditions. For these two

patients, bleeding occurred at times when factor levels were within hemostatic ranges (FVIII:C at 126 IU/dL and VWF:RCo at 120 IU/dL). Both patients did not require transfusion of packed cells or reoperation to control bleeding. Ten patients experienced blood loss of >1,000 mL. Half of them received blood transfusions prescribed before surgery (1) or postoperatively (4).

The products were administered using individualized dosing including a safety margin dose to anticipate the factor consumption.

In HA patients, pdFVIII was given as a loading dose of mean (min–max) 65 IU/kg (48–86) and CI started with a rate of 6.8 IU/kg/h (4.5–8.9) in Study 1 while a lower loading dose (47 IU/kg [37–53]) and infusion rate (5.6 IU/kg/h [3.2–10.7]) were given in Study 2 in accordance with PK data. Mean FVIII:C levels were comparable 6 hours later: 88.6 IU/dL (71–126) and 99.8 IU/dL (88–126) in studies 1 and 2, respectively.

In VWD, all patients received a bolus dose of pdVWF (mean 56 IU/kg) the day prior to the intervention. As a consequence, FVIII:C levels varied between 66 and 133 IU/dL (mean 86.7 IU/dL) at the time of the procedure, and no additional FVIII concentrate was then used. Thereafter, the mean loading dose of pdVWF was 40 IU/kg (28–56), the initial infusion rate of CI was 5.8 IU/kg/h (4.8–6.9), and the VWF:RCo level 6 hours later was 127 IU/dL (98–152).

The infusion rates administered that take into account the decreasing planned multiplying coefficient during the first 2 days and the calculated clearance is shown in ► **Table 3**. The clearance of FVIII:C or VWF:RCo decreased overtime (► **Fig. 1**). It was evidenced that the factor consumption decreased over the course of 3 days in HA and 2 days in VWD patients. After 48 hours, the subsequent infusion rates were between 2.2 and 2.7 IU/kg/h either for pdFVIII or pdVWF products. Median (min–max) consumption per surgery was 608 IU/kg (376–1074) for pdFVIII and 579 IU/kg (411–825) for pdVWF.

In HA patients (► **Fig. 2A, B**), mean FVIII:C levels reached the desired level of 80 IU/dL throughout the 6 days of CI. In

Table 2 Characteristics of surgeries and details of factor administration by continuous infusion and blood loss

Patient	Disorder	Type of surgery	Surgery duration (h:min)	Individual incremental recovery (IU/dL)/ (IU/kg)	Loading bolus dose (IU/kg)	Continuous infusion period				Blood loss volume			RBC transfusion and time
						Individual clearance (mL/h/kg)	Initial rate H0-H12 (IU/kg/h)	Rate at H48-H72 (IU/kg/h)	Total dose (IU/kg)	Total days	Predicted min-max (mL)	Actual (mL)	
1	HA	Total hip arthroplasty revision	1:55	2.0	64.4	2.74	8.1	2.5	708.9 ^a	9	500-1,500	1,060	600 mL (H12)
2	HA	Inguinal hernia repair	0:50	2.0	47.5	2.33	6.6	2.0	474.5	7	30-70	60	-
3	HA	Total knee replacement ^b	1:45	2.1	65.7	1.63	5.4	2.0	640.2	13	500-1,500	1,425	-
4	HA	Socket of hip arthroplasty revision	1:15	1.7	67.1	2.96	8.9	3.3	993.5 ^c	13	500-1,500	800	-
5	HA	Total knee arthroplasty revision ^b	2:00	1.6	72.9	2.50	7.0	2.6	802.3	12	500-1,500	1,210	-
6	HA	Bilateral total knee replacement ^b	2:15	2.5	54.4	1.63	4.5	1.7	421.4 ^d	8	1,000-2,000	1,570	600 mL (H12) 300 mL (D2, D3)
7	HA	Total hip replacement	0:55	2.4	50.1	1.69	5.3	1.6	363.5	7	500-1,500	725	-
8	HA	Total hip replacement	1:15	1.4	85.6	2.84	8.3	3.0	613.3	7	500-1,500	860	-
9	HA	Bilateral total knee replacement ^b	3:20	2.3	52.8	1.75	5.3	1.8	390.8	7	1,500-2,500	2,460	300 mL (D4)
10	HA	Total knee replacement ^b	2:50	1.6	73.4	2.83	7.4	3.1	587.5	7	500-1,500	1,191	-
11	HA	Total knee replacement ^b	2:15	1.7	65.6	3.20	7.6	2.8	577.7	7	500-1,500	1,110	-
12	HA	Total knee replacement ^b	2:30	1.4	79.7	3.04	6.7	2.7	493.9	7	500-1,500	660	-
13	HA	Total knee replacement	1:16	2.9	37.1	1.6	3.2	1.6	339.1	7	400-1,000	600	-
14	HA	Total knee replacement ^b	1:45	2.3	53.1	4.1	10.7	4.2	789.5	7	400-1,000	1,910	-
15	HA	Total knee arthroplasty revision ^b	2:45	1.9	52.8	2.0	4.2	2.8	486.2	7	700-1,300	1,250	400 mL (D3)
16	HA	Total knee replacement	1:25	2.2	43.3	1.9	4.4	2.2	430.5	7	400-1,000	960	-
17	Type 3 VWD	Total knee replacement	4:37	2.8	56.0	4.7 ^e	6.6	2.0	509.4	9	500-1,500	1,150	500 mL (D0) ^f
18	Type 3 VWD	Inguinal hernia repair	0:53	2.2	36.8	3.5 ^e	4.9	2.5	462.4	7	10-30	0	-
19	Type 3 VWD	orthopedic procedure ^g	1:25	2.4	33.3	4.7 ^e	6.5	0.9	317.8	7	300-700	500	-
20	Type 3 VWD	Total knee replacement ^b	1:15	2.2	45.4	6.6	6.9	2.5	722.6	9	300-700	940	-
21	Type 1 VWD	Hemicolectomy	3:55	2.2	27.7	5.4	4.8	3.1	513.6	8	250-750	550	750 mL (D0) ^f
22	Type 1 VWD	Hysterosalpingo-oophorectomy	2:35	1.4	38.8	3.6	4.9	2.5	428.0	7	< 500	3	-

Abbreviations: D, day; H, hour (after loading bolus dose); HA, hemophilia A; VWD, von Willebrand disease; RBCs, red blood cells.

Note: Patient no. 1-12: Study 1; no. 13-16: Study 2; no. 17-22: Study 3.

^aThe patient received an additional bolus dose of 16 IU/kg.

^bUse of tourniquet.

^cThe patient received an additional bolus dose of 13 IU/kg.

^dThe patient received an additional bolus dose of 14 IU/kg.

^eCompartmental analysis.

^fTransfusion prescribed before surgery (hemoglobin 9.8 and 8.1 g/dL in patient 17 and 21, respectively) and administered during the surgery.

^gArthroscopy of the left knee, shaving and micro fractures of chondral defects, synovectomy and arthroscopy and arthrolysis, removal of adhesions.

Table 3 Infusion rates and evolution of clearance during the first 2 days by study

	H0–H12		H12–H24		H24–H48	
	Infusion rate (IU/kg/h)	Clearance (mL/h/kg)	Infusion rate (IU/kg/h)	Clearance (mL/h/kg)	Infusion rate (IU/kg/h)	Clearance (mL/h/kg)
Study 1 (HA), N = 12						
Recommended multiplying coefficient	× 2.5		× 2		× 1.5	
Mean (SD)	6.8 (1.4)	6.9 (1.4)	5.3 (1.0)	4.4 (0.9)	3.9 (0.8)	3.2 (0.6)
Median (min–max)	6.8 (4.5–8.9)	7.4 (4.9–8.7)	5.3 (3.6–6.8)	4.5 (3.0–5.8)	4.2 (2.7–4.7)	3.3 (2.2–4.2)
Study 2 (HA), N = 4						
Recommended multiplying coefficient	× 2.5		× 2		× 1.5	
Mean (SD)	5.6 (3.4)	5.4 (2.5)	5.0 (2.5)	4.4 (1.6)	3.8 (1.9)	3.8 (1.1)
Median (min–max)	4.3 (3.2–10.7)	4.7 (3.2–9.0)	4.4 (2.6–8.5)	4.6 (2.6–6.0)	3.4 (2.1–6.4)	3.7 (2.5–5.2)
Study 3 (VWD), N = 6						
Recommended multiplying coefficient	× 2.0 ^a		× 1.5 ^a		No corrective factor	
Mean (SD)	5.8 (1.0)	4.0 (0.7)	4.6 (1.3)	2.8 (1.0) ^b	2.5 (0.5)	1.8 (0.5)
Median (min–max)	5.7 (4.8–6.9)	4.0 (2.8–4.7)	4.3 (3.3–6.9)	2.6 (1.7–4.3) ^b	2.5 (1.6–3.1)	1.8 (1.1–2.4)

Abbreviations: H, hour (after loading bolus dose); HA, hemophilia A; N, number of patients; SD, standard deviation; VWD, von Willebrand disease. Note: The recommended multiplying coefficient was applied in the infusion rate formula as follows: rate of infusion (IU/kg/h) = multiplying coefficient × individual clearance (mL/h/kg) × desired factor level (IU/mL).

^aAs per protocol, the recommended multiplying coefficients (2.0 for the first 12 hours and 1.5 for the following 12 hours) was applied for the 4 first enrolled patients. After a protocol amendment, the multiplying coefficients remained at the investigator's discretion.

^bVWF:RCo level missing in one patient.

the first 72 hours after surgery, four FVIII:C levels were below the target level in four patients but without being lower than 71 IU/dL. As per protocol, three of them received an additional bolus injection with pdFVIII (between 13 and 16 IU/kg) to correct levels. In VWD patients (► Fig. 2C), median VWF:RCo levels were maintained over 70 IU/dL and FVIII:C

levels over 100 IU/dL along 6 days, indicating an effective FVIII binding to VWF infused. ► Table 4 shows individual data in both diseases. A total of 14/174 (8%) FVIII:C or VWF:RCo levels were lower than expected during the perioperative period, hence daily 92% were on target. The six surgeries in these patients with severe VWD were performed without adding FVIII concentrate.

No unfractionated heparin nor low-molecular-weight heparin or antifibrinolytics were administered in HA patients. Prophylactic enoxaparin was administered in two patients with VWD: the first undergoing a total knee replacement and the second a hemicolectomy, both starting from the operative day. The first patient also received tranexamic acid the day of the surgery.

Safety

The CI period ranged from 7 to 13 days with a median factor consumption per surgery (after the loading dose) of 69 IU/kg of FVIII per day in Study 1, 65 IU/kg of FVIII per day in Study 2, and 65 IU/kg of VWF:RCo per day in Study 3. No side effects were recorded. Across all studies, a total of three nonserious adverse events related to treatment were reported in two patients: an infusion site reaction followed by an increase in diastolic blood pressure during the bolus administration for the preoperative PK resolved within 10 minutes without medication (Study 3); a venipuncture site inflammation occurring after 2 days of CI, which led to the interruption of the study drug for few minutes to change the infusion site and resolved without other action (Study 3).

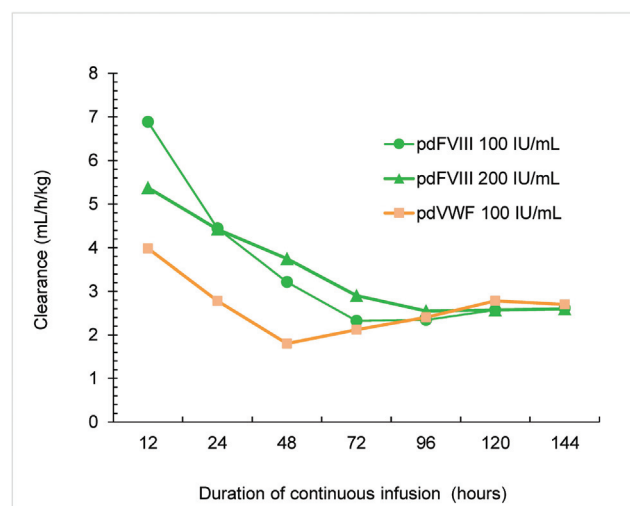


Fig. 1 Evolution of the mean clearance of FVIII:C and VWF:RCo during the course of continuous infusion with pdFVIII (100 IU/mL and 200 IU/mL) and pdVWF (100 IU/mL). Clearances were calculated from factor infusion rate and factor measurements at the steady state. pdFVIII, plasma-derived factor VIII; pdVWF, plasma-derived von Willebrand factor; VWF:RCo, von Willebrand factor ristocetin cofactor.

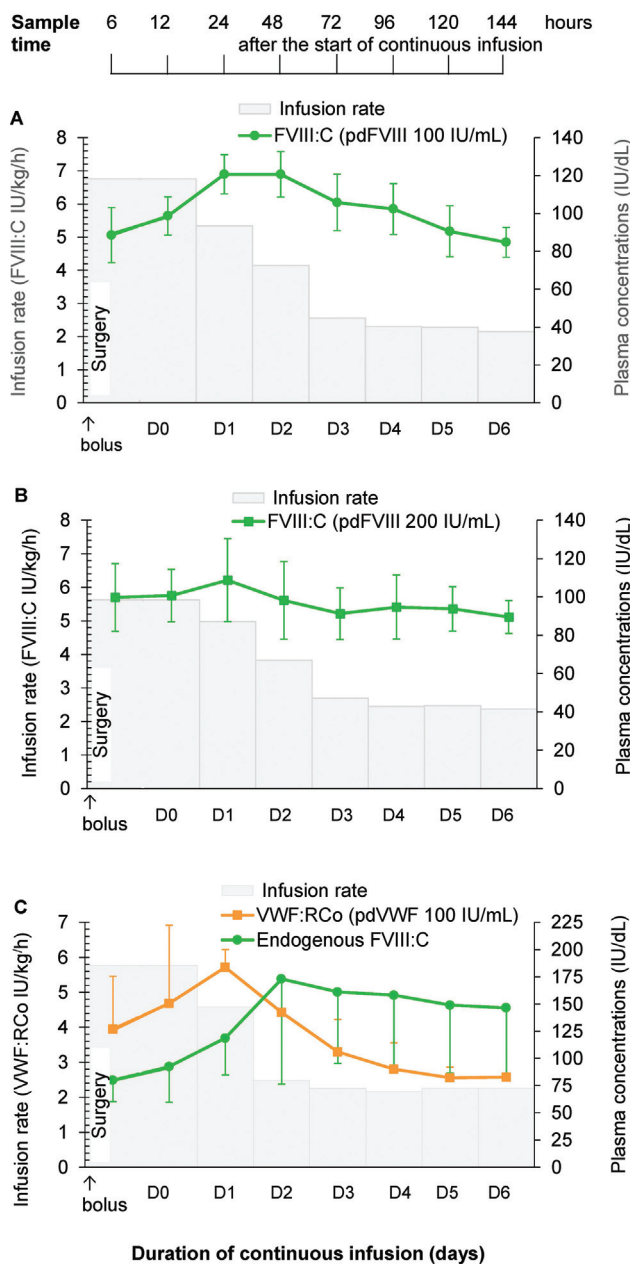


Fig. 2 Mean (SD) plasma concentration and infusion rate during the course of continuous infusion with pdFVIII 100 IU/mL (A), pdFVIII 200 IU/mL (B), and pdVWF (C). pdFVIII, plasma-derived factor VIII; pdVWF, plasma-derived von Willebrand factor; SD, standard deviation.

There was no sign of local thrombophlebitis or infection during daily inspection of the catheter site. None of the patients developed inhibitors during the study periods.

Discussion

The data from the three clinical studies demonstrated the clinical feasibility and relevance of replacement therapy with pdFVIII and pdVWF administered for at least 6 days by CI in patients undergoing major surgeries. No treatment-related serious adverse events, development of inhibitory antibodies, or thrombotic events were reported.

As a prerequisite for application via CI, pharmaceutical stability of products was demonstrated: no changes in the

FVIII and VWF concentrate characteristics were detected at least within 72 hours when stored in ambulatory pumps. Strengths up to 200 IU/mL of the pdFVIII concentrates appear favorable for CI as no dilution was required after reconstitution avoiding a possible denaturation.

For all 22 surgeries, hemostatic efficacy assessment scores were classified as excellent except for one surgery classified as good. Importantly, results were comparable with those reported in pivotal studies with the same product but administered by bolus.^{24,25} The treatment recommendations called for levels of FVIII:C above 80 IU/dL in HA, and levels of VWF:RCo above 70 IU/dL in VWD during the post-operative period, and these objectives were met. In patients with VWD, mean FVIII:C remained stable over time after the second day of VWF treatment (►Fig. 2C). These findings are in line with those from an earlier study reported by Borel-Derlon et al, which also provide identical FVIII profile when patients received intermittent boluses.²⁵ Most patients with HA or VWD achieved plasma levels (94% for FVIII:C and 100% for VWF:RCo, respectively) above the lowest predefined target range levels during the first 24 hours after surgery, a well-known crucial period. This result was in contrast to published data by Hazendonk et al in a retrospective study evaluating a large population of 119 HA patients undergoing a total of 198 surgical procedures including 115 surgeries performed by CI. The authors found that 44.5% (137/308) of FVIII levels were below the same lowest predefined target range.³⁵ Although the sample sizes were different between studies to allow for a strict comparison, our results were in favor of mitigating the risk of drop under the targeted FVIII level by increasing the initial infusion rate.^{36,37} The initial infusion rate was based on the baseline clearance corrected by a multiplying coefficient to anticipate coagulation factor consumption. While a decreasing multiplying coefficient from 2.5 to 1.5 over 48 hours provides an effective guide to managing initial infusion rates in HA, its use from 2.0 to 1.5 over a shorter period (24 hours) in VWD seemed not clearly optimal since some levels of VWF:RCo >200 IU/dL were observed. Two of four patients with type 3 VWD had VWF:RCo levels at 211 and 294 IU/dL 24 hours after the CI initiation, suggesting that the multiplying coefficient could be reduced. In both diseases, the inter-patient variability with respect to incremental recovery and estimated clearance observed at baseline stressed the importance of a presurgical PK evaluation and individualized approach. The decline in clearances of infused FVIII observed in our patients over the treatment period remained comparable to other studies.^{33,38}

The CI treatment regimen successfully stabilized FVIII or VWF levels, mitigating the risk of thrombosis since constitutively high plasma FVIII levels have been reported to be associated with increased risk of venous thromboembolism.^{39,40}

Other safety issues in the context of replacement therapy with CI are potential risk of infection or phlebitis at the infusion site, but no sign of local thrombophlebitis or infection during daily inspection of catheter sites was observed during the observation period of the three studies. No adverse events such as thromboses, wound infection, or inhibitor development were observed.

Table 4 Individual perioperative plasma levels in different time points during continuous infusion

Patient	Disorder	Type of surgery	H6	H12	H24	H48	H72	H96	H120	H144
			Factor VIII:C levels (IU/dL)							
1	HA	Total hip arthroplasty revision	72	110 ^a	138	130	118	92	74	77
2	HA	Inguinal hernia repair	88	98	100	140	96	92	91	88
3	HA	Total knee replacement	92	108	132	126	120	116	106	86
4	HA	Socket of hip arthroplasty revision	76	102 ^b	120	120	92	90	86	80
5	HA	Total knee arthroplasty revision	88	86	118	120	102	94	82	100
6	HA	Bilateral total knee replacement	80	92	120	110	78	84 ^c	80	75
7	HA	Total hip replacement	90	108	122	104	104	108	96	87
8	HA	Total hip replacement	126	110	118	132	120	118	90	84
9	HA	Bilateral total knee replacement	98	88	110	108	88	88	70	72
10	HA	Total knee replacement	94	102	134	104	124	112	96	86
11	HA	Total knee replacement	88	100	116	132	118	120	118	88
12	HA	Total knee replacement	71	80	120	122	110	114	98	94
13	HA	Total knee replacement	91	101	99	84	81	78	87	85
14	HA	Total knee replacement	126	119	140	125	107	117	110	102
15	HA	Total knee arthroplasty revision	88	86	91	103	98	87	84	83
16	HA	Total knee replacement	94	97	105	81	79	97	94	88
			VWF:ristocetin cofactor levels (IU/dL)							
17	Type 3 VWD	Total knee replacement	152	236	294	168	138	91	80	83
18	Type 3 VWD	Inguinal hernia repair	128	120	144	136	96	112	88	88
19	Type 3 VWD	Orthopedic procedure	150	172	211	142	66	49	48	70
20	Type 3 VWD	Total knee replacement	120	150	161	123	115	85	74	98
21	Type 1 VWD	Hemicolectomy	98	102	nd	142	138	133	123	82
22	Type 1 VWD	Hysterosalpingo-oophorectomy	114	123	109	nd	83	70	80	75

Abbreviations: HA, hemophilia A; H, hour (after loading bolus dose); nd, not done; VWD, von Willebrand disease.

Note: Patient no. 1–12: Study 1; no. 13–16: Study 2; no. 17–22: Study 3.

^aThe patient received an additional bolus dose of 16 IU/kg infused 4 hours before.

^bThe patient received an additional bolus dose of 13 IU/kg infused 5 hours before.

^cThe patient received an additional bolus dose of 14 IU/kg infused 24 hours before.

In conclusion, taken together, the results reported in the present article show that products used by CI are effective and well tolerated when used to cover major surgical procedures.

What is known about this topic?

- Replacement therapy by continuous infusion aims to provide patients with a safe and constant level of the deficient coagulation factor.
- Continuous infusion is known to be an effective alternative to bolus injections in clinical management of surgical procedures in patients suffering from bleeding disorders.
- Causes influencing continuous infusion rates are the product, its adsorption in the infusion system, its dilution, the type and course of surgery, and the inter-patient pharmacokinetic variability.

What does this paper add?

- Continuous infusion of pdFVIII or pdVWF, i.e., Factane and Wilfactin respectively, is effective to control bleeding, and represents a safe alternative to bolus injections to patients undergoing major surgery.
- Continuous infusion of undiluted pdFVIII or pdVWF maintains factor levels within the hemostatic target range during surgery and in the postoperative period.
- Considering inter-patient variability of FVIII and VWF pharmacokinetic parameters, a presurgical pharmacokinetic evaluation is helpful to individualize treatment.

Author Contributions

J.W., C.N., and V.C. contributed in designing the studies, and analyzed and interpreted the data. B.G., L.R., A.F., and

E.S.-W. contributed to patient enrolment and collected the data. S.P. and C.H. contributed to the analysis and wrote the manuscript. F.B. designed the studies, interpreted the data, and wrote the manuscript. All authors critically revised the manuscript and approved the final version.

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Conflict of Interest

J.W. received grant support from Alnylam Pharmaceuticals, Baxalta, LFB, Novo Nordisk, Octapharma, Rigel Pharmaceuticals, Roche, Shire/Takeda, and Sobi; also sponsored lectures from Alexion, Baxalta, CSL Behring, Ferring Pharmaceuticals, Novo Nordisk, Octapharma, Roche, Sanofi/Genzyme, Shire/Takeda, Siemens, Sobi, and Werfen. B.G. has received grant support from CSL Behring, Octapharma and Sobi; also sponsored lectures from CSL Behring, Novo Nordisk, Roche, and Shire/Takeda. L.R. has no conflicts of interest to declare. E.S.-W. has no conflicts of interest to declare. V.C. has received honoraria or consultation fees from Roche, Novo Nordisk, and Sobi, also support for attending scientific meetings from LFB and Sobi. S.P. is an employee of LFB; C.H. is an employee of LFB. F.B. is a former employee of LFB. C.N. received research grant or honoraria or participated in clinical trials from Alnylam/Sanofi, Bayer, Biomarin, Bioverativ/Sobi, Bayer, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche/Spark, and Shire/Takeda.

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References

- Luck JV Jr, Kasper CK. Surgical management of advanced hemophilic arthropathy. An overview of 20 years' experience. *Clin Orthop Relat Res* 1989;(242):60–82
- Leebeek FWG, Eikenboom JCJ. Von Willebrand's disease. *N Engl J Med* 2016;375(21):2067–2080
- van Galen KP, Timmer M, de Kleijn P, et al; WiN Study Group. Long-term outcome after joint bleeds in von Willebrand disease compared to haemophilia A: a post hoc analysis. *Thromb Haemost* 2018;118(10):1690–1700
- Windyga J, von Depka-Prondzinski M. European Wilate® Study Group. Efficacy and safety of a new generation von Willebrand factor/factor VIII concentrate (Wilate®) in the management of perioperative haemostasis in von Willebrand disease patients undergoing surgery. *Thromb Haemost* 2011;105(06):1072–1079
- Coppola A, Windyga J, Tufano A, Yeung C, Di Minno MND. Treatment for preventing bleeding in people with haemophilia or other congenital bleeding disorders undergoing surgery. *Cochrane Database Syst Rev* 2015;2:CD009961
- Chevalier Y, Dargaud Y, Lienhart A, Chamouard V, Negrier C. Seventy-two total knee arthroplasties performed in patients with haemophilia using continuous infusion. *Vox Sang* 2013;104(02):135–143
- Hathaway WE, Christian MJ, Clarke SL, Hasiba U. Comparison of continuous and intermittent factor VIII concentrate therapy in hemophilia A. *Am J Hematol* 1984;17(01):85–88
- Batorova A, Martinowitz U. Intermittent injections vs. continuous infusion of factor VIII in haemophilia patients undergoing major surgery. *Br J Haematol* 2000;110(03):715–720
- Hay CR, Doughty HI, Savidge GF. Continuous infusion of factor VIII for surgery and major bleeding. *Blood Coagul Fibrinolysis* 1996;7 (Suppl 1):S15–S19
- Tagariello G, Davoli PG, Gajo GB, et al. Safety and efficacy of high-purity concentrates in haemophilic patients undergoing surgery by continuous infusion. *Haemophilia* 1999;5(06):426–430
- Rochat C, McFadyen ML, Schwyzer R, Gillham A, Cruickshank A. Continuous infusion of intermediate-purity factor VIII in haemophilia A patients undergoing elective surgery. *Haemophilia* 1999; 5(03):181–186
- Négrier C, Lienhart A, Meunier S, et al. Surgeries in patients with haemophilia A performed with a continuous infusion of Recombinate. Paper presented at: 18th Congress of the International Society on Thrombosis and Haemostasis; July 6–12, 2001; Paris, France
- Stieltjes N, Altisent C, Auerswald G, et al. Continuous infusion of B-domain deleted recombinant factor VIII (ReFacto) in patients with haemophilia A undergoing surgery: clinical experience. *Haemophilia* 2004;10(05):452–458
- Takedani H. Continuous infusion during total joint arthroplasty in Japanese haemophilia A patients: comparison study among two recombinants and one plasma-derived factor VIII. *Haemophilia* 2010;16(05):740–746
- Rahmé M, Ehlinger M, Faradji A, et al. Total knee arthroplasty in severe haemophilic patients under continuous infusion of clotting factors. *Knee Surg Sports Traumatol Arthrosc* 2012;20(09):1781–1786
- Meijer K, Rauchensteiner S, Santagostino E, et al. Continuous infusion of recombinant factor VIII formulated with sucrose in surgery: non-interventional, observational study in patients with severe haemophilia A. *Haemophilia* 2015;21(01):e19–e25
- Park YS, Shin WJ, Kim KI. Comparison of continuous infusion versus bolus injection of factor concentrates for blood management after total knee arthroplasty in patients with hemophilia. *BMC Musculoskelet Disord* 2017;18(01):356
- Kremer Hovinga ICL, Schutgens REG, van der Valk PR, van Vulpen LFD, Mauer-Bunschoten EP, Fisher K. Continuous infusion of extended half-life factor VIII (efmoroctocog alpha) for surgery in severe haemophilia A. *Haemophilia* 2018;24(04):e280–e283
- Holme PA, Tjønnfjord GE, Batorova A. Continuous infusion of coagulation factor concentrates during intensive treatment. *Haemophilia* 2018;24(01):24–32
- Holme PA, Tjønnfjord GE. Continuous infusion of simoctocog alfa in haemophilia A patients undergoing surgeries. *Haemophilia* 2019;25(01):54–59
- Auerswald G, Bade A, Haubold K, Overberg D, Masurat S, Moorthi C. No inhibitor development after continuous infusion of factor concentrates in subjects with bleeding disorders undergoing surgery: a prospective study. *Haemophilia* 2013;19(03):438–444
- Lubetsky A, Schulman S, Varon D, et al. Safety and efficacy of continuous infusion of a combined factor VIII-von Willebrand

- factor (vWF) concentrate (Haemate-P™) in patients with von Willebrand disease. *Thromb Haemost* 1999;81(02):229–233
- 23 Chapin J, Bamme J, Hsu F, Christos P, DeSancho M. Outcomes in patients with hemophilia and von Willebrand disease undergoing invasive or surgical procedures. *Clin Appl Thromb Hemost* 2017; 23(02):148–154
 - 24 Rothschild C, Goudemand J, Alcalay M, et al. Efficacy and safety of the first nanofiltered plasma-derived FVIII (FACTANE®) in previously-treated haemophilia A patients. Paper presented at: 19th Congress of International Society on Thrombosis and Haemostasis; July 12–18, 2003; Birmingham, England
 - 25 Borel-Derlon A, Federici AB, Roussel-Robert V, et al. Treatment of severe von Willebrand disease with a high-purity von Willebrand factor concentrate (Wilfactin®): a prospective study of 50 patients. *J Thromb Haemost* 2007;5(06):1115–1124
 - 26 Chamouard V, Moreau S, Attali O, Négrier C. Stability and microbiological safety of clotting factor concentrates in CADD PRIZM VIP™ pump: a preliminary study. *J Pharm Clin* 2001;20(03): 149–155
 - 27 Peyrezabes E, Chamouard V, Bridey F, et al. Evaluation of in-vitro stability and microbiological safety of reconstituted von Willebrand factor concentrate. Paper presented at: 21st Congress of the International Society on Thrombosis and Haemostasis; July 6–12, 2007; Geneva, Switzerland
 - 28 ICH. Tripartite harmonised guideline: Good Clinical Practice: Consolidated Guideline (E6). Accessed June 21, 2022 at: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf
 - 29 World Medical Association. Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Accessed June 21, 2022 at: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects>
 - 30 EMA. Committee for medicinal products for human use (CHMP). Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products EMA/CHMP/BPWP/144533/2009. Draft 2009, adopted by CHMP 2011. Accessed June 21, 2022 at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-recombinant-investigation-human-plasma-derived-factor-viii-products-first-version_en.pdf
 - 31 EMA. Guideline on the clinical investigation of human plasma-derived von Willebrand factor products. CPMP/BPWG/220/02. Draft 2002, adopted by CHMP 2005. Accessed June 21, 2022 at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-human-plasma-derived-von-willebrand-factor-products-cmp/bpwg/220/02_en.pdf
 - 32 Lee M, Morfini M, Négrier C, Chamouard V. The pharmacokinetics of coagulation factors. *Haemophilia* 2006;12(Suppl 3):1–7
 - 33 Martinowitz U, Schulman S, Gitel S, Horowitzski H, Heim M, Varon D. Adjusted dose continuous infusion of factor VIII in patients with haemophilia A. *Br J Haematol* 1992;82(04):729–734
 - 34 Verbruggen B, Novakova I, Wessels H, Boezeman J, van den Berg M, Mauser-Bunschoten E. The Nijmegen modification of the Bethesda assay for factor VIII:C inhibitors: improved specificity and reliability. *Thromb Haemost* 1995;73(02):247–251
 - 35 Hazendonk HCAM, Lock J, Mathôt RAA, et al. Perioperative treatment of hemophilia A patients: blood group O patients are at risk of bleeding complications. *J Thromb Haemost* 2016;14(03): 468–478
 - 36 Longo G, Messori A, Morfini M, et al. Evaluation of factor VIII pharmacokinetics in hemophilia-A subjects undergoing surgery and description of a nomogram for dosing calculations. *Am J Hematol* 1989;30(03):140–149
 - 37 Kalairajah Y, Simpson D, Cossey AJ, Verrall GM, Spriggins AJ. Blood loss after total knee replacement: effects of computer-assisted surgery. *J Bone Joint Surg Br* 2005;87(11):1480–1482
 - 38 Schulman SrFVIIa-CI Group. Continuous infusion of recombinant factor VIIa in hemophilic patients with inhibitors: safety, monitoring, and cost effectiveness. *Semin Thromb Hemost* 2000;26 (04):421–424
 - 39 Kahlon A, Grabell J, Tuttle A, et al. Quantification of perioperative changes in von Willebrand factor and factor VIII during elective orthopaedic surgery in normal individuals. *Haemophilia* 2013;19 (05):758–764
 - 40 Kyrle PA, Minar E, Hirschl M, et al. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. *N Engl J Med* 2000;343(07):457–462