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LETTER TO THE EDITOR

An open-label, multi-centre, post-marketing study to assess the efficacy and safety of a plasma-derived VWF/FVIII concentrate in patients with von Willebrand disease

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, and is estimated to affect 0.1%–1% of the general population[1]; the range in prevalence is likely due to the diagnostic criteria used to make the VWD diagnosis, on which there is currently no clear consensus. Plasma-derived von Willebrand Factor (VWF)/factor VIII (FVIII) (pdVWF/FVIII; Voncento®, CSL Behring, Germany) is a high-concentration, low-volume, high-purity concentrate with an average VWF:RCo/FVIII ratio of 2.4:1 which is approved for prophylaxis and treatment of haemorrhage or prevention and treatment of surgical bleeding in patients with VWD, when desmopressin (DDAVP) treatment alone is ineffective or contraindicated. pdVWF/FVIII has been shown to be well-tolerated and to provide excellent haemostatic efficacy in the treatment and prevention of bleeds for both adult and paediatric patients with VWD.[2–5]

The aim of this post-marketing study was to collect long-term data on the haemostatic efficacy and safety of pdVWF/FVIII in patients with VWD requiring a VWF-containing product for prophylaxis or on-demand therapy, including during surgery. This study included patients of all ages with severe type 1 or 2A VWD (VWF:RCo < 20%), or type 3 VWD, in line with the scientific guidelines from the European Medicines Agency (EMA) for the clinical investigation of human plasma-derived VWF products.[6] Ethics approval and informed consent were obtained prior to enrolment and the trial is registered at ClinicalTrials.gov as NCT02552576.

The assigned treatment regimen was based on disease severity as judged by the study investigators, based on the patient's bleeding history and previous VWF treatment. For on-demand treatment of both adult and paediatric patients, usually 40–80 IU/kg of VWF:RCo corresponding to around 20–40 IU FVIII:C/kg body weight were recommended to achieve haemostasis. For long-term prophylaxis, 25–40 IU of VWF:RCo/kg body weight and 40–80 IU VWF:RCo/kg were considered for adult and paediatric (<12 years) patients, respectively, at a frequency of 1–3 times per week. The clinical efficacy parameters assessed were pdVWF/FVIII usage, haemostasis assessment for each bleeding event by the investigator and subject, and surgeon's assessment of blood loss during a surgical procedure (judged as 'less', 'equivalent' or 'more' compared with the expected blood loss from a patient without a bleeding disorder undergoing the same procedure). The severity of non-surgical bleeding (NSB) events was assessed by the investigator as either major/life-threatening (any bleeding into a joint, muscle, or in the brain, or a mucosal bleeding of the gastrointestinal tract, excluding nasal or oral bleeding) or minor/moderate (all other NSB events, unless the investigator assessment noted otherwise). Clinical assessments of haemostatic efficacy were based on a four-point grading scale: 'excellent' if haemostasis or cessation of bleeding was achieved, 'good' if slight oozing or partial but adequate control of bleeding was achieved and the patient did not require additional product for unplanned treatment, 'moderate' if moderate bleeding or moderate control of bleeding was achieved and the patient required additional product for unplanned treatment, or 'none' if severe uncontrolled bleeding was observed. Safety assessments included the nature and incidence of adverse events (AEs), including serious AEs (SAEs), and the incidence of VWF and FVIII inhibitors.

A total of 25 subjects were treated with pdVWF/FVIII: 14 received regular prophylaxis and 11 on-demand treatment. The mean age was 35.8 years, with four patients <12 years (one patient in the on-demand arm and three in the prophylaxis arm); patient demographic information is provided in Table 1. In both treatment arms, the majority of patients had type 3 VWD, similar to the distribution of VWD type in the previous adult/adolescent study,[2] albeit the number of patients with type 3 was higher in the prophylaxis arm. All 11 patients in the on-demand arm and 10 patients in the prophylaxis arm completed 12 months of treatment in the study.

The 11 patients in the on-demand arm experienced a total of 82 NSB events, all minor/moderate in severity, and the 14 patients in the prophylaxis arm experienced a total of 78 NSB events of which the majority were minor/moderate in severity (Table 2). There were eight NSB events rated as major/life-threatening in severity in five patients in the prophylaxis arm; five were mucosal bleeds (four gastrointestinal and one uterine) and three were joint bleeds (two elbow and one knee). Of the total NSB events, 69 (on-demand arm) and 72 (prophylaxis arm) were treated with pdVWF/FVIII, predominantly with 1 infusion (55.1% and 70.8%, respectively). The median annualised bleeding rate (ABR) was 2.99 for all NSB events and 0.95

TABLE 1 Patient demographics and baseline characteristics.

Characteristic	On-demand ($n = 11$)	Prophylaxis ($n = 14$)	Overall ($n = 25$)
Sex, *n* (%)			
Male	7 (63.6)	6 (42.9)	13 (52.0)
Female	4 (36.4)	8 (57.1)	12 (48.0)
Age (years)			
Mean (SD)	37.2 (18.20)	34.6 (20.44)	35.8 (19.13)
<12 years, *n* (%)	1 (9.1)	3 (21.4)	4 (16.0)
≥12–<18 years, *n*	0	0	0
≥18 years, *n* (%)	10 (90.0)	11 (78.6)	21 (84.0)
VWD phenotype, *n* (%)			
1	2 (18.2)	0	2 (8.0)
2A	3 (27.3)	2 (21.4)	6 (24.0)
3	6 (54.5)	11 (78.6)	17 (68.0)
Previous treatment, *n* (%)			
Any previous treatment	10 (90.9)	14 (100)	24 (96.0)
Type of treatment			
FVIII concentrate	5 (45.5)	2 (14.3)	7 (28.0)
VWF concentrate[a]	5 (45.5)	13 (92.9)	18 (72.0)
Treatment modality			
Prophylaxis	1 (9.1)	10 (71.4)	11 (4.0)
On-demand	9 (81.8)	7 (50.0)	16 (64.0)

Abbreviations: SD, standard deviation; VWD, von Willebrand disease.
[a]Details regarding type of VWF concentrate (e.g., plasma-derived or recombinant, with or without FVIII) were not recorded.

for spontaneous bleeding events in the on-demand arm, and 4.36 for all NSB events and 3.33 for spontaneous bleeding events in the prophylaxis arm. The corresponding numbers of NSB events for the 12 months prior to study entry were 4.0 and 2.0 for the on-demand arm and 6.5 and 4.5 for the prophylaxis arm, respectively. Haemostatic efficacy was rated as excellent/good by the investigator for the majority of NSB events (58 [84.1%] for the on-demand arm, 64 [88.9%] for the prophylaxis arm); for the remaining events, haemostatic efficacy was assessed as moderate. The patient's assessment of haemostatic efficacy based on assessment of each bleeding day (when the bleed occurred and while it was ongoing) was generally slightly lower than the investigator's assessment, with higher proportions of 'moderate' or 'none' ratings. In the on-demand arm, patients assessed the haemostatic efficacy of pdVWF/FVIII as excellent for 14 bleeding days (10.0%), good for 77 days (55.0%), and moderate for 49 days (35.0%), while in the prophylaxis arm patients assessed the haemostatic efficacy of pdVWF/FVIII as excellent for 52 bleeding days (24.0%), good for 45 days (20.7%) and moderate for 14 days (6.5%). A single patient with type 2A VWD accounted for the remaining 106 bleeding days (48.8%) in the prophylaxis arm. The haemostatic efficacy for these was assessed as 'none' and the patient withdrew their informed consent after 8 months in the study due to a lack of treatment response to the four events that were the cause of the 106 bleeding days. This patient had also reported a lack of response to their prior treatment with a different pdVWF/FVIII product (Fahndi), and the final diagnosis for these gastrointestinal bleeds was confirmed as small intestine angiodysplasia.

Haemostatic efficacy in the nine surgical events in the on-demand arm were all rated as excellent (44.4%) or good (55.6%). Blood loss during surgery was assessed as equivalent to that expected in eight events, and less than expected in the remaining event. Four surgical events occurred in the prophylaxis arm; haemostatic efficacy was rated as excellent in all three events assessed, with blood loss equivalent to that expected in two events and less than expected in one event (assessment was missing for the fourth event).

Overall, patients across the entire study received a median (range) of 52.0 (3–196) infusions with a median dose of 41.3 (25.6–115.5) IU/VWF:RCo/kg per infusion. As would be expected, the number of infusions in patients receiving on-demand treatment was lower than those receiving scheduled, prophylactic treatment, with a median of 16.0 (3–90) infusions in the on-demand arm versus 106.5 (34–196) in the prophylactic arm. The patient who received a total of 34 doses in the prophylactic arm was assigned to twice-weekly prophylaxis, but was later lost to follow-up with data only available for three months.

The paediatric patient in the on-demand arm experienced a total of four NSB events, with the haemostatic efficacy of pdVWF/FVIII rated as excellent in all events and a median (range) total dose per bleeding event of 177.0 (54–432) IU VWF:RCo/kg. The three paediatric patients in the prophylaxis arm experienced a total of 33 NSB events, all but one were minor/moderate in severity. Haemostatic efficacy was

TABLE 2 Efficacy outcomes in the on-demand and prophylaxis treatment arms.

Parameter	On-demand ($n = 11$)	Prophylaxis ($n = 14$)
Total number of NSB events, *n* (%)	82 (100)	78 (100)
Severity of the bleed, *n* (%)		
Minor/Moderate	82 (100)	70 (89.7)
Major/Life-threatening	0	8 (10.3)
Nature of the bleed, *n* (%)		
Spontaneous	72 (87.8)	44 (56.4)
Traumatic	10 (12.2)	33 (42.3)
Post-surgery	0	1 (1.3)
Location of bleed, *n* (%)		
Mucosal	51 (62.2)	36 (46.2)
Joint[a]	4 (4.9)	16 (20.5)
Muscle	10 (12.2)	6 (7.7)
Other[b]	17 (20.7)	20 (25.6)
Number of infusions of pdVWF/FVIII required, *n* (%)		
0	13 (15.9)	6 (7.7)
1	38 (46.3)	51 (65.4)
2	10 (12.2)	5 (6.4)
>2–≤7	18 (22.0)	14 (17.9)
>7	3 (3.7)[c]	2 (2.6)[d]
Duration of treatment period (days) per patient,[e] median (range)	372.0 (364–389)	373.0 (155–391)
Total treated bleeds, median (range)		
Number of bleeding events per subject	3.0 (0–25)	4.0 (0–28)
ABR (bleeds/year) per subject[f]	2.99 (0.0–24.6)	4.36 (0.0–26.3)
Treated spontaneous bleeds, median (range)		
Number of bleeding events per subject	1.0 (0–25)	2.5 (0–6)
ABR (bleeds/year) per subject[f]	0.95 (0.0–24.6)	3.33 (0.0–11.3)

Abbreviations: ABR, annualised bleeding rate; NSB, non-surgical bleeding.

[a]Includes the following affected joints: In the on-demand arm three patients (two with Type 3 and one with type 2A VWD) experienced a total of four NSB events in joints. The locations of the joint bleeds were right shoulder ($n = 1$), right ankle ($n = 1$) and left elbow ($n = 2$). In the prophylaxis arm 16 NSB events were reported by six patients, all of whom had Type 3 VWD. The locations of the joint bleeds were left knee ($n = 5$), left wrist ($n = 1$), middle finger ($n = 1$), right elbow ($n = 5$), right elbow and left ankle ($n = 2$), right and left elbow ($n = 1$) and right knee ($n = 1$).

[b]Includes menstrual bleedings and locations such as eye, lip, tongue, nasal, forehead, skin or cheek.

[c]These three events occurred in three patients: an 11-year-old male with type 2A VWD had a minor/moderate NSB event in the muscle that required eight infusions; a 48-year-old male with type 3 VWD had a minor/moderate NSB event in the muscle that required nine infusions; a 36-year-old male with type 3 VWD had a minor/moderate NSB event in the joint that required 21 infusions.

[d]Both of these events occurred in one patient: a 51-year-old female with type 2A VWD experienced a major/life-threatening spontaneous mucosal bleeding event in the gastrointestinal tract requiring 22 infusions of pdVWF/FVIII and transfusions of 5 units of erythrocytes and 6 units of platelets and a minor/moderate spontaneous mucosal bleeding event in the gastrointestinal tract requiring 30 infusions of pdVWF/FVIII and transfusion of 3 units of erythrocytes.

[e]Duration of treatment period (days) = end date of the period minus start date of the period plus 1.

[f]The ABR (bleeds/year) was derived for each subject as: (number of treated bleeding events)/(duration of treatment period) × 365.25.

rated as excellent by the investigator in 32 of these events (97.0%) and moderate in the remaining event (3.0%). The patient's assessment of haemostatic efficacy per bleeding day was excellent (93.9%) or good (6.1%). Patients received a median (range) of 1.0 (1–3) infusions per NSB event, and a median total pdVWF/FVIII dose per event of 171.0 (40–554) IU VWF:RCo/kg.

Overall, seven patients (63.6%) in the on-demand arm reported a total of 13 treatment-related AEs (TEAEs) and 12 patients (85.7%) in the prophylaxis arm reported a total of 84 TEAEs. Two patients reported a total of 3 serious TEAEs: two events of asthma in one patient (on-demand arm; patient had a history of asthma since 1998) and one event of abdominal pain in one patient (prophylaxis arm). Three

of the four paediatric patients, all in the prophylaxis arm, reported a total of 17 TEAEs; these were mostly characteristic for this age group and none were considered related to study medication. None of the serious TEAEs were assessed as being related to the study drug, and no TEAEs leading to study discontinuation or death occurred during the study. No VWF or FVIII inhibitors were observed at any of the timepoints assessed (Screening, Day 1, Month 3, 6, 9, and Final Visit). These results reflect the safety findings of previous clinical studies of pdVWF/FVIII.[2–5,7]

The results of this study are consistent with another pdVWF/FVIII (Haemate® P), where studies have demonstrated efficacy for on-demand and prophylactic treatment and a favourable safety profile in patients with VWD.[8–10] A recombinant VWF (vonicog alfa, Veyvondi®) has also demonstrated safety and efficacy for on-demand treatment of bleeds in patients with VWD, with bleed control rated as excellent/good in all patients (192 bleeds in 22 patients), with a single infusion effective in 81.8% of bleeds.[11]

In conclusion, the results of this post-marketing study in patients with severe VWD were generally consistent with those observed in previous clinical studies, supporting the excellent haemostatic efficacy and tolerability of pdVWF/FVIII for VWD treatment.

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CONFLICT OF INTEREST STATEMENT

WM has received consultant and personal fees from Bayer, Biotest, CSL Behring, Pfizer, Octapharma, LFB, SOBI, Biogen and BPL; SH has received honoraria for speaking from Bayer Healthcare, Baxalta Innovation, Biotest, CSL Behring, Novartis Pharma, Novo Nordisk, Octapharma and Pfizer and research grants from Bayer Healthcare, Baxalta, Biotest, CSL Behring, Novo Nordisk, Octapharma and Pfizer; MP-D has received personal fees from Shire, Novo Nordisk, Amgen, Alexion, Orphan and CSL Behring; JZ has received speaking fees from NovoNordisk, Roche, Shire/Takeda, Novartis, CSL Behring, SOBI, Amgen; BK has received grant/research support from CSL Behring; PC has received grants from CSL Behring, Bayer, Novo Nordisk, Pfizer, and SOBI and personal fees from Bayer, Biogen Idec, Chugai, CSL Behring, Freeline, Novo Nordisk, Pfizer, Roche, Shire/Takeda, and SOBI; SA has received speaker fees from Pfizer, Octapharma, Grifols, LFB, SOBI, Baxalta/Shire, and BPL and travel support from Novo Nordisk, CSL Behring, BPL, Shire, and Octapharma and grant/research support from Grifols, Baxalta, and SOBI; CM has received research support from CSL Behring, Grifols, and Takeda and fees as an advisor and speaker from CSL Behring, LFB, Novo Nordisk, Octapharma, Takeda, and SOBI; TR is an employee of CSL Behring; IP has received unrestricted grant, speaker and consultancy fees from CSL Behring; HP, and JA have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

CSL Behring will only consider requests to share data that are received from systematic review groups or bona-fide researchers. CSL will not process or act on data requests until 12 months after article publication on a public website. A data request will not be considered by CSL unless the proposed research question seeks to answer a significant and unknown medical science or patient care question. Applicable country specific privacy and other laws and regulations will be considered and may prevent sharing of data. Requests for use of the data will be reviewed by an internal CSL review committee. If the request is approved, and the researcher agrees to the applicable terms and conditions in a data sharing agreement, data that has been appropriately anonymized will be made available. Supporting documents including study protocol and Statistical Analysis Plan will also be provided. For information on the process and requirements for submitting a voluntary data sharing request for data, please contact CSL at clinicaltrials@cslbehring.com.

ETHICS STATEMENT

This study was approved by the Independent Ethics Committees/Institutional Review Boards of the participating centres, registered at www.clinicaltrials.gov (NCT02552576), and performed in accordance with the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) Good Clinical Practice guidelines, the Declaration of Helsinki and local regulatory requirements. Written informed consent was obtained before undergoing any study-specific procedures and consent could be withdrawn at any time.

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