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Prophylaxis with recombinant von Willebrand factor in patients with type 3 von Willebrand disease: Results of a post hoc analysis from a phase 3 trial

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Abstract

Objectives: To describe efficacy/safety of recombinant von Willebrand factor (rVWF) prophylaxis in patients with type 3 von Willebrand disease (VWD).

Methods: This post hoc analysis of a phase 3 open-label trial provides a more detailed analysis of adults with type 3 VWD, categorized based on prior treatment at screening: "Prior On-Demand (OD)" (OD VWF; ≥3 documented spontaneous bleeding events [BEs] requiring VWF in previous 12 months) or "Switch" (plasma-derived [pd] VWF prophylaxis for ≥12 months). Annualized bleeding rates (ABRs) were evaluated during 12 months of rVWF prophylaxis versus historical data from medical records.

Results: In the Prior OD group ($n = 10$), mean spontaneous ABR (sABR) for treated BEs was reduced by 91.6% (ratio, 0.08; 95% CI, 0.02–0.45) versus mean historical sABR. In the Switch group ($n = 8$), mean sABR for treated BEs was reduced by 47% (ratio, 0.53; 95% CI, 0.08–3.62). One non-serious adverse event (AE) was considered

possibly related to rVWF. No treatment-related, fatal, or life-threatening serious AEs were reported, and no patient developed VWF inhibitors.

Conclusions: rVWF prophylaxis reduced sABR in type 3 VWD patients previously treated with OD VWF therapy, and maintained a similar level of hemostatic control in those switching from pdVWF prophylaxis to rVWF prophylaxis.

KEYWORDS

bleeding, prophylaxis, recombinant von Willebrand factor, von Willebrand disease type 3

Novelty statements

What is the new aspect of your work?

This analysis provides data for recombinant von Willebrand factor (rVWF) prophylaxis in patients with type 3 von Willebrand disease (VWD), a rare population with limited data available, and highlights the prevalence of untreated bleeding events.

What is the central finding of your work?

rVWF prophylaxis effectively reduced bleeding rates in patients with type 3 VWD previously treated with on-demand VWF, and maintained a similar level of hemostatic control in those patients with type 3 VWD switching from plasma-derived VWF prophylaxis to rVWF prophylaxis.

What is (or could be) the specific clinical relevance of your work?

rVWF prophylaxis may reduce the incidence of bleeding events in patients with type 3 VWD.

1 | INTRODUCTION

With an estimated prevalence of 0.6%–1.3% overall,[1] von Willebrand disease (VWD) is the most common inherited bleeding disorder.[2,3] It is characterized by deficiencies in levels and/or function of von Willebrand factor (VWF), a plasma glycoprotein crucial for normal hemostasis because it mediates platelet adhesion/aggregation and stabilizes factor VIII (FVIII) circulation in blood.[2,4] VWD is subdivided into three main disease types:[2] type 1, which involves quantitative VWF deficiency and accounts for 70%–80% of cases; type 2, which involves dysfunctional VWF in the presence of normal or reduced VWF levels and accounts for ~20% of cases; and type 3, a very rare condition (<5% of cases; prevalence 1–9 per 100 000) that involves almost absence of circulating VWF.[2,5]

Patients with type 3 VWD have a more severe bleeding phenotype (as assessed by Tosetto bleeding scores) than those with types 1 or 2 VWD.[6,7] Epistaxis is reportedly the most prevalent clinical symptom in these patients, followed by hemarthrosis in males and menorrhagia in females.[7] Several bleeding manifestations have been found to be overrepresented in patients with type 3 VWD versus those with type 1 VWD, with ≥5-fold increases observed in the frequency of intracranial or oral cavity bleeding, hemarthrosis, or deep hematomas, and ≥2-fold increase in gastrointestinal (GI) bleeding.[7] Angiodysplasia is the most frequent cause of recurrent GI bleeding in patients with VWD, especially in those who lack high-molecular-weight multimers (i.e., those with type 2 or 3 VWD).[8,9] However, often no cause can be identified owing to the difficulty in diagnosing angiodysplasia.[9] Patients with type 3 VWD also have reduced health-related quality of life compared with those with type 1 and/or 2 VWD.[10–12] In patients with type 3 VWD, replacement therapy with concentrates containing either plasma-derived VWF (pdVWF) or recombinant VWF (rVWF) is the treatment of choice.[2,13] Treatment can be given on demand (OD) to treat bleeding events (BEs) or prophylactically. Long-term VWF prophylaxis has been shown to reduce the risk of recurrent bleeds in patients with severe VWD,[14–17] and recent international management guidelines for VWD conditionally recommend long-term prophylaxis in patients with VWD who have a history of severe/frequent bleeds.[13] However, the evidence base for prophylaxis is limited, and further studies are needed to establish the role of prophylactic therapy in patients with VWD.[13]

In a recent phase 3 study, prophylaxis with rVWF (vonicog alfa, VONVENDI® [US, Japan]/VEYVONDI™ [Europe, Australia], Takeda Pharmaceuticals USA, Lexington, Massachusetts) was shown to reduce treated spontaneous bleeding rates in patients with severe VWD who were previously receiving OD VWF therapy.[18] In the same study, patients switching to rVWF prophylaxis from prophylactic pdVWF concentrates maintained at least the same level of hemostatic control. The observed safety profile of rVWF was consistent with previous studies.[18–20] Here, we report the outcomes of a post hoc analysis of this study, focusing on the efficacy/safety of rVWF

prophylaxis in patients with type 3 VWD. In addition, we provide pharmacokinetic (PK)/pharmacodynamic (PD) data from patients with type 3 VWD receiving rVWF prophylaxis.

2 | MATERIALS AND METHODS

2.1 | Trial summary

This was a post hoc analysis of a phase 3, prospective, open-label, nonrandomized, multicenter study (ClinicalTrials.gov NCT02973087; EudraCT 2016-001478-14) designed to investigate the efficacy, safety, PK, and PD of rVWF when used prophylactically in adults with severe VWD.[18] In summary, two patient cohorts were defined, based on the VWF treatment that enrolled patients received during the 12 months before enrollment. The Prior OD group included patients who were receiving OD VWF treatment at screening and during the 12 months before enrollment, and who had ≥3 documented spontaneous BEs (not including menorrhagia) requiring VWF treatment during the previous 12 months. The "Switch" group included patients who received pdVWF prophylaxis for ≥12 months prior to and at screening.

The planned treatment duration per patient was 12 months, with an actual treatment period of ≤18 months to allow for uninterrupted rVWF prophylaxis in patients progressing or enrolling into a planned phase 3b extension/continuation study. In the Prior OD group, the starting dose regimen was 50 ± 10 IU/kg VWF:ristocetin cofactor activity (VWF:RCo) twice weekly. In the Switch group, the starting dose and frequency were based on each patient's prior pdVWF prophylaxis dosing regimen, with the weekly equivalent (±10%) of pdVWF dose divided into one to three weekly infusions (maximum of 80 IU/kg per infusion). The rVWF dosage could be individualized (≤80 IU/kg per infusion) based on available historical PK data, type and severity of historical BEs, and monitoring of appropriate clinical and laboratory measures.

The study protocol was approved by the respective institutional review boards or ethics committees and applicable regulatory authorities before patient enrollment. The study was conducted in compliance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization. All patients provided written informed consent.

2.2 | Patients

Further details of the entry criteria have been published previously.[18] This post hoc analysis focused on patients with type 3 VWD from the overall study population of patients with severe VWD (defined as a baseline VWF:RCo of <20 IU/dL[21]). Genetic testing and multimer analysis at screening were used to confirm the VWD type; patients with type 3 VWD were required to have a VWF antigen level ≤3 IU/dL. All patients were required to have reliable medical records documenting the management of BEs for ≥12 months prestudy. Patients with inhibitors to VWF and/or FVIII historically or at screening, and those with a history of thromboembolic events, were excluded.

2.3 | Outcome measures

Annualized bleeding rates (ABRs), as assessed by the investigator, were evaluated during the first 12 months of rVWF prophylaxis versus historical data based on reliable medical records, as reported by the investigator. ABRs were assessed for treated spontaneous bleeds, as well as all bleeds (treated and untreated spontaneous and/or traumatic BEs). In addition, the proportions of patients with reduction or preservation success for ABR based on treated spontaneous BEs, all BEs (spontaneous, traumatic, treated, and untreated), all spontaneous BEs (treated and untreated), and all spontaneous joint BEs (treated and untreated) were assessed in intrapatient comparisons of historical versus on-study data. For the Prior OD group, ABR reduction success was defined as a ≥25% reduction in ABR from historical OD treatment to on-study rVWF prophylaxis. For the Switch group, ABR preservation success was defined as an ABR during on-study rVWF prophylaxis equal to or less than the historical ABR during pdVWF prophylaxis. Categorized number of ABRs (0, >0–2, >2–5, or >5) and ABRs by bleed location were also assessed, as was rVWF consumption (number of infusions, mean infusions per week, and weight-adjusted consumption).

PK/PD parameters (including trough FVIII levels and VWF:RCo incremental recovery) after a single rVWF prophylactic dose in the Prior OD group, and after multiple rVWF prophylactic doses in both groups, were derived using noncompartmental methods, as previously described.[18]

Treatment-emergent adverse events (AEs), serious AEs, and AEs of special interest, such as thromboembolic events, hypersensitivity reactions, and immunogenicity (development of neutralizing and binding antibodies to VWF and FVIII) were assessed throughout the study. AEs were categorized according to the Medical Dictionary for Regulatory Activities (version 23.0).

2.4 | Statistical analysis

These post hoc efficacy and safety analyses included all patients with type 3 VWD from the overall study population who received rVWF prophylaxis. PK/PD parameters were estimated in the patient subset who received ≥1 rVWF infusion and had sufficient PK/PD measurements after administration.

Point estimates of the mean and 95% CI for the ratio of ABR during rVWF prophylaxis (on study) to historical ABR were calculated within each group (Prior OD and Switch) using a generalized linear model fitting a negative binomial distribution, including the period (historical or on study) as a fixed effect.[18]

Descriptive statistics were also performed for all endpoints. Clopper–Pearson CIs at the 95% level were provided for percentages when appropriate. Log-transformed PK parameter estimates at the initial visit and study end were analyzed using a linear mixed-effect model with timepoint as an independent fixed effect and patient as a random effect. The model estimates of the least squares (LS) mean, difference between

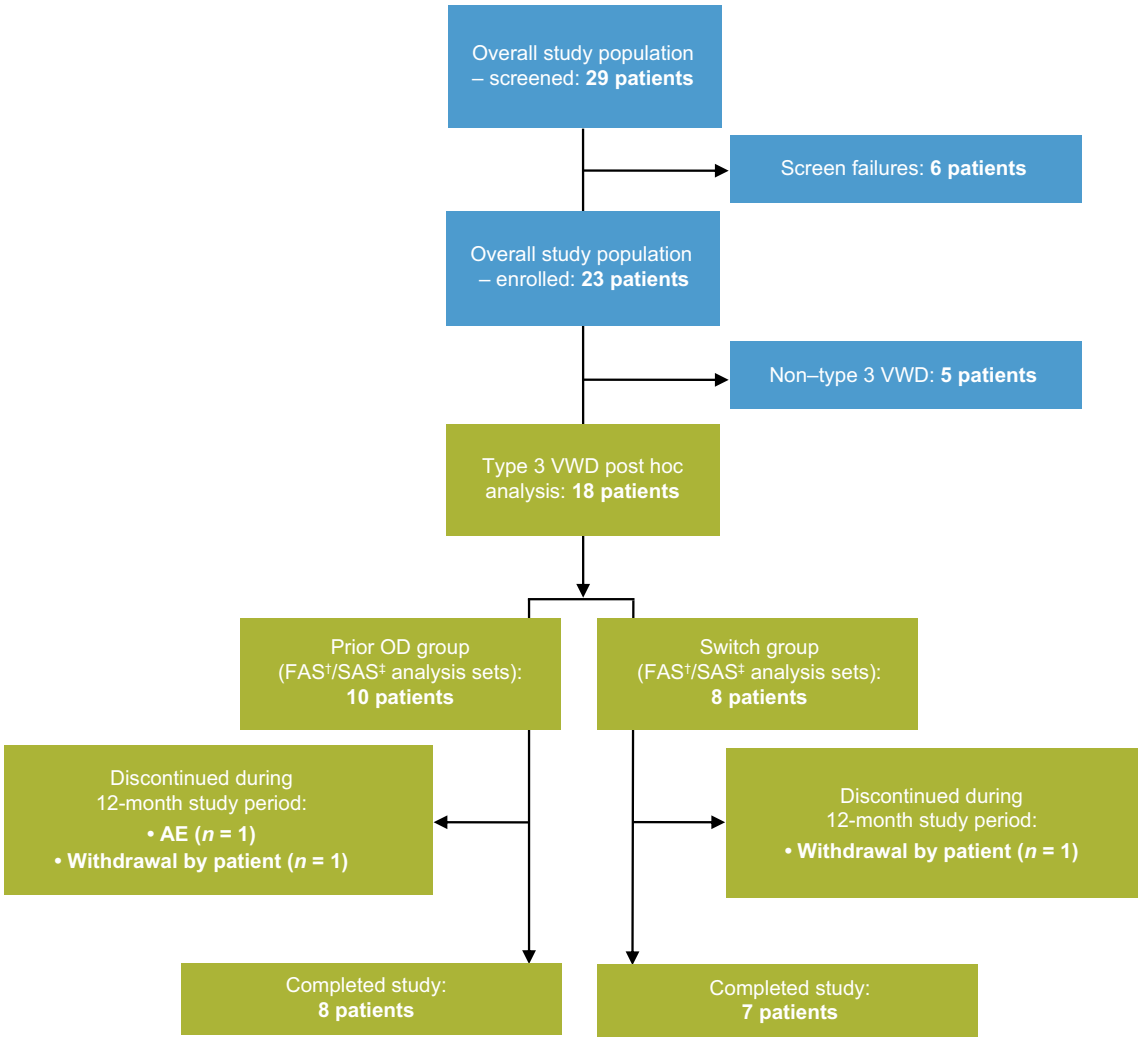

FIGURE 1 Patient disposition. †All enrolled patients with type 3 VWD who received any amount of rVWF. ‡All patients with type 3 VWD who received rVWF prophylaxis. AE, adverse event; FAS, full analysis set; OD, On Demand; SAS, safety analysis set; rVWF, recombinant von Willebrand factor; VWD, von Willebrand disease.

LS mean, and corresponding CI were exponentiated to obtain the geometric LS mean, paired ratio, and corresponding CI. Only PK parameters with $n \geq 3$ for both sample timepoints were included in the analysis.

3 | RESULTS

3.1 | Study population

In total, 18 patients with type 3 VWD (Prior OD group, $n = 10$; Switch group, $n = 8$) were included in the post hoc analyses (Figure 1). Patient baseline characteristics are shown in Table 1.

3.2 | Efficacy

In the Prior OD group, the model-based mean ABR for treated spontaneous BEs was reduced by 91.6% (ratio, 0.08; 95% CI, 0.02–0.45) during the 12-month study period for patients with type 3 VWD, relative to the mean historical ABR. Mean ABR for treated spontaneous BEs decreased from 8.09 (95% CI, 2.37–27.55) to 0.68 (95% CI, 0.15–3.12; Table 2). In the Switch group, the model-based mean ABR for treated spontaneous BEs was reduced by 47% (ratio, 0.53; 95% CI, 0.08–3.62), from 0.95 (95% CI, 0.08–10.69) to 0.50 (95% CI, 0.04–6.02). Findings from the model-based analysis were supported by descriptive statistics (Table 2) and the results were in line with outcomes of the overall study population reported previously.[18]

Overall treated spontaneous ABR reduction success in the Prior OD group was 90.0% (95% CI, 55.5–99.7), whereas treated spontaneous ABR preservation success in the Switch group was 87.5% (95% CI, 47.3–99.7). In total, 72% of patients achieved an ABR of 0 for treated spontaneous BEs while on study, including 8/10 patients in the Prior OD group and 5/8 patients in the Switch group (Table 2) compared with 0 and four patients prestudy, respectively. On-study treated spontaneous BEs were reported in five patients with type 3 VWD (27 BEs). Most of these were mucosal BEs (oral or nasal), with only

TABLE 1 Patient baseline characteristics.

	Prior OD group[a] ($n = 10$)	Switch group[b] ($n = 8$)
Age, years		
Mean ± SD	38.6 ± 15.9	35.8 ± 15.2
Median (range)	37.5 (20–63)	31.0 (18–60)
Sex, *n* (%)		
Female	7 (70.0)	3 (37.5)
Male	3 (30.0)	5 (62.5)
Race, *n* (%)		
White	10 (100)	7 (87.5)
Not reported	0	1 (12.5)
VWF:RCo, IU/dL[c]		
Mean ± SD	<8.0 ± <8.0	<8.0 ± <8.0
Median (range)	<8.0 (<8.0 to <8.0)	<8.0 (<8.0 to <8.0)
FVIII:C, IU/dL		
Mean ± SD	6.5 ± 10.0	6.0 ± 7.2
Median (range)	2.5 (2.0–34.0)	2.0 (1.0–21.0)

Abbreviations: FVIII:C, factor VIII coagulation activity; OD, On Demand; pdVWF, plasma-derived von Willebrand factor; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:RCo, von Willebrand factor:ristocetin cofactor activity.
[a]Patients with VWD type 3 who were treated on-demand with any VWF during the 12-month period before entering this study.
[b]Patients with VWD type 3 who were treated prophylactically with a plasma-derived VWF for ≥12 months before entering this study.
[c]Less than 8.0 IU/dL was below the limit of quantification.

one joint BE in the Prior OD group. No muscle and soft tissue, skin, GI, central nervous system, or body cavity treated spontaneous BEs, and no hematuria, were reported. Historical treated spontaneous GI BEs were reported in two patients (both in the Prior OD group); one patient had no GI BEs during the study, whereas the other patient had one GI BE, but this did not require VWF treatment.

In addition to the above analyses for treated spontaneous BEs, further analyses were performed comparing historic versus on-study ABRs for all types of bleeds (spontaneous and/or traumatic, treated, or untreated; Table 2). Overall, compared with historical data, patients with type 3 VWD in the Prior OD group experienced reductions in BEs and ABRs based on modeling and descriptive statistics, regardless of whether spontaneous and/or traumatic bleeds were considered, and whether they were treated or untreated. Similarly, patients with type 3 VWD in the Switch group experienced preserved hemostatic control overall versus historical data, regardless of bleed type or treatment status (Table 2). However, when untreated BEs were added to assess bleeding rates in the Prior OD group, the mean historical ABR estimate decreased and the mean on-study ABR estimate increased (vs. estimates for treated spontaneous BEs; Table 2). The model-based mean ABR for all BEs was reduced by 33.3% (ratio, 0.67; 95% CI, 0.32–1.37) during the 12-month study period for patients with type 3 VWD, relative to the mean historical ABR (Table 2). In the Switch group, there was a small increase in both the historical and on-study mean ABR estimates when untreated spontaneous BEs were added. The model-based mean ABR for all BEs increased by 9.2% (ratio, 1.09; 95% CI, 0.43–2.78) during the 12-month study period for patients with type 3 VWD, versus the mean historical ABR (Table 2). Results were similar when these analyses were performed for the overall study population, including all 23 patients with severe VWD, independent of the VWD type (Table S1).

When all treated and untreated spontaneous/traumatic BEs were evaluated, the percentage of patients with an ABR of 0 increased in the Prior OD group from 0% at historical baseline (this was expected because inclusion criteria required ≥3 VWF treated bleeds during the 12 months prior to enrollment for this group) to 40.0% through month 12 and in the Switch group from 25.0% to 37.5% (Figure 2A). The proportion of patients in the Switch group with >5 treated/untreated spontaneous/traumatic BEs increased from 12.5% to 37.5% as a result of an increase in untreated and/or traumatic bleeds in two patients. The majority of on-study all-cause treated/untreated BEs were oral or other mucosal BEs (Figure 2B).

In the Prior OD group, the proportion of patients achieving reduction success for all BEs (spontaneous, traumatic, treated, and untreated), all spontaneous BEs (treated and untreated), and all spontaneous joint BEs (treated and untreated) was 70.0% (95% CI: 34.8–93.3), 80.0% (95% CI: 44.4–97.5), and 60.0% (95% CI: 54.1–100.0), respectively. In the Switch group, the proportion of patients achieving preservation success for all BEs was 50.0% (95% CI: 15.7–84.3), for all spontaneous BEs 50.0% (95% CI: 15.7–84.3), and for all spontaneous joint BEs 87.5% (95% CI: 47.3–99.7).

3.3 | rVWF prophylactic consumption

Most patients with type 3 VWD started on a twice-weekly rVWF prophylaxis regimen (Prior OD group, 100%; Switch group, 87.5%). One patient in the Prior OD group and two in the Switch group had ≥1 change in dosing frequency to three times weekly or every 3 days. The mean ± SD total number of infusions per patient and infusions per week per patient were 72.2 ± 38.2 and 1.8 ± 0.6 in the Prior OD group, respectively, and 100.5 ± 15.6 and 2.0 ± 0.1 in the Switch group, respectively. The mean ± SD of average weight-adjusted dose per infusion was 52.3 ± 4.3 IU/kg in the Prior OD group and 48.9 ± 14.8 IU/kg in the Switch group, while the mean ± SD weight-adjusted dose per patient per week was 92.6 ± 33.9 and 96.7 ± 32.4 IU/kg in the Prior OD and Switch groups, respectively.

3.4 | Treatment of breakthrough BEs

In total, 31 all-cause treated BEs occurred, with 12 of these occurring in four patients in the Prior OD group (40.0%) and 19 in three patients in the Switch group (37.5%). Most treated BEs through month 12 were spontaneous and mild or moderate, occurred in mucosal locations, and were treated with one infusion of rVWF (with or without recombinant FVIII [rFVIII]; Table S2). All treated on-study BEs were treated with ≥1

TABLE 2 Summary of efficacy results for patients with type 3 VWD treated with rVWF prophylaxis for ≥12 months.

Endpoint	Number of historical/ on-study BEs	Model based[a]			Descriptive statistics, median ABR (min, max)		Patients with zero BEs on study, % (*n*/*N*)
		Mean ABR (95% CI)		Percentage change from historical (95% CI)			
		Historical	On study		Historical	On study	
Prior OD group ($n = 10$)[b]							
Treated spontaneous bleeds	191/9	8.09 (2.37–27.55)	0.68 (0.15–3.12)	−91.6 (−98.4 to −55.4)	3.0 (3, 155)	0 (0, 5.78)	80.0 (8/10)
Treated spontaneous or traumatic bleeds	197/12	8.04 (2.80–23.09)	1.13 (0.33–3.83)	−85.9 (−96.0 to −50.0)	5.0 (3, 156)	0 (0, 5.78)	60.0 (6/10)
Treated spontaneous or traumatic joint bleeds	23/3	2.30 (1.07–4.93)	0.34 (0.08–1.45)	−85.3 (−97.2 to −23.9)	2.0 (0, 7)	0 (0.0, 1.93)	80.0 (8/10)
All spontaneous bleeds[c]	195/33	5.29 (1.71–16.33)	2.70 (0.85–8.58)	−48.9 (−78.4 to 20.7)	3.5 (3, 158)	0.96 (0, 157.94)	50.0 (5/10)
All spontaneous or traumatic bleeds[c]	201/38	5.39 (1.93–15.07)	3.59 (1.25–10.29)	−33.3 (−67.6 to 37.4)	5.0 (3, 159)	2.35 (0, 157.94)	40.0 (4/10)
All spontaneous or traumatic joint bleeds[c]	23/3	2.30 (1.07–4.93)	0.34 (0.08–1.45)	−85.3 (−97.2 to −23.9)	2.0 (0, 7)	0 (0.0, 1.93)	80.0 (8/10)
Switch group ($n = 8$)[d]							
Treated spontaneous bleeds	50/18	0.95 (0.08–10.69)	0.50 (0.04–6.02)	−47.0 (−92.3 to 262.3)	0.5 (0, 46)	0 (0, 12.08)	62.5 (5/8)
Treated spontaneous or traumatic bleeds	53/19	1.35 (0.10–17.67)	0.71 (0.06–9.32)	−47.3 (−93.9 to 357.4)	0.5 (0, 47)	0 (0, 12.08)	62.5 (5/8)
Treated spontaneous or traumatic joint bleeds	1/1	NE	NE	NE	0 (0, 1)	0 (0, 0.98)	87.5 (7/8)
All spontaneous bleeds[c]	54/43	1.45 (0.25–8.30)	1.51 (0.26–8.86)	4.6 (−61.5 to 184.0)	1.0 (0, 46)	2.97 (0, 26.95)	37.5 (3/8)
All spontaneous or traumatic bleeds[c]	57/46	1.60 (0.28–9.29)	1.75 (0.30–10.25)	9.2 (−57.1 to 178.3)	1.0 (0, 47)	3.89 (0, 26.95)	37.5 (3/8)
All spontaneous or traumatic joint bleeds[c]	2/3	0.12 (0.01–1.77)	0.18 (0.02–2.16)	54.9 (−85.4 to 1540.0)	0 (0, 1)	0 (0, 1.96)	75.0 (6/8)

Abbreviations: ABR, annualized bleeding rate; BE, bleeding event; NE, not evaluated; OD, On Demand; rVWF, recombinant VWF; VWD, von Willebrand disease; VWF, von Willebrand factor.

[a]Based on negative binomial regression model.

[b]Patients who were treated on demand with any VWF during the 12-month period before entering this study.

[c]Treated and untreated BEs.

[d]Patients who were treated prophylactically with a plasma-derived VWF for ≥12 months before entering this study.

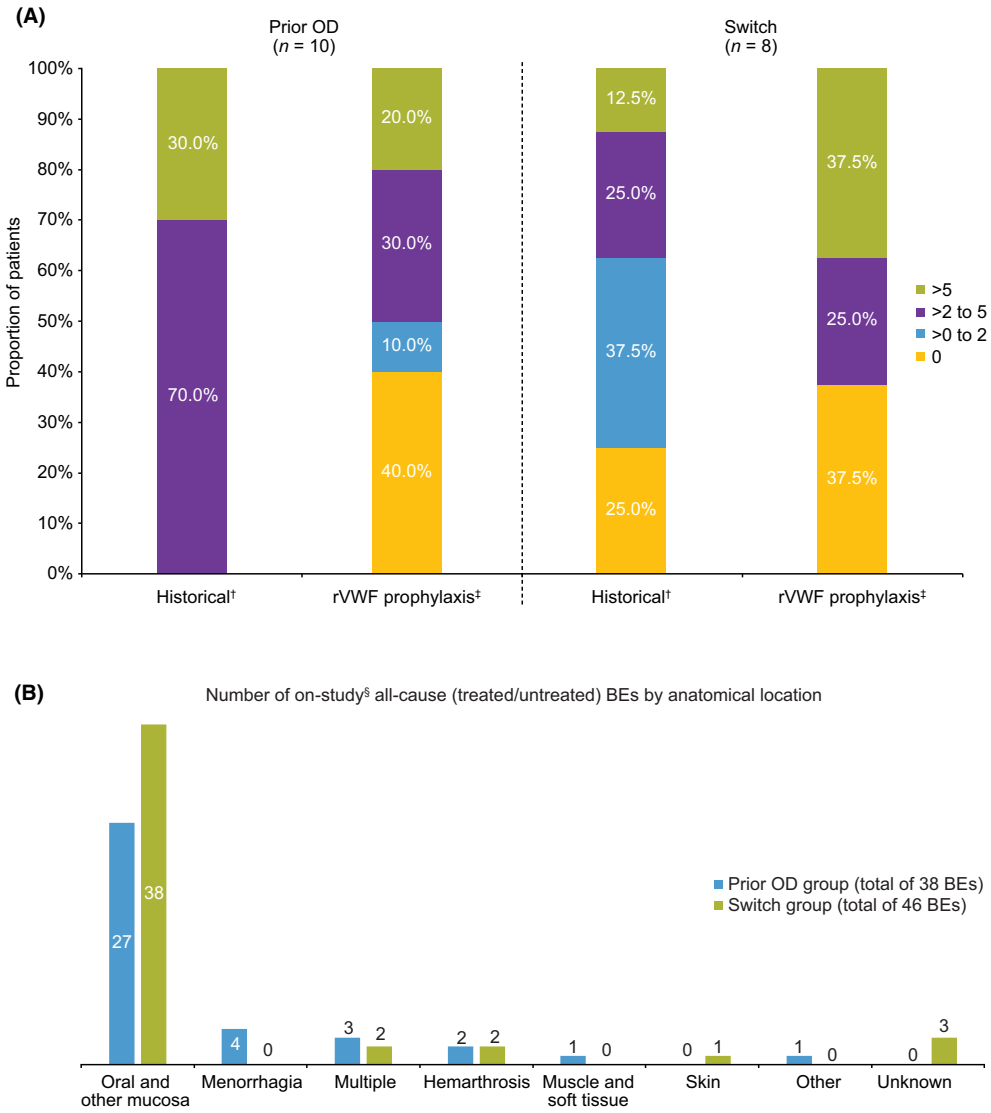

FIGURE 2 Categorized spontaneous and traumatic annualized bleeding rate (A) and bleed location (B) for all bleeds (treated and untreated). †Documented in medical records in the 12 months preceding enrollment. ‡On study through month 12. §Through month 12. BE, bleeding event; OD, On Demand, rVWF, recombinant von Willebrand factor.

rVWF infusion except for one nosebleed, which was treated with Haemate P (Antihemophilic Factor/VWF Complex [Human], CSL Behring GmBH, Marburg, Germany).

Four all-cause BEs in the Prior OD group and three in the Switch group were treated with rVWF plus rFVIII (octocog alfa, ADVATE, Baxalta US Inc., a Takeda company, Lexington, Massachusetts). In the Prior OD group, one patient received two infusions of rVWF (49.3 IU/kg) plus one infusion of rFVIII (29.0 IU/kg) for a spontaneous BE categorized as other, and one infusion each of rVWF (48.9–55.0 IU/kg) plus rFVIII (26.2–28.8 IU/kg) for three further spontaneous BEs (nosebleed, $n = 2$; menorrhagia, $n = 1$). In the Switch group, two patients received one infusion of rVWF (36.7–59.4 IU/kg) and rFVIII (16.4–26.20 IU/kg) per BE (all spontaneous): an ankle joint BE in one patient and two mucosal bleeds (gum and nose) in the other patient. OD infusions were also administered for one spontaneous ankle joint BE in one patient in the Switch group (rVWF infusion of 36.7 IU/kg and rFVIII infusion of 26.2 IU/kg) and one traumatic elbow joint BE (rVWF infusion of 56.4 IU/kg) plus multiple traumatic joint (elbow and knee)/soft tissue BEs (one rVWF infusion of 66.7 IU/kg and two rVWF infusions of 44.5 IU/kg) in one patient in the Prior OD group.

3.5 | Pharmacokinetic/pharmacodynamic

PK parameters for VWF:RCo are shown in Table S3 and for FVIII coagulation activity (FVIII:C) in Table S4. VWF:RCo activity was stable throughout the 12-month study period in both groups: mean ± SD incremental recovery ranged from 1.1 ± 0.7 and 1.3 ± 0.4 (IU/dL)/(IU/kg) at the prophylaxis visit to 1.7 ± 0.5 and 1.6 ± 0.4 (IU/dL)/(IU/kg) at month 9 in the Prior OD and Switch groups, respectively (Figure 3). As expected, trough levels of VWF:RCo tended to be below the limit of detection at each assessment, with the exception of one outlier (patient described above who had traumatic joint BEs) in the Prior OD group (levels between 10.3 and 12.1 IU/dL at 4/7 assessments) and three outliers in the Switch group (levels between 8.3 and 24.7 IU/dL at 1 to 3 assessments). The patient in the Switch group who had the spontaneous joint BE had trough VWF:RCo levels below the limit of detection at

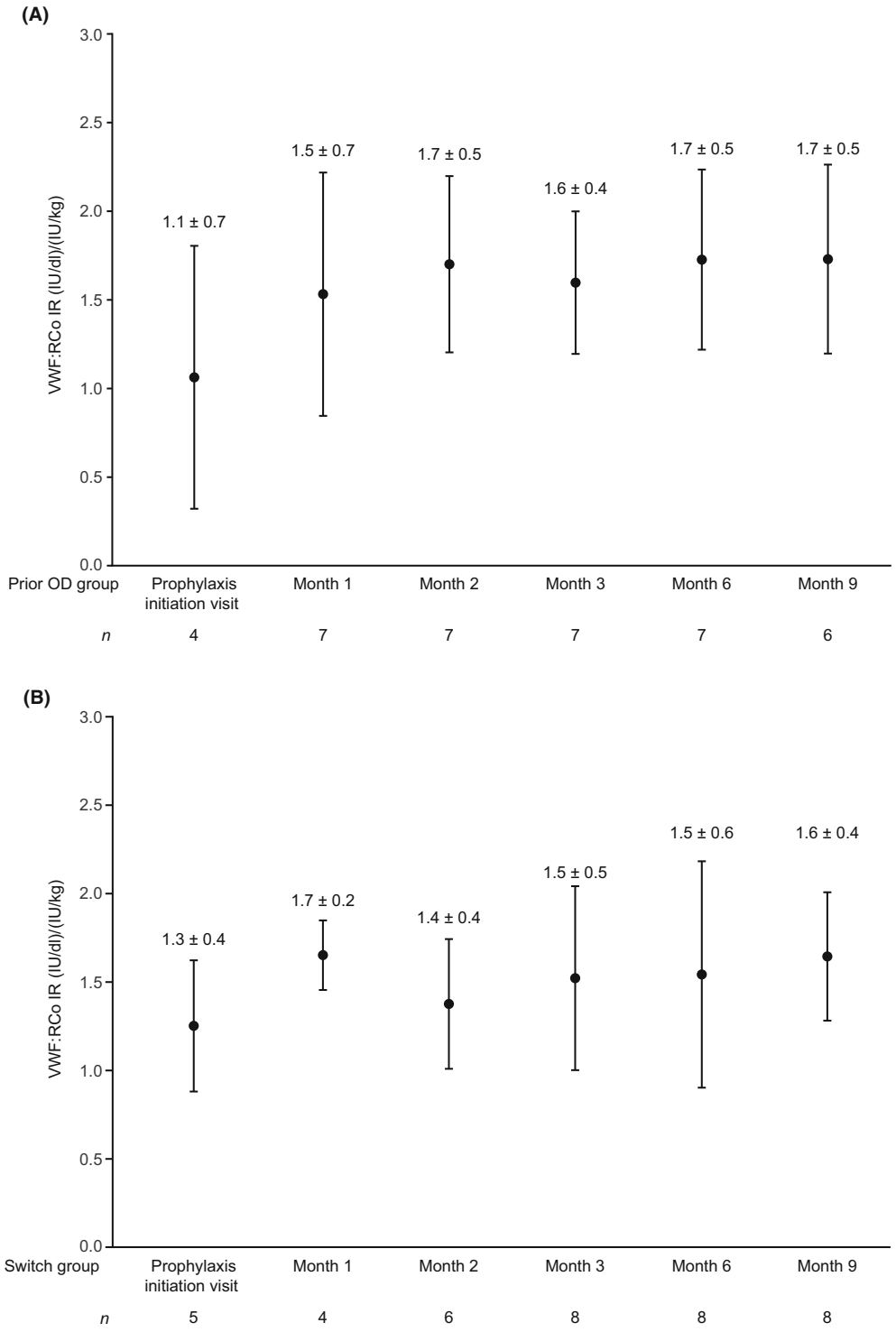

FIGURE 3 Mean ± SD VWF:RCo IR for patients with type 3 VWD treated with rVWF prophylaxis and available PK/PD data: (A) Prior OD group and (B) Switch group. IR, incremental recovery; n, number of patients with assessment data, OD, On Demand; PD, pharmacodynamic; PK, pharmacokinetic; rVWF, recombinant von Willebrand factor; VWF:RCo, von Willebrand factor:ristocetin cofactor activity.

all assessments through month 9 (levels were not available at study completion).

In the Prior OD group, there was a five-fold increase in FVIII:C trough levels between the initial and final assessments (after 12 months of rVWF prophylaxis; Figure 4 and Table S4). FVIII:C trough levels in the Switch group remained stable between the initial and final assessments (Figure 4). FVIII:C trough levels through to month 9 ranged from 85 to 148 IU/dL for the patient in the Prior OD group with traumatic joint BEs, and from 1 to 38 IU/dL for the patient with a spontaneous joint BE in the Switch group; at the study completion assessment, the FVIII:C trough levels in these patients were 6 IU/mL and not available, respectively.

3.6 | Safety

Treatment-emergent AEs were experienced by nine patients in the Prior OD group (25 events) and by five patients in the Switch group (10 events). Overall, the observed safety outcomes for patients with

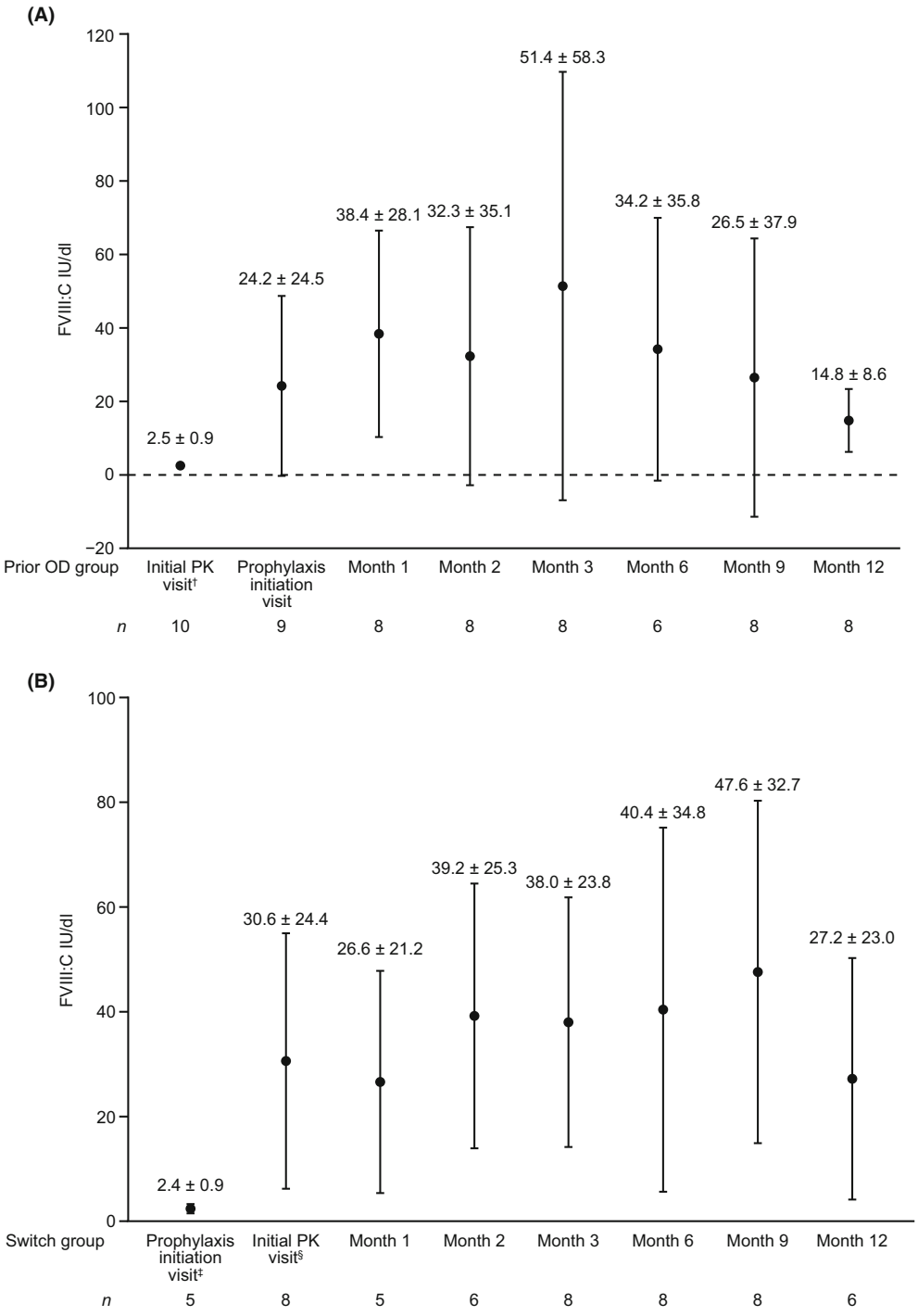

FIGURE 4 Mean ± SD FVIII:C trough levels for patients with type 3 VWD treated with rVWF prophylaxis and available PK/PD data: (A) Prior OD group and (B) Switch group. †Baseline visit, within 42 days of screening, after washout. ‡Within 42 days of screening, no washout. §First PK assessment, 11 days after initiation of rVWF prophylaxis. FVIII:C, factor VIII coagulation activity; n, number of patients with assessments; OD, On Demand; PD, pharmacodynamic; PK, pharmacokinetic; VWD, von Willebrand disease.

type 3 VWD were in line with the results reported for the overall study population of patients with severe VWD.[18] Only one AE in a patient with type 3 VWD (nonserious AE of headache of moderate severity in a patient in the Prior OD group) was considered possibly related to rVWF according to the investigator; this AE led to rVWF discontinuation and study withdrawal. One patient in the Prior OD group experienced an AE of special interest: purpura, which developed due to trauma, was classified as a thromboembolic event (per broad standardized MedDRA query). No serious AEs were considered related to VWF treatment. No fatal or life-threatening serious AEs were reported, there were no cases of hypersensitivity, severe allergic reactions, or anaphylactic reactions, and no patient developed inhibitors to VWF or FVIII.

4 | DISCUSSION

This post hoc analysis focused on the subset of patients with type 3 VWD from the recently published phase 3, prospective, open-label, nonrandomized multicenter study of rVWF prophylaxis in adults with

severe VWD.[18] Patients with type 3 VWD have the most severe bleeding phenotype versus patients with other VWD types and are, therefore, most in need of long-term prophylaxis.[6,7,17]

In those previously treated OD with VWF, reductions in ABR were observed for treated spontaneous BEs, as well as for all BEs irrespective of cause or treatment status. In addition, FVIII:C trough levels, which were low at baseline in this patient cohort, increased by approximately five-fold from baseline to steady state and were maintained during 1 year of rVWF prophylaxis, whereas VWF:RCo activity was stable during this period. In patients with type 3 VWD who switched from pdVWF prophylaxis to rVWF prophylaxis, at least the same level of hemostatic control was maintained, with most PK/PD parameters for FVIII:C and VWF:RCo during prophylaxis being similar between initial and end-of-study assessments. These findings are notable considering that patients with the lowest levels of VWF and/or FVIII have previously been reported to have the highest bleeding scores,[6,7] with a strong inverse association between FVIII levels and bleeding scores observed in patients with type 3 VWD.[6]

The safety profile of rVWF prophylaxis in patients with type 3 VWD was consistent with the previously reported safety profile for all patients in this study,[18] with only one nonserious AE considered possibly related to treatment, and no cases of hypersensitivity, severe allergic reactions, anaphylactic reactions, or development of inhibitors to VWF or FVIII. The efficacy and PK/PD results in this post hoc analysis were also consistent with those seen in the overall population with severe VWD from the phase 3 rVWF prophylaxis study.[18] This was not unexpected because 18/23 patients in the study had type 3 VWD, and all on-study treated BEs were reported in patients with type 3 VWD. However, this analysis adds to the limited data on the use of long-term VWF prophylaxis, specifically in this rare subtype of VWD.[22,23]

The analyses of all BEs (untreated and treated; spontaneous and traumatic) and sensitivity analyses (treated and untreated spontaneous BEs; treated spontaneous and traumatic BEs) confirm efficacy results reported previously for treated spontaneous BEs in patients with severe VWD and reported herein for patients with type 3 VWD.[18] Furthermore, analyses of treated spontaneous/traumatic or all spontaneous/traumatic joint bleeds highlighted the small number of joint BEs in the study. These analyses also highlight the potential underreporting of untreated historical bleeds (based on the patients' medical records as reported by the investigators), as previously reported in clinical practice in patients with hemophilia.[24] In the rVWF prophylaxis study, the majority of historical BEs were treated. Therefore, when untreated spontaneous BEs were added to the ABR in the Prior OD group the mean historical ABR estimate decreased, whereas the mean on-study ABR increased. In the Switch group, there was a small increase in both the historical and on-study mean ABR estimates. When all BEs were analyzed, increased estimates of mean on-study ABRs were observed for both groups when compared with the primary ABR analysis for treated spontaneous BEs, and there was a smaller reduction versus the historical period for the Prior OD group and an increase versus historical period for the Switch group.

The statistical model used for the primary endpoint analysis of the rVWF prophylaxis study was intended to compare on-study versus historical ABRs for treated spontaneous BEs. The findings from the additional bleeding rate analyses reported herein suggest that comparison of these ABRs is not appropriate when both treated and untreated BEs are considered, given the high likelihood of underreporting of historical untreated BEs in medical records. The potential underreporting of historical untreated bleeds may also explain, at least in part, the increase in the number of patients in the Switch group who experienced more than five BEs during the 12-month rVWF prophylaxis on-study period versus the historical period. This increase was driven by an increase in untreated and/or traumatic BEs in two patients. Additionally, the ABR for treated spontaneous BEs may be considered to be a more clinically relevant and meaningful measure of prophylactic efficacy than the ABR for all bleeds because there are confounding factors for traumatic BEs, and the requirement for treatment is an indicator for bleed severity.

In contrast to patients with severe hemophilia receiving prophylaxis, no data are available on the trough levels that have to be targeted to reduce BEs in patients with type 3 VWD receiving VWF prophylaxis. In this study, we measured trough levels of VWF and FVIII based on clinical visit schedules and not during BEs. As expected, given the half-life of VWF, trough levels of VWF:RCo were below the limit of detection (with the exception of a few outliers) in individuals treated twice weekly. However, FVIII trough levels were in the normal range. This may explain the low rates of severe BEs, especially of joint bleeding, in our cohort. Only one patient (from the Switch group; with trough levels of VWF:RCo below the level of detection and FVIII:C between 1 and 38 IU/dL at assessments between screening and month 9) suffered a spontaneous joint bleed during rVWF prophylaxis. Levels of VWF:RCo and FVIII:C were not available for the specific time period of this joint BE.

Per study protocol, the initial dosing regimen used in the Switch group matched (±10%) the weekly pdVWF dose of the prior pdVWF prophylaxis regimen. Patients in this cohort received a mean average dose of 49 IU/kg rVWF per infusion with a mean of two infusions per week, which was similar to the dosing regimens administered to patients in the Prior OD group during on-study rVWF prophylaxis. Given the similar level of hemostatic control achieved with rVWF prophylaxis versus previous pdVWF prophylaxis, the dosing regimen used for these patients can be considered appropriate. However, a population PK analysis, modeling, and simulation, using previous data from patients with all types of VWD, suggests that VWF:RCo exposure in patients receiving rVWF is higher and more prolonged than in those receiving pdVWF at the same doses, with a 64% faster clearance with pdVWF than with rVWF.[25] Therefore, it is reasonable to consider further exploring optimal dosing of rVWF prophylaxis, possibly with lower dose and/or dosing frequency.

Limitations of this study include the small number of patients with type 3 VWD that were enrolled. In addition, most BEs were mucocutaneous, with joint or GI bleeding—a frequent reason for starting prophylaxis in clinical practice[17]—reported in few patients. It is, therefore, difficult to assess whether rVWF prophylaxis is effective to prevent all types of severe bleeding complications.

In conclusion, this post hoc analysis demonstrates that rVWF prophylaxis effectively reduces bleeding rates in patients with type

3 VWD previously receiving OD VWF and maintains a similar level of hemostatic control in those patients who switch from pdVWF prophylaxis to rVWF prophylaxis. The analyses also provide novel findings with respect to untreated BEs, indicating the potential underreporting of untreated BEs in real-world settings.

AUTHOR CONTRIBUTIONS

Frank W. G. Leebeek contributed significantly to the analysis and interpretation of data and study conduct. Flora Peyvandi contributed to the amendment in the design of the study, and to the analysis and interpretation of the data; Miguel Escobar, Andreas Tiede, Giancarlo Castaman, Wolfgang Miesbach, Sophie Susen, Michael Wang, and Bulent Zülfikar contributed to the analysis and interpretation of the data and study conduct. Gülden Özen and Jingmei Zhang contributed significantly to the conception and design of the study and study conduct as well as to the analysis and interpretation of data. Scarlett Wang and Yi Wang contributed significantly to the analysis and interpretation of data. All authors had access to data outputs, had key roles in the writing/editing of the article, and have primary responsibility for the final approved article.

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CONFLICT OF INTEREST STATEMENT

Frank W. G. Leebeek has received grants/research funding from CSL Behring, Sobi, Takeda, and uniQure; consultancy fees from BioMarin, CSL Behring, Takeda, and uniQure (all fees to university); and was a data safety monitoring board member for Roche. Flora Peyvandi has participated in advisory boards of BioMarin, Grifols, Roche, Sanofi, Sobi, and Takeda. Andreas Tiede has received honoraria from Bayer, Biotest, Chugai, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi, and Takeda. Giancarlo Castaman has served on advisory boards or been a consultant for Bayer, BioMarin, CSL Behring, Grifols, Kedrion, LFB, Novo Nordisk, Roche, Sanofi, Sobi, Takeda, and uniQure. Miguel Escobar has received consulting fees from Bayer, BioMarin, CSL Behring, Genentech/Roche, Hemabiologics/LFB, Kedrion, NHF, Novo Nordisk, Pfizer, Sanofi, and Takeda, and research funding from CSL Behring, Genentech, Novo Nordisk, Sanofi, Takeda, and uniQure. Michael Wang has served on advisory boards or been a consultant for Bayer, BioMarin, Bioverativ, Catalyst Biosciences, CSL Behring, Genentech, Hema Biologics, Novo Nordisk, and Takeda. Bulent Zülfikar has received research funding from Pfizer and Sobi, and honoraria for advisory boards from Genveon, Novo Nordisk, Pfizer, Roche, and Takeda. Sophie Susen has received grants/research funding from CSL Behring, Roche-Chugai, Siemens Healthineers, Stago, and Sobi; advisory boards or consultant fees from BioMarin, CSL Behring, LFB, Novo-Nordisk, Roche-Chugai, Sobi, Sanofi, and Takeda (all fees to university). Wolfgang Miesbach has received grants from Bayer, Biotest, CSL Behring, LFB, Pfizer, Sanofi, and Takeda; consulting fees from Bayer, BioMarin, Biotest, Chugai, CSL Behring, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Takeda, and UniQure; honoraria from Bayer, BioMarin, Biotest, Chugai, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, and Takeda. Scarlett Wang, Yi Wang, Jingmei Zhang, and Gülden Özen are employees of Takeda Development Center Americas, Inc., and Takeda stockholders.

DATA AVAILABILITY STATEMENT

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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