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ORIGINAL ARTICLE *Von Willebrand disease*

Efficacy and safety of a VWF/FVIII concentrate (wilate®) in inherited von Willebrand disease patients undergoing surgical procedures

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Introduction: Surgical procedures in von Willebrand disease (VWD) patients may require prophylactic treatment with exogenous von Willebrand factor (VWF) and coagulation factor VIII (FVIII) to prevent excessive bleeding. Wilate® is a plasma-derived, double virus-inactivated, highly purified, freeze-dried VWF/FVIII concentrate, containing both factors in a physiological activity ratio of 1:1. **Aim:** To investigate the efficacy and safety of wilate® in maintaining haemostasis in VWD patients undergoing surgical procedures. **Methods:** This prospective, open-label multinational clinical study documents 28 individuals who underwent 30 surgical procedures managed with wilate®. Twenty-one patients had VWD Type 3, and 21 surgeries were major. Efficacy was assessed intra- and postoperatively by the surgeon and investigator, respectively, and adjudicated by an Independent Data Monitoring Committee, using an objective scale based on blood loss, transfusion requirements and postoperative bleeding and oozing. Treatment success (primary endpoint) was determined using a composite assessment algorithm and was formally assessed. **Results:** Surgical prophylaxis with wilate® was successful in 29 of 30 procedures. The overall rate of success was 96.7% (98.75% CI: 0.784, 1.000). All 21 surgeries in patients with VWD Type 3 were managed successfully. There was no accumulation of VWF or FVIII after multiple dosing, and no thromboembolic events or inhibitors to VWF or FVIII were observed. **Conclusions:** Wilate® demonstrated effective prevention and treatment of bleeding in inherited VWD patients undergoing surgery, with no clinically significant safety concerns.

Keywords: coagulation factor VIII, surgery, von Willebrand disease, von Willebrand factor, wilate®

Introduction

von Willebrand disease (VWD) is the most common inherited bleeding disorder with a prevalence estimated to range from 1 to 100 in 10 000 [1]. VWD is caused by quantitative (Types 1 and 3) or qualitative (Type 2) deficiency in von Willebrand factor (VWF) and is markedly heterogeneous in type and severity [1–4]. Surgical procedures in patients with VWD can be associated with a life-threatening risk of excessive bleeding and may require prophylactic treatment with a combined VWF/FVIII concentrate [5]. Dosing of VWF/FVIII concentrates for surgical haemostasis depends on disease severity and surgery type [6]. Several prospective and retrospective studies have demonstrated the haemostatic effect of VWF/FVIII-containing concentrates in surgical procedures [5,7–14]. Although rare, repeated administrations of VWF/FVIII products, as often needed during surgery, have been associated with thrombotic events linked to abnormally high plasma levels of FVIII coagulant activity (FVIII:C) or VWF ristocetin cofactor activity (VWF:RCo) [15].

Wilate® is a double virus-inactivated, plasma-derived concentrate with the native VWF and FVIII complex in a physiological 1:1 activity ratio [7,16–18]. The efficacy, safety and tolerability of wilate® in

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the prevention and treatment of bleeding in adults and children with VWD have been reported in several prospective clinical trials [7,8,19–21], which included surgical procedures. This current study (WONDERS) investigated the clinical efficacy and safety of wilate® in the prevention and treatment of surgical bleeding, under well-defined, stringent protocol-driven and centrally monitored conditions, in patients with inherited VWD.

Methods

Study design

A prospective, open-label, multinational, phase III clinical study was performed in paediatric and adult patients with inherited VWD undergoing surgery to evaluate the haemostatic efficacy and safety of wilate® in maintaining intra- and postoperative haemostasis in surgical procedures (ClinicalTrials.gov Identifier: NCT01365546). The study originally planned to examine up to 41 surgical procedures. A single interim analysis was planned after 30 procedures, with the possibility for early study termination if predefined success criteria were achieved. Early success was defined by a two-sided 98.75% confidence interval (CI) for the overall success rate of >0.60 (equivalent to ≥25 successes in 30 procedures). The interim analysis showed that the prespecified success rate for study termination was reached after 30 procedures.

Patients could have multiple independent surgeries that were counted as separate surgical events. Patients were monitored for 30 days from the start of each surgery or until discharge, whichever came later. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and national regulatory requirements [22]. The final protocol was reviewed and approved by the responsible regulatory authorities and institutional ethics committees.

Enrolment criteria

The study enrolled males or females aged ≥6 years with inherited VWD (any type) requiring a VWF/FVIII concentrate to cover surgical procedures. Patients were excluded if they had any other known coagulation disorder, had received a VWF/FVIII-containing product within 3 days of the screening visit, had any known inhibitor activity against VWF or FVIII and if continuous infusion was planned. Additional exclusion criteria included: active hepatic disease, known or suspected hypersensitivity and receiving immune-modulating drugs at study start. Patients or parents/legal guardians of paediatric patients provided full informed consent.

Dosing

All doses were administered as a bolus intravenous infusion. All patients received 60 IU kg^{-1} of wilate® for the *in vivo* recovery (IVR) investigation at study start to calculate the recommended dosing for surgeries; additionally, the following guidelines were given:

Major surgery. A loading dose of 40–60 VWF:RCo IU kg^{-1} within 3 h of start of procedure was given to achieve peak plasma VWF:RCo level of 100%. A maintenance dose of 20–40 VWF:RCo IU kg^{-1} or half of the loading dose was given every 12–24 h. Trough levels of VWF:RCo were to be maintained at >50% for at least 6 days. At least two maintenance doses were to be administered within the first 24 h after the start of surgery.

Minor surgery. A loading dose of 30–60 VWF:RCo IU kg^{-1} within 3 h of start of procedure was given to achieve peak plasma VWF: RCo level of 50%. A maintenance dose of 20–40 VWF: RCo IU kg^{-1} or half of the loading dose was given every 12–24 h. Trough levels of VWF: RCo were to be maintained at >30% for at least 2 days.

These dosing recommendations were adjusted for each patient using the results of the baseline IVR and at the investigator's discretion based on the clinical situation. FVIII:C and VWF:RCo levels were monitored throughout the treatment period, with the aim of not exceeding a recommended maximum level of 250% FVIII:C and maintaining a recommended trough level of at least 50% VWF:RCo for major surgeries and 30% VWF:RCo for minor surgeries. No VWF/FVIII preparations other than wilate® were to be administered, except in emergency situations.

Efficacy and safety evaluations

Surgical prophylaxis. Efficacy of wilate® was assessed by the surgeon at the end of each surgical procedure (last suture) using a stringent and objective 4-point efficacy scale (excellent, good, moderate or none) based on blood loss and transfusion requirements during surgery, and postoperatively by the investigator based on postoperative bleeding and oozing, covering the time period from the end of the procedure up to 24 h following the last wilate® infusion. In the event of a discrepancy between surgeons' and investigators' assessments, falling into one of the categories marked 'primary adjudication' in Table 1, the classification of success or failure was determined by the Independent Data Monitoring Committee (IDMC).

Plasma levels of haemostatic parameters and IVR. IVR of FVIII:C, VWF:RCo and von Willebrand factor antigen (VWF:Ag) were determined at a central laboratory

Table 1. Composite assessment algorithm to determine the overall effectiveness of wilate® treatment.

	Postoperative assessment			
Intraoperative assessment	Excellent	Good	Moderate	None
Excellent	Success	Success	Success	Primary adjudication
Good	Success	Success	Primary adjudication	Failure
Moderate	Success	Primary adjudication	Failure	Failure
None	Primary adjudication	Failure	Failure	Failure

In the event of a discrepancy between surgeons' and investigators' assessments, falling into one of the categories marked 'primary adjudication', the classification of success or failure was determined by the IDMC. In addition, the IDMC conducted an independent and blinded adjudication of all haemostatic efficacy results ('secondary adjudication'), and the overall success (primary endpoint) was based on both the intra- and postoperative IDMC efficacy assessments.

for all patients at the screening/baseline visit, and used to calculate the recommended dosing (VWF:RCo). Plasma levels of haemostatic parameters and IVR were additionally determined for every maintenance infusion 30 min before and after every infusion. These plasma samples were analysed locally for monitoring purposes and confirmed later by the central laboratory.

Safety. Clinical tolerability was assessed by monitoring vital signs, laboratory parameters (including VWF inhibitors and virus markers) and adverse events.

Statistics

The primary analysis focused on the overall proportion of surgeries rated as successful (Table 1). For the overall efficacy assessment, a CI of 98.75% was used, and for the intra- and postoperative assessment, a CI of 95% was used.

Results

Patient demographics

The study enrolled 39 individual patients (safety population), of whom 28 individual patients underwent 30 surgeries (intent-to-treat [ITT] population). All 39 enrolled patients were included in the safety population as all received an infusion of wilate® for IVR determination, but not all underwent surgery. As the prespecified criteria for success were met at the interim analysis, the study was terminated early (after 30 surgeries). Demographic characteristics (ITT) are shown in Table 2. Median (range) baseline levels of VWF:RCo were 22.5 IU dL^{-1} (3–38 IU dL^{-1}), 6.5 IU dL^{-1} (4–9 IU dL) and 0.0 IU dL^{-1} (0–10 IU dL^{-1}) for patients with VWD Type 1, Type 2 and Type 3, respectively. Median (range) baseline levels of FVIII:C were 43.0 IU dL^{-1} (2–65 IU dL^{-1}), 25.5 IU dL^{-1} (21–30 IU dL^{-1}) and 1.0 IU dL^{-1} (0–39 IU dL^{-1}), respectively. Seven procedures were performed in patients with VWD Type 1 (23.3%), two in patients with VWD Type 2 (6.7%) and 21 in patients with VWD Type 3 (70.0%). One patient with VWD Type 1 and one with VWD Type 3 underwent two surgeries.

Efficacy in surgical prophylaxis

Of the 30 surgical procedures, 21 were major and nine were minor. Of the 21 procedures in VWD Type 3 patients, 17 (81.0%) were major. Major procedures included orthopaedic (8), obstetric/gynaecological (5), gastrointestinal (4), dental (2) and ear, nose and throat (2) surgeries. Minor procedures included dental (5), orthopaedic (2), ophthalmologic (1) and ear, nose and throat (1) surgeries.

The overall success rate of wilate® treatment was 96.7% based on objective criteria and as adjudicated by the IDMC (98.75% CI: 0.784, 1.000) (Table 3A).

Table 2. Demographic and baseline clinical characteristics of ITT population.

Parameters	ITT population (*N* = 30*)
Age at screening (years)	
Mean (SD)	38.3 (16.8)
Median (range)	36.0 (12–74)
Height (cm)	
Mean (SD)	161.9 (11.2)
Median (range)	162.0 (141–187)
Weight (kg)	
Mean (SD)	69.4 (23.6)
Median (range)	63.7 (39–126)
Gender, *N* (%)	
Male	9 (30.0)
Female	21 (70.0)
Race, *N* (%)	
White	18 (60.0)
Asian	12 (40.0)
VWD Type, *N* (%)	
Type 1	7 (23.3)
Type 2	2 (6.7)
Type 3	21 (70.0)
Family history of VWD, *N* (%)	
Yes	11 (36.7)
No	16 (53.3)
Unknown	3 (10.0)
VWF inhibitor activity, *N* (%)	
Yes	0 (0)
No	30 (100)

N, number of surgeries.
*Two patients were enrolled in two surgeries each; therefore, there were 28 individual patients.

The success rate was 100.0% for minor surgeries (98.75% CI: 0.569, 1.000) and 95.2% for major surgeries (98.75% CI: 0.704, 1.000). The overall success rate was 100.0% in VWD Type 3 (98.75% CI: 0.785, 1.000) and Type 2 (98.75% CI: 0.079, 1.000) patients, and 85.7% in VWD Type 1 patients (98.75% CI: 0.328, 0.999) (Table 3B). Only one procedure was considered non-successful due to an intraoperative haemostatic efficacy rating of moderate by both the surgeon and IDMC, and a postoperative efficacy rating of good and moderate by the investigator and IDMC, respectively. This VWD Type 1 patient (baseline VWF:RCo plasma level: 21 IU dL^{-1}) underwent left lumbar spine laminectomy (major surgery). The blood loss observed was slightly greater (25 mL) than the expected maximum in a patient with normal haemostasis (20 mL). No transfusions or additional doses of VWF/FVIII concentrate were needed for this patient. Postoperatively, the patient developed bruising and induration, and the wound had healed by the time the patient was discharged. The investigator later noted that these issues were due to an intraoperative complication.

Dosing for surgical procedures

Exposure to wilate® during surgeries and the dosages required are summarized in Table 4. For loading and maintenance infusions, patients received wilate® for a mean of 7.7 days (median: 7.0; range: 3–17), and received a mean total cumulative dose of 293.1 IU VWF:RCo kg^{-1} (median: 270.6; range: 66–700). The mean duration of major surgery was 9 days (median: 8.0; range: 4–17) and mean total cumulative dose was 368.9 IU kg^{-1} (median: 360; range: 147–700). The mean duration of minor surgery was 4.7 days (median: 4.0; range: 3–10) and the mean total cumulative dose was 116.2 IU kg^{-1} (median: 127.5; range: 66–163). The mean daily doses administered over time following major and minor surgeries are shown in Fig. 1. Patients with VWD Type 3 had the longest mean exposure time (8.8 days; median: 8.0; range: 4–17) and received the highest mean cumulative doses (330.7 IU VWF:RCo kg^{-1}; median: 340.4; range: 107–700). This was not unexpected as these patients have the most severe form of VWD, and a higher proportion of major surgeries were performed in VWD Type 3 patients.

The mean total loading dose was 51.4 IU VWF:RCo kg^{-1} per infusion (median: 52.1; range: 27–77) and the mean maintenance dose was 28.5 IU VWF:RCo kg^{-1} per infusion (median: 28.5; range: 8–63).

Intra- and postoperative blood loss and blood transfusions

Intraoperative blood loss was lower than the maximal expected in 28 of 30 procedures (mean [SD] difference –294.9 [502.2] mL); maximal blood loss was higher than expected during a lumbar laminectomy (25 mL actual vs. 20 mL expected) and a partial amputation of a big toe (50 mL actual vs. 30 mL maximal expected). Greater postoperative bleeding and oozing than the maximal expected was recorded during the lumbar laminectomy and an ankle arthrodesis; the bleeding was not excessive in either case and did not require additional doses of wilate® or transfusions. Based on the algorithm for overall efficacy (Table 1), only the lumbar laminectomy was classified as a treatment failure in cases of higher than expected blood loss. Intraoperative transfusions were electively planned for five patients undergoing major surgeries, but were only required in two patients. In these patients, the mean actual transfusion volume (287.5 mL) was lower than

Table 3. Haemostatic efficacy assessment by severity of surgery (A) and type of VWD (B).

	Surgery type		
(A) Efficacy assessment*	Minor (*N* = 9)	Major (*N* = 21)	All surgeries (*N* = 30)
Success			
N (%)	9 (100)	20 (95.2)	29 (96.7)
Rate (98.75% CI)	1.000 (0.569, 1.000)	0.952 (0.704, 1.000)	0.967 (0.784, 1.000)
Failure†			
N (%)	0 (0)	1 (4.8)	1 (3.3)

	VWD type		
(B) Efficacy assessment*	Type 1 (*N* = 7)	Type 2 (*N* = 2)	Type 3 (*N* = 21)
Success			
N (%)	6 (85.7)	2 (100)	21 (100)
Rate (98.75% CI)	0.857 (0.328, 0.999)	1.000 (0.079, 1.000)	1.000 (0.785, 1.000)
Failure†			
N (%)	1 (14.3)	0 (0)	0 (0)

N, number of surgeries.
*Derived overall assessment = Based on the derived overall assessment (derived from the intra- and postoperative assessment of the IDMC, based on blood loss, transfusion requirements and postoperative bleeding and oozing).
†Primary adjudication.

Table 4. Summary of wilate® doses administered during the study.

Parameters	Major	Minor	Total
Exposure days*	*N = 21*	*N = 9*	*N = 30*
	9.0 ± 3.5	4.7 ± 2.4	7.7 ± 3.8
	8.0 (4–17)	4.0 (3–10)	7.0 (3–17)
Total dose, IU VWF:RCo*	*N = 21*	*N = 9*	*N = 30*
	25 933 (12 257)	7389 (3090)	20 370 (13 452)
	27 000 (11 000–60 000)	6500 (3000–13 000)	16 000 (3000–60 000)
Total dose, IU VWF:RCo kg^{-1}*	*N = 21*	*N = 9*	*N = 30*
	368.9 ± 139.8	116.2 ± 32.2	293.1 ± 166.3
	360.0 (147–700)	127.5 (66–163)	270.6 (66–700)
Preoperative loading dose, IU per procedure	*N = 21*	*N = 9*	*N = 30*
	4691 (2205)	2667 (1146)	4083 (2146)
	4000 (3000–13 000)	3000 (1000–5000)	4000 (1000–13 000)
Preoperative loading dose, IU kg^{-1} per procedure	*N = 21*	*N = 9*	*N = 30*
	67.7 (27.3)	41.9 (15.0)	60.0 (26.8)
	61.4 (41–169)	37.5 (27–77)	57.3 (27–169)
Preoperative loading dose†, IU per infusion	*n = 26*	*n = 9*	*n = 35*
	3789 (1176)	2667 (1146)	3500 (1254)
	4000 (2000–7000)	3000 (1000–5000)	3000 (1000–7000)
Preoperative loading dose†, IU kg^{-1} per infusion	*n = 26*	*n = 9*	*n = 35*
	54.7 (10.1)	41.9 (15.0)	51.4 (12.6)
	55.5 (36–69)	37.5 (27–77)	52.1 (27–77)
Maintenance dose, IU per infusion	*n = 214*	*n = 31*	*n = 245*
	2085 (1023)	1371 (670)	1994 (1012)
	2000 (600–8000)	1000 (500–3000)	2000 (500–8000)
Maintenance dose, IU kg^{-1} per infusion	*n = 214*	*n = 31*	*n = 245*
	29.6 (9.3)	21.6 (6.4)	28.5 (9.3)
	30.0 (8–63)	20.6 (14–38)	28.5 (8–63)

N, number of surgeries; *n*, number of infusions.
*Includes wilate® administrations for loading and maintenance infusions only.
†Three patients received two loading doses and one patient received three loading doses. These additional loading doses were not administered due to insufficient efficacy of the initial dose, but due to delays in the start of surgery or to a presurgical procedure.

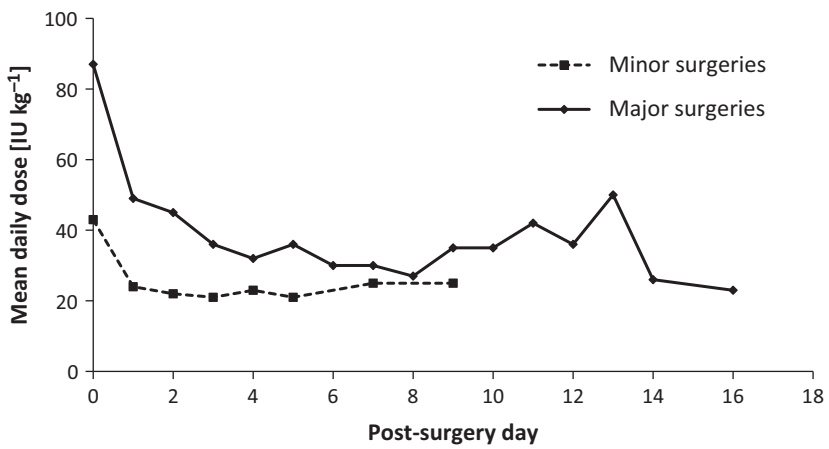

Fig. 1. Mean daily dose of VWF/FVIII in major and minor surgeries.

the mean expected volume (1190 mL). Aminocaproic acid and tranexamic acid were planned and administered intraoperatively in five patients.

Plasma levels of haemostatic parameters over time

FVIII:C, VWF:RCo and VWF:Ag plasma levels were monitored throughout the postoperative period. Figure 2 shows mean peak and trough levels over time in all surgeries (Fig. 2a), major surgeries (Fig. 2b) and minor surgeries (Fig. 2c). Mean plasma levels of haemostatic parameters remained stable during maintenance dose administrations. While VWF:RCo trough levels were sometimes low between maintenance doses, FVIII levels were sufficient to maintain haemostasis. Six patients had instances of FVIII:C values >250 IU dL^{-1} (range: 256–395) during maintenance infusions; however, in most cases, this correlated with higher dosing, which was corrected by decreasing the dose. No accumulation of FVIII:C was observed over time and no thromboembolic events occurred.

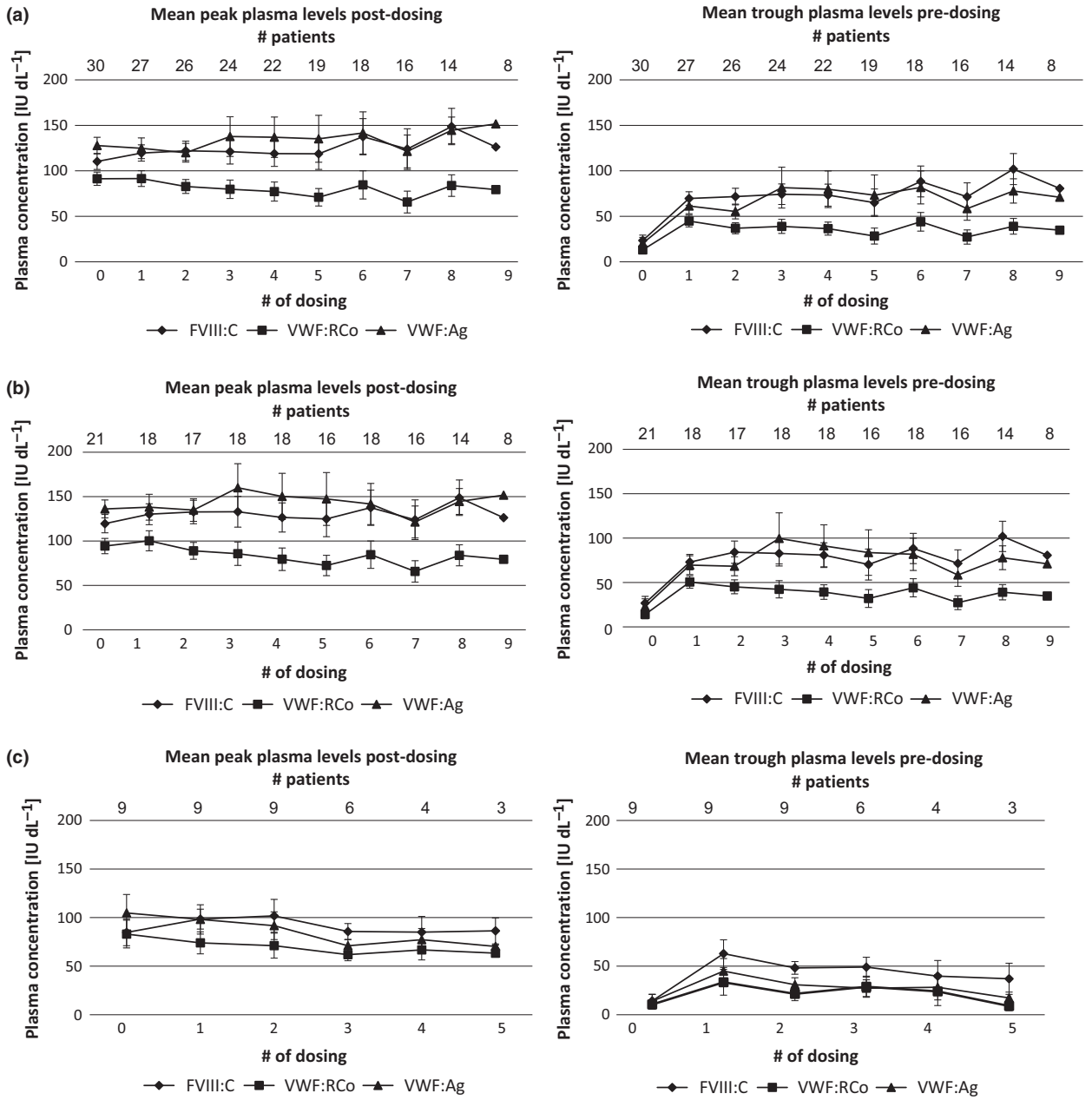

Fig. 2. Mean peak plasma VWF/FVIII levels post-dosing and mean trough plasma VWF/FVIII levels pre-dosing. Mean peak and trough plasma concentrations of VWF and FVIII over time in the ITT population are shown by dose in all surgeries (a), major surgeries (b) and minor surgeries (c). Only the maintenance infusions with values available for more than one patient are shown. Numbers at the top of each figure represent the number of patients contributing to that particular time point. 0 = presurgery loading dose. Error bars represent the standard error of the mean.

Recovery investigations over time

The majority of IVR values for FVIII and VWF were in the expected range over the entire study period (Fig. 3). Several patients had IVR values that were higher or lower than physiologically plausible, but nearly all of these outliers were present at only one or two time points, and could be attributed to possible errors in the assay or sample handling.

Safety and tolerability

The mean cumulative dose per procedure for the 30 surgical procedures (in 28 patients) was 24 653 IU (739 590 IU overall). Of 262 exposure days to

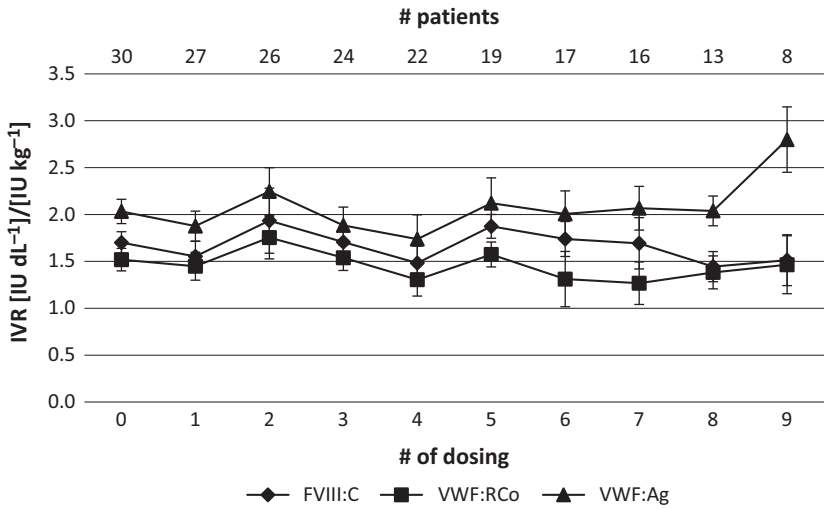

Fig. 3. Observed IVR values over time by maintenance dose. Mean IVR values over different wilate® administrations are shown. Only the maintenance infusions with values available for more than one patient are shown. Numbers at the top of each figure represent the number of patients contributing to that particular time point. 0 = presurgery loading dose. Error bars represent the standard error of the mean.

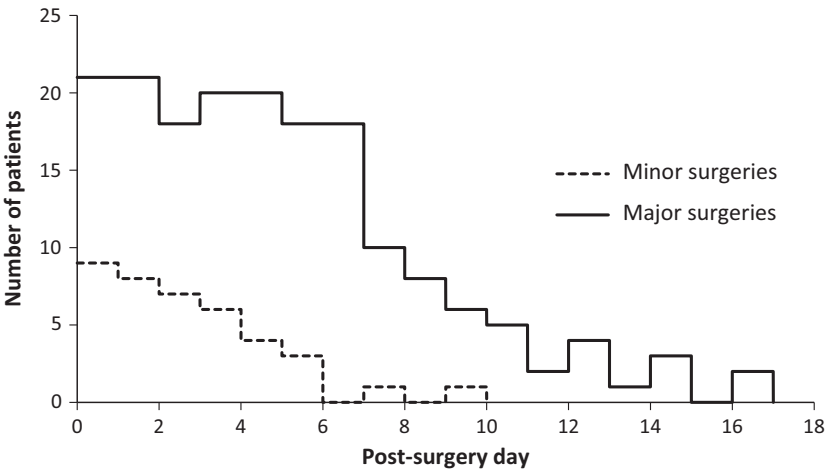

Fig. 4. Treatment duration in patients after major and minor surgery.

wilate®, 250 were for surgical prophylaxis. The duration of wilate® treatment following major and minor surgery is shown in Fig. 4.

Eight non-serious adverse events in five patients were considered to be probably related to treatment, and included hypersensitivity, chest discomfort, feeling hot, dizziness and decrease in blood pressure. All were mild or moderate in intensity, and all resolved without sequelae. One of these patients experienced moderate hypersensitivity that led to discontinuation of wilate® during the presurgery loading infusion. The patient subsequently withdrew consent and received no further wilate® infusions. The investigator/nurse noted that the patient appeared extremely anxious and time-conscious and that the symptoms were most likely related to anxiety. Postoperative haematomas occurred in four procedures (three patients); however, none required evacuation.

There were no thromboembolic events and antithrombotic agents were not administered to any patients. No VWF or FVIII inhibitors or virus seroconversions were observed.

Discussion

This prospective study addressed the efficacy and safety of wilate® in the maintenance of haemostasis in patients with inherited VWD undergoing surgery. The study used stringent, objective efficacy criteria to assess efficacy during and after surgical procedures, as well as blinded adjudication of all efficacy assessments by the IDMC and statistical analysis, to provide a conservative, unbiased efficacy assessment of wilate®. The use of objective assessment criteria for surgical prophylaxis in this study is in line with recently developed objective efficacy criteria in non-surgical settings [23].

The success of wilate® in surgical prophylaxis was established at the planned interim analysis in all but one (29/30) surgical procedures. As the prespecified success criteria were met, the study was terminated early as recommended by the IDMC. The overall success rate was 96.7% (98.75% CI: 0.784, 1.000). This is particularly noteworthy in the light of the high percentage of major surgeries performed (70%) and that

70% were in VWD Type 3. All procedures in Type 3 patients were successful. In addition, although the number of paediatric procedures was low (three surgeries in three patients), efficacy was rated as excellent or good in all procedures.

The overall haemostatic efficacy rate obtained in this study is in line with a previous pooled analysis of four prospective clinical trials that included evaluation of wilate® efficacy during surgery [7]. In the pooled analysis (53 rated procedures in 32 patients), efficacy was excellent or good in 51 of 53 (96%) procedures. Also consistent with the results from this study are those reported in VWD patients receiving wilate® in real-life, clinical settings in the UK [8,24]. Based on a subjective 4-point scale, surgical efficacy of wilate® in the UK cohort was rated excellent or good in 66 of 70 (94%) procedures (34 patients). Therefore, despite the objective, more stringent efficacy criteria used in this study, efficacy rates were similar to those reported in studies using more subjective criteria.

A number of studies evaluating the efficacy of VWF/FVIII concentrates other than wilate® in a surgical setting have been published. In two prospective studies, Humate-P® was deemed effective (excellent or good overall efficacy) in 94.3% and 100% of 35 elective surgeries and 42 urgent surgical procedures, respectively [13,14]. The overall number of patients with VWD Type 3 was much lower in these studies compared with this study (37% and 21% vs. 70%), although the proportion of major procedures was comparable (71% and 60% vs. 70%). In a review of several VWF/FVIII concentrates other than wilate®, efficacy rates during surgery ranged from 91% to 100%, as assessed by mostly subjective criteria [10].

In this study, wilate® dosing was comparable or lower than dosing reported for other concentrates in VWD patients undergoing surgery. In this study, patients received a median loading dose per infusion of 52.1 IU VWF:RCo kg^{-1} (range: 27–77) compared with 82.3 IU VWF:RCo kg^{-1} (range: 32.5–216.8) with Humate-P® and 62.4 IU VWF:RCo kg^{-1} (interquartile range: 50.1–87.0) with Haemate® P [12,13]. For maintenance infusions, in this study, patients received a median of 28.5 IU VWF:RCo kg^{-1} (range: 8–63), while in the studies with Humate-P® and Haemate® P, median maintenance doses were 52.8 IU VWF:RCo kg^{-1} (range: 24.2–196.5) and 38.9 to 46.8 IU VWF:RCo kg^{-1}, respectively [12,13].

Although rare, thromboembolic complications are a concern in surgeries covered with any VWF/FVIII concentrate due to the potentially frequent and high doses administered over a longer period and possible accumulation of VWF and FVIII. Plasma levels of VWF and FVIII remained stable during wilate® maintenance dose administrations and no sustained FVIII accumulation over time or thromboembolic events were observed during this study. In contrast, accumulation of FVIII has been observed in studies with other VWF/FVIII concentrates [12,14]. In one study with Humate-P®, a modest rise in FVIII:C was observed over time in some patients, with nine patients experiencing FVIII:C >200 IU dL^{-1} in 52 instances [14]. In another study with Haemate® P, FVIII:C progressively increased before each therapeutic/maintenance dose, suggesting some accumulation of FVIII over time [12]. Additionally, one patient developed a pulmonary embolism during the study, with a high FVIII:C plasma level of 450 IU dL^{-1} recorded the previous day. The data in this study indicate that a product with a 1:1 VWF to FVIII ratio can be easily dosed using a FVIII haemostatic target. In addition, dosing can be based on either VWF:RCo or FVIII:C IU as observed plasma levels run in parallel after repeat dosing. The parallel decay curves for VWF and FVIII activity was predicted from the single-dose pharmacokinetics of wilate®, which was shown to be significantly different from other VWF concentrates [17]. FVIII accumulation is not seen in these data, which should reduce the issue of increased thrombogenicity with multiple dosing that has been reported with other VWF/FVIII concentrates. Moreover, using a FVIII assay to predict VWF levels enables more convenient monitoring. Given that peak FVIII:C plasma levels were mostly between 125 and 150% and trough levels between 75 and 100% during major surgeries, it is likely that haemostasis could be achieved with 25–30% lower doses of wilate® if FVIII:C was used as a marker for adequacy of haemostasis instead of targeting presumed haemostatic levels of VWF:RCo. Such an approach would avoid reaching unnecessarily high levels of FVIII:C, which are implicated in increased thrombotic risk, and in most cases would be easier to perform and be potentially more reliable.

No treatment-related severe or serious adverse events occurred in this study. Importantly, no cases of VWF or FVIII inhibitors were observed and no virus seroconversions occurred. We therefore conclude that wilate® is well tolerated and effective in achieving surgical haemostasis in patients with all types of VWD with no accumulation of FVIII after repeat dosing.

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Disclosures

M. Serban has conducted clinical trials for Biotest, Baxter, Bayer, Novo Nordisk, CSL Behring and attendances of international congresses on haemophilia have been supported by Biotest, Baxter, Novo-Nordisk, CSL Behring. C. M. Kessler has served on advisory boards for Baxalta, Bayer, Biogen, Grifols, Novo Nordisk, Octapharma, Pfizer and Roche. He has received research funding from Baxalta, Bayer, Grifols, Novo Nordisk, Octapharma and Roche. He has received honoraria from Octapharma for consulting. A. Srivastava stated that he had no interests which might be perceived as posing a conflict or bias. B. A. Schwartz and S. Werner are employees of Octapharma USA Inc. All authors were involved in the design of the study and in analysis and interpretation of the study data. A. Srivastava, C. M. Kessler and B. A. Schwartz reviewed the literature for assessment and discussion of the results. All authors critically reviewed the manuscript and approved the final version for submission. Support for writing and formatting was provided by nspm ltd, Meggen, Switzerland.

References

1 Lillicrap D. von Willebrand disease: advances in pathogenetic understanding, diagnosis, and therapy. *Blood* 2013; **122**: 3735–40.

2 Nichols WL, Hultin MB, James AH *et al.* von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). *Haemophilia* 2008; **14**: 171–232.

3 Kreuz W. von Willebrand's disease: from discovery to therapy – milestones in the last 25 years. *Haemophilia* 2008; **14**(Suppl. 5): 1–2.

4 Goodeve A, James P. von Willebrand Disease. Available at http://www.ncbi.nlm.nih.gov/books/NBK7014/. Accessed July 24, 2014.

5 Mannucci PM, Kyrle PA, Schulman S, Di Paola J, Schneppenheim R, Cox Gill J. Prophylactic efficacy and pharmacokinetically guided dosing of a von Willebrand factor/factor VIII concentrate in adults and children with von Willebrand's disease undergoing elective surgery: a pooled and comparative analysis of data from USA and European Union clinical trials. *Blood Transfus* 2013; **11**: 533–40.

6 Tuohy E, Litt E, Alikhan R. Treatment of patients with von Willebrand disease. *J Blood Med* 2011; **2**: 49–57.

7 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**: 1072–9.

8 Batty P, Chen YH, Bowles L, Hart DP, Platton S, Pasi KJ. Safety and efficacy of a von Willebrand factor/factor VIII concentrate (Wilate®): a single centre experience. *Haemophilia* 2014; **20**: 846–53.

9 Siboni SM, Biguzzi E, Solimeno LP *et al.* Orthopaedic surgery in patients with von Willebrand disease. *Haemophilia* 2014; **20**: 133–40.

10 Franchini M. Surgical prophylaxis in von Willebrand's disease: a difficult balance to manage. *Blood Transfus* 2008; **6**(Suppl. 2): s33–8.

11 Hernandez-Navarro F, Quintana M, Jimenez-Yuste V, Alvarez MT, Fernandez-Morata R. Clinical efficacy in bleeding and surgery in von Willebrand patients treated with Fanhdi® a highly purified, doubly inactivated FVIII/VWF concentrate. *Haemophilia* 2008; **14**: 963–7.

12 Lethagen S, Kyrle PA, Castaman G, Haertel S, Mannucci PM, Haemate® P Surgical Study Group. von Willebrand factor/factor VIII concentrate (Haemate® P) dosing based on pharmacokinetics: a prospective multicenter trial in elective surgery. *J Thromb Haemost* 2007; **5**: 1420–30.

13 Thompson AR, Gill JC, Ewenstein BM, Mueller-Velten G, Schwartz BA. Successful treatment for patients with von Willebrand disease undergoing urgent surgery using factor VIII/VWF concentrate (Humate-P®). *Haemophilia* 2004; **10**: 42–51.

14 Gill JC, Shapiro A, Valentino LA *et al.* von Willebrand factor/factor VIII concentrate (Humate-P®) for management of elective surgery in adults and children with von Willebrand disease. *Haemophilia* 2011; **17**: 895–905.

15 Gill JC, Mannucci PM. Thromboembolic incidence with transiently elevated levels of coagulation factors in patients with von Willebrand disease treated with VWF:FVIII concentrate during surgery. *Haemophilia* 2014; **20**: e404–6.

16 Stadler M, Gruber G, Kannicht C *et al.* Characterisation of a novel high-purity, double virus inactivated von Willebrand factor and factor VIII concentrate (Wilate®). *Biologicals* 2006; **34**: 281–8.

17 Kessler CM, Friedman K, Schwartz BA, Gill JC, Powell JS, Wilate PK Study Investigators. The pharmacokinetic diversity of two von Willebrand factor (VWF)/factor VIII (FVIII) concentrates in subjects with congenital von Willebrand disease. Results from a prospective, randomised crossover study. *Thromb Haemost* 2011; **106**: 279–88.

18 Svae TE, Biesert L, Neisser-Svae A, Kannicht C, Romisch J. On "Composition, quality control, and labeling of plasma-derived products for the treatment of von Willebrand disease" (Semin Thromb Hemost 2006; 32: 529–36). *Semin Thromb Hemost* 2007; **33**: 215–6.

19 Berntorp E, Windyga J, European Wilate® Study Group. Treatment and prevention of acute bleedings in von Willebrand disease – efficacy and safety of Wilate®, a new generation von Willebrand factor/factor VIII concentrate. *Haemophilia* 2009; **15**: 122–30.

20 Halimeh S, Krumpel A, Rott H *et al.* Long-term secondary prophylaxis in children, adolescents and young adults with von Willebrand disease. Results of a cohort study. *Thromb Haemost* 2011; **105**: 597–604.

21 Nowak-Gottl U, Krumpel A, Russo A, Jansen M. Efficacy and safety of Wilate® in paediatric VWD patients under 6 years of age – results of a prospective multicentre clinical study including recovery information. *Haemophilia* 2013; **19**: 887–92.

22 Guideline for good clinical practice E6(R1). Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf. International Conference on Harmonisation of Technical requirements for Registration of Pharmaceuticals for Human Use 1996. Accessed May 1, 2016.

23 Kessler CM, Windyga J, Schwartz BA, Knaub S. Use of objective efficacy criteria for evaluation of von Willebrand factor/factor VIII concentrates. *Blood Coagul Fibrinolysis* 2012; **23**: 262–7.

24 Khair K, Batty P, Riat R *et al.* Wilate use in 47 children with von Willebrand disease: the North London paediatric haemophilia network experience. *Haemophilia* 2015; **21**: e44–50.

