

Thrombosis and Haemostasis

A systematic review of efficacy and safety of plasma-derived von Willebrand factor/Factor VIII concentrate (Voncento®) in von Willebrand Disease

Lucia Rugeri, William Thomas, Kathrin Schirner, Lisa Heyder, Günter Auerswald.

Affiliations below.

DOI: 10.1055/a-2253-9701

Please cite this article as: Rugeri L, Thomas W, Schirner K et al. A systematic review of efficacy and safety of plasma-derived von Willebrand factor/Factor VIII concentrate (Voncento®) in von Willebrand Disease. *Thromb Haemost* 2024. doi: 10.1055/a-2253-9701

Conflict of Interest: LR has been a consultant for: CSL Behring and Octapharma and received honoraria from LFB for speeches at congresses. GA received honoraria from CSL Behring for speeches at congresses and travel expenses. WT has received speakers' fees from Takeda, Bayer, Sobi, Pfizer, NovoNordisk, CSL Behring, Alexion, Portola, Sanofi and participated in advisory boards for Pfizer, Takeda, Ablynx, Sanofi, Daiichi Sankyo, LFB, Grifols and Novo Nordisk. KS and LH are employees of CSL Behring.

Abstract:

Abstract

Background: For the treatment of von Willebrand disease (VWD), von Willebrand Factor (VWF) concentrates can be used in on-demand, long-term prophylaxis and surgical prophylaxis regimens.

Methods: This systematic literature review was conducted to evaluate the efficacy, consumption and safety of plasma-derived human coagulation FVIII/human VWF (pdVWF/FVIII; Voncento®/Biostate®) for the treatment of patients with any inherited VWD type. An electronic search was conducted in MEDLINE® and Cochrane Library databases on VWD therapies. All retrieved publications were assessed against predefined inclusion/exclusion criteria following the Cochrane group recommendations. Associated pharmacovigilance data were collected across the same time period.

Results: Eleven publications from eight study cohorts were identified for data retrieval. All were from multicenter studies and included both pediatric and adult patients. Eight publications included evaluations of the efficacy of pdVWF/FVIII for on-demand treatment, eight included long-term prophylactic treatment, and eight included surgical prophylaxis. Treatment protocols and VWF administration methods differed between studies, as did safety evaluations. The clinical response was rated as excellent/good for on-demand treatment in 67–100% of non-surgical bleeds, 88.9–100% in the treatment of breakthrough bleeds during long-term prophylaxis treatment, and hemostatic efficacy in surgical procedures was 75–100%. Pharmacovigilance data confirmed a low incidence of adverse events in treated patients.

Conclusions: This review provides a comprehensive summary of studies that evaluated the use of pdVWF/FVIII in VWD demonstrating the long-term effectiveness and safety of this pdVWF/FVIII across all ages, types of VWD and treatment settings.

Corresponding Author:

Dr. Lucia Rugeri, Centre Hospitalier Universitaire de Lyon, Unité hémostase Clinique, Hôpital Lopuis Pradel, 69677 Bron, France, lucia.rugeri@chu-lyon.fr

Affiliations:

Lucia Rugeri, Centre Hospitalier Universitaire de Lyon, Unité hémostase Clinique, Bron, France

William Thomas, Addenbrooke's Hospital, Cambridge, United Kingdom of Great Britain and Northern Ireland

Kathrin Schirner, CSL Behring Innovation GmbH, Marburg, Germany

Lisa Heyder, CSL Behring Innovation GmbH, Marburg, Germany

Günter Auerswald, Prof.-Hess-Kinderklinik, Bremen, Germany



A systematic review of efficacy and safety of plasma-derived von Willebrand factor/Factor VIII concentrate (Voncento®) in von Willebrand Disease

Lucia Rugeri¹, Will Thomas², Kathrin Schirner³, Lisa Heyder³, Günter Auerswald⁴

1. Unite d'Hemostase Clinique, Hôpital Cardiologique, Hospices Civils de Lyon, France.
2. Cambridge University Hospitals NHS Foundation Trust, Cambridge Biomedical Campus, Cambridge, United Kingdom
3. CSL Behring Innovation GmbH, Marburg, Germany
4. Coagulation Centre, Bremen Central Clinic, GeNo Ltd., Parent-Child-Centre Prof. Hess, Bremen, Germany

Corresponding author: Dr Lucia Rugeri, MD

Address: Unite d'Hemostase Clinique, Hôpital Cardiologique, Hospices Civils de Lyon, France.

Email: lucia.rugeri@chu-lyon.fr

ORCID IDs:

Lucia Rugeri: 0000-0002-3103-1737

Will Thomas: 0000-0001-8740-0194

Kathrin Schirner: 0000-0002-4705-8475

Lisa Heyder: 0000-0003-0977-6422

Günter Auerswald: 0000-0003-3517-7052

Abstract

Background: For the treatment of von Willebrand disease (VWD), von Willebrand Factor (VWF) concentrates can be used in on-demand, long-term prophylaxis and surgical prophylaxis regimens.

Methods: This systematic literature review was conducted to evaluate the efficacy, consumption and safety of plasma-derived human coagulation FVIII/human VWF (pdVWF/FVIII; Voncento®/Biostate®) for the treatment of patients with any inherited VWD type. An electronic search was conducted in MEDLINE® and Cochrane Library databases on VWD therapies. All retrieved publications were assessed against predefined inclusion/exclusion criteria following the Cochrane group recommendations. Associated pharmacovigilance data were collected across the same time period.

Results: Eleven publications from eight study cohorts were identified for data retrieval. All were from multicenter studies and included both pediatric and adult patients. Eight publications included evaluations of the efficacy of pdVWF/FVIII for on-demand treatment, eight included long-term prophylactic treatment, and eight included surgical prophylaxis. Treatment protocols and VWF administration methods differed between studies, as did safety evaluations. The clinical response was rated as excellent/good for on-demand treatment in 66–100% of non-surgical bleeds, 89–100% in the treatment of breakthrough bleeds during long-term prophylaxis treatment, and hemostatic efficacy in surgical procedures was 75–100%. Pharmacovigilance data confirmed a low incidence of adverse events in treated patients.

Conclusions: This review provides a comprehensive summary of studies that evaluated the use of pdVWF/FVIII in VWD demonstrating the long-term effectiveness and safety of this pdVWF/FVIII across all ages, types of VWD and treatment settings.

Keywords: Blood products; Factor VIII; Systematic review; Von Willebrand Diseases; Von Willebrand factor.

Quick summary

What is known on this topic?	<ul style="list-style-type: none">• The therapeutic goal in VWD patient management is to treat or prevent bleeding events by correcting the deficiency of VWF and FVIII plasma levels.• Depending on VWD type and bleeding pattern, therapeutic strategies can be summarized as non-factor replacement and VWF-replacement therapy.• Clinical trial design in a rare disease setting, such as VWD, is limited by low prevalence and population heterogeneity, which hinders the conduction of classically designed randomized clinical trials.
What does this paper add?	<ul style="list-style-type: none">• This systematic review was conducted to evaluate the data available regarding efficacy, safety, and consumption of pdVWF/FVIII for the treatment of patients of all ages with all types of inherited VWD.• In addition, it includes novel reporting of pharmacovigilance data for the lifetime of pdVWF/FVIII.• This systematic review confirms the long-term efficacy and safety of pdVWF/FVIII when used for OD, LTP, and SP treatment regimens in adult and pediatric patients with VWD of all types.

LTP: long-term prophylaxis; OD: on demand; pdVWF/FVIII: plasma-derived human coagulation FVIII/human VWF; SP: surgical prophylaxis; VWD: Von Willebrand disease; VWF, Von Willebrand factor.

Introduction

The therapeutic goal in von Willebrand disease (VWD) patient management is to treat or prevent bleeding events by correcting the deficiency of von Willebrand Factor (VWF) and Factor VIII (FVIII) plasma levels.^{1,2} Depending on VWD type and bleeding pattern, therapeutic strategies can be summarized in two main categories: non-factor replacement

(antifibrinolytics and 1-deamino-8-D-arginine vasopressin [DDAVP]) and VWF-replacement therapy (RT). Different VWF RT regimens may be applied, including on-demand (OD) treatment for non-surgical bleeds (NSBs), long-term prophylaxis (LTP; also referred to as continuous prophylaxis), and prophylaxis for surgical procedures (SP).²⁻⁴ Treatment of heavy menstrual bleeding (HMB) is considered an NSB and treatment regimens are tailored to individual need, falling within OD treatment or intermittent prophylaxis, also known as short-term prophylaxis or non-surgical intermittent prophylaxis.²

Plasma-derived human coagulation FVIII/human VWF (Voncento®/Biostate®, CSL Behring, Marburg, Germany; herein referred to as pdVWF/FVIII) is a highly purified, low volume concentrate with an average von Willebrand factor Ristocetin Cofactor/FVIII clotting activity (VWF:RCO/FVIII:C) ratio of 2.4:1.^{5,6} pdVWF/FVIII was first marketed in Australia (International birth date 7 August 2000), and later in the European Union (EU birth date 12 August 2013). The same product has been marketed under various names (Voncento®, Biostate®, Aleviate®, TBSF High Purity Factor VIII/VWF Concentrate) and is currently authorized in approximately 40 countries worldwide. pdVWF/FVIII is indicated in all age groups for prophylaxis and treatment of hemorrhage or surgical bleeding in patients with VWD when DDAVP treatment alone is ineffective or contraindicated, as well as prophylaxis and treatment of bleeds in patients with hemophilia A.⁵ Clinical trial design in a rare disease setting, such as VWD, is limited by low prevalence and population heterogeneity, which hinders the conduction of classically designed randomized clinical trials.⁷ This systematic review was conducted to evaluate the data available regarding the efficacy, consumption and safety of pdVWF/FVIII for the treatment of patients of all ages with all VWD types, and includes novel reporting of pharmacovigilance data for the first time in this product's lifetime.

Methods

Search strategy

An electronic search was conducted in the following databases on 31st May 2023: MEDLINE® (1946 to present) and MEDLINE® In-Process Citations, through Pubmed.com interface; Cochrane Library, including the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR). Search terms were designed to identify publications reporting studies in patients with inherited VWD of all ages treated with pdVWF/FVIII (Voncento®/Biostate®); the full search strategy is described in Supplemental Methods and Supplemental Tables 1–5.

Data extraction

Data were extracted into pre-prepared data tables to prevent reporting bias and to allow comparisons for all available outcomes of interest. Once data extraction was complete, comparable results were combined to form the summary tables within this review. To enable comparison between studies, where pdVWF/FVIII dosing was quoted as FVIII:C IU/kg, the VWF:RCo IU/kg dose was estimated using the VWF:RCo/FVIII:C ratio of 2.4:1;⁵ the original FVIII:C dosing was also reported. Finally, outcomes for hemostatic efficacy and safety were pooled across studies to produce an overall estimate of hemostatic efficacy for OD, LTP and SP where data were comparable.

Pharmacovigilance data

Pharmacovigilance data including spontaneous reports, reports from post-marketing trials, regulatory agencies, and cases identified from a review of the worldwide scientific literature, were analyzed for the period up to 31st May 2023. Only adverse events (AEs) with suspected causal relationship between product and occurrence (adverse drug reactions;

ADRs) were included in the pharmacovigilance data analysis. ADRs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0, and the events were classified as serious or non-serious according to regulatory definition; further details provided in supplemental methods.

Only reports associated with the specific pdVWF/FVIII product (Voncento®/Biostate®) were included.⁵ No distinctions were made between ADRs reported for the indications of VWD or hemophilia A; therefore, all ADRs for pdVWF/FVIII (Voncento®/Biostate®) were reported.

Results

Systematic review

The literature search identified 119 individual records, of which 108 were included in full-text screening and 31 were identified in the grey literature review (Figure 1). Further screening removed records superseded by subsequent publication updates, resulting in 11 unique publications from eight study cohorts for qualitative data analysis.

Of the 11 included publications, five were interventional studies, including three from the SWIFT study program (Studies with von Willebrand factor/Factor VIII),^{6,8-11} four were prospective observational studies from the OPALE (Observatoire des patients présentant une Maladie de Willebrand et traités par Voncento®) study cohort,¹²⁻¹⁵ and two were retrospective observational studies^{16,17} (summarized in Supplemental Results and Supplemental Table 6). Population characteristics, which included pediatric and adolescent patients, are presented in Table 1. All VWD types were represented, with cases of severe type 3 VWD included in all studies where reported (data unavailable for post-marketing study CS-12-83, Table 1).

Hemostatic Efficacy Outcomes

Hemostatic efficacy outcomes for OD, LTP and SP treatment regimens are summarized in Table 2 and Supplemental Table 7. Eight publications evaluated pdVWF/FVIII for OD treatment of bleeding events (Table 2). All eight publications reported hemostatic efficacy, with minor differences between rating categories and efficacy assessment. Overall, efficacy was rated as excellent/good for the control of NSB events in 66–100% of treated bleeds (Table 2). Hemostatic efficacy scores were pooled from 799 treated bleeds from 127 patients across eight studies (Figure 2A), where 96% of bleeds (N=761) were resolved with excellent/good efficacy and 3% (N=24) had moderate efficacy; data unavailable for 1% (N=6).^{6,8-10,12,15,16,18}

Six studies reported consumption data for pdVWF/FVIII for OD treatment of bleeding events (Supplemental Table 8).^{6,8-11,16} Reporting of OD treatment regimen varied, with number of infusions per patient, infusions per event number of NSBs and dose per infusion.

Eight studies evaluated the efficacy of pdVWF/FVIII for LTP treatment (Table 2). Prophylactic efficacy was reported as excellent/good in 98–100% of patients in four publications,^{10,14,15} and 89% of patients in a fifth (Table 2).¹⁸ The OPALE study reported hemostatic efficacy according to VWD type, where excellent/good effectiveness was reported in 100% of patients (N=23) with types 2A (N=1), 2B (N=5), and 3 (N=16) where these data were available.¹⁴ Pooled hemostatic efficacy scores for treatment of breakthrough bleeds were pooled from 252 treated bleeds from 37 patients across nine studies (Figure 2B), where 96% of bleeds (N=242) were resolved with excellent/good efficacy and 4% (N=10) had moderate efficacy.^{6,8-10,13-16,18} Three studies reported consumption data for pdVWF/FVIII for LTP treatment,^{6,10,11} and LTP regimen were reported in 6 of 8 studies reporting LTP outcomes.^{6,8-}

^{10,14,18} Dosing was reported as mean VWF:RCo IU per infusion, weekly dose and median dose to treat NSB events (Supplemental Table 8).

One case of intermittent prophylaxis was reported;⁶ therefore, no efficacy data are presented for intermittent prophylaxis (case discussed in supplemental results).

Eight studies evaluated the efficacy of pdVWF/FVIII for SP. There were variations between studies in surgical procedure category classification and hemostatic efficacy evaluation (Supplemental Table 7). The proportion of procedures for which the overall hemostatic efficacy was rated as excellent/good ranged from 75–100% (Table 2). Hemostatic efficacy was reported according to VWD type in one study, in which hemostatic efficacy was excellent/good in 100% of cases in all types studied (types 1 [N=32], 2A, [N=13], 2B [N=4] and 3 [N=9]).¹⁷ Pooled hemostatic efficacy scores for 266 procedures in 202 patients are shown in Figure 2C, where 97.4% of bleeds (N=221) were resolved with excellent/good efficacy and 2.2% (N=5) had moderate efficacy; data unavailable for 0.4% (N=1).^{6,8,10,14–18} Five publications reported consumption data for pdVWF/FVIII for SP,^{10,11,13,16,17} although reporting of loading doses, duration of treatment and use of adjunctive therapy varied (Supplemental Table 8). Mean pre-operative loading doses were adapted according to surgical procedure severity, with a higher mean dose in major procedures compared to minor (69.6–175.2 IU VWF:RCo/kg and 79.2–96 IU VWF:RCo/kg, respectively; Supplemental Table 8).^{10,16,17} Use of adjunctive therapies in surgical events, such as tranexamic acid (TXA) or other antifibrinolytics, were reported in four studies.^{10,13,16,17}

Safety Outcomes

Safety outcomes for OD, LTP and SP treatment regimens are summarized in Table 3. There were differences in safety evaluation between studies, such as variation in patient follow-up time and reporting of AEs.

Seven publications reported safety outcomes for OD treatment of bleedings, eight reported safety outcomes for LTP, and five for SP (Table 3). The incidence of AEs and serious AEs (SAEs) varied from 0–100% and 0–43% of treated patients, respectively (Table 3). In studies reporting these data, no patient discontinued treatment due to an AE and no thromboembolic events (TEEs) were reported during patient follow-up.

Eight studies reporting LTP evaluated the safety of pdVWF/FVIII for prophylactic treatment (Table 3), where reported AE incidence ranged from 0–100% of patients. No patient discontinued LTP treatment due to an AE and no TEEs were reported during patient follow-up.

Five study reports evaluated the safety of pdVWF/FVIII for SP (Table 3). Six AEs were reported in the OPALE surgery study population of 66 patients.¹³ No treatment-related AE or SAE was reported during follow-up in the study from Shortt *et al.*¹⁷ From three studies that reported TEE incidence, only one case of deep vein thrombosis (DVT) was reported, occurring 10 days after the last infusion of pdVWF/FVIII and classified by the investigator as unrelated to treatment (case discussed in supplemental results).¹³

Pooled safety data for OD treatment of bleedings, LTP, and SP are summarized in Table 4. Approximately one third of patients treated with pdVWF/FVIII with OD or LTP regimen had an AE (33% and 35%, respectively), although a quarter of AEs were considered treatment-related with LTP (27%) and only 1% AEs were treatment-related for OD (Table 4). The AE rate was much lower in SP (4%). Patients with any SAE was low for all regimens, where 4%,

3% and 0 patients experienced SAEs with OD, LTP and SP regimens, respectively. No SAEs were considered treatment-related. No hypersensitivity reactions were reported across 350 patients included in the pooled clinical trial safety data, and only 1 thrombotic event occurred with SP regimen.

Pharmacovigilance data

Pharmacovigilance data reported in clinical trials

The clinical trial program for pdVWF/FVIII included 246 patients with hemophilia A or VWD (Table 5). A total of 34 SAEs were reported in 24 cases; including cases from trials reported within this review. Five case reports from clinical trial populations described a total of 5 AEs (all serious) specifically pertaining to development of inhibitors; all were FVIII inhibitors. Four of these cases were reported within hemophilia A clinical trial populations.^{19,20} The fifth case was a patient with type 3 VWD with a low responding inhibitor noted after 4 years of prophylaxis; this patient was excluded from the dosing and efficacy analyses of the study.¹⁶

Out of a total clinical exposure of 246 patients, 1 serious case of ischemic stroke deemed unrelated to pdVWF/FVIII administration was reported within pharmacovigilance reporting of clinical trials but was not part of the studies included in this review. No case reports pertaining to hypersensitivity and/or anaphylaxis were identified from clinical trials. One serious case of transmission of infectious agents reported an Epstein-Barr virus infection, comprising 2 AEs in one patient, however, the virus transmission was not confirmed to be associated with pdVWF/FVIII administration.²⁰

Pharmacovigilance data reported in post-marketing surveillance

From 1st marketing authorization in 2000 until 31st May 2023, 1,375,313,750 IU of FVIII (representing 3,300,753,000 IUs VWF) were sold globally corresponding to 916,875 single

dose exposures, or 5,877 patient years (using 1500 IU FVIII/3600 IU VWF as standard dose per single administration; Table 5). A total of 241 case reports for pdVWF/FVIII with 494 ADRs were received. Of these, 150 cases with 378 ADRs pertain specifically to Voncento®/Biostate®; cases pertaining to Human Factor VIII VWF (generic) were excluded. The number of case reports associated with the development of FVIII/VWF inhibitors was nine and described a total of 11 ADRs (10 serious, 1 non-serious); there was only one event of VWF inhibition.²¹

Cumulatively, five serious cases of TEEs for pdVWF/FVIII were reported; two within the OPALE non-interventional study (one case unpublished),¹³ the other three reported spontaneously. A total of 34 cases reported 62 ADRs (34 serious, 28 non-serious) pertaining to hypersensitivity reactions. The most common hypersensitivity ADRs were mild (rash, urticaria, hypersensitivity, angioedema). Seven cases described anaphylactic reactions. One case report was received for transmission of infectious agents pertaining to pdVWF/FVIII and reported a viral infection, presumed to be mumps. This infection was attributed to a mumps outbreak in the region where the patient lived and hence did not present a transmission of an infectious agent associated with pdVWF/FVIII.

Discussion

This systematic review summarizes eight individual study cohorts from 11 publications where pdVWF/FVIII was used in treatment of adults and children with inherited VWD, and reports over 20 years of pharmacovigilance surveillance data for the first time.

Most of the included clinical trial publications reported single-arm interventional studies, with four reporting main phase II/III clinical trials.^{6,8-10} All study cohorts met the EMA guidelines for appropriate study population size for trials in VWD (≥ 12 patients with severe

VWD, including six with type 3 VWD [most severe]).²² Pediatric and adult patients were included in most studies, with approximately half of patients being female.

For patients treated OD, the bleeding pattern tended towards mucosal and mild bleeding events, with the majority of events being spontaneous, as expected in VWD.^{1,23} Prophylactic treatment was reserved for patients with severe phenotypes and recurrent bleeding history, in line with current treatment guidelines.² Although annualized bleeding rate may be considered a valuable outcome to assess prophylaxis efficacy, this was only included in three studies.^{6,11,13}

Overall, hemostatic efficacy for pdVWF/FVIII treatment was rated good/excellent in 96.8 %, 96.0% and 97.4% of patients for the OD, LTP and SP regimens, respectively. This agrees with a previously published survey, where overall hemostatic efficacy for pdWVD/FVIII was excellent/good in 90–100% of cases receiving SP.²⁴ Hemostatic efficacy according to the VWD type was inconsistently reported, although no obvious differences in responses by type were reported.

This review included studies of intermittent prophylaxis, however, only one case was reported within an LTP cohort as “monthly prophylactic dosing”.⁶ Consumption data reporting varied between studies, with doses being reported per event, per infusion or per patient, making comparisons difficult. Preoperative loading doses were also inconsistently reported, although doses were in line with guidelines at the time of the study.²⁵

Safety data were heterogeneously reported across studies but the rate of SAEs was low with no cases of severe hypersensitivity reactions, in agreement with previous studies with similar products.^{24,26} The only TEE reported from 307 clinical trial patients within this review was a DVT, and was classified as unrelated to treatment.¹³

Pharmacovigilance data summarized key risks associated with pdVWF/FVIII treatment including development of FVIII/VWF inhibitors, TEEs, hypersensitivity reactions including anaphylaxis, and transmission of infectious agents. Of 11 ADRs that identified the development of inhibitors, the majority were to FVIII and one case reported alloantibodies to VWF in a type 3 VWD patient.²¹ It was not always possible to discern whether FVIII inhibitors were in patients with hemophilia A or VWD. The pharmacovigilance findings agree with published literature, where inhibitors against FVIII are more common than those against VWF,²⁷ developing in approximately 30% of previously untreated patients with hemophilia A.²⁷ The majority of VWD patients that develop inhibitors to VWF are those with partial or complete VWF gene deletions.^{1,28,29} VWF alloantibodies have been reported in approximately 10–15% of type 3 VWD patients who have received multiple transfusions,^{30,31} where type 3 VWD prevalence is <10% of all VWD cases.²⁸ Risk factors for inhibitor development include patient- and treatment-related factors,^{32,33} including genetics, positive family history for inhibitors, FVIII genotype, polymorphisms in immune modulatory genes, intensity of FVIII treatment, severity of disease, and number of exposure days.³⁴

Three instances of TEEs were reported in pharmacovigilance surveillance, two were reported in the OPAL study, and were considered not caused by treatment,¹³ continuing to support a low TEE incidence with pdVWF/FVIII administration (an incidence of 0.82% in pharmacovigilance data from clinical studies). The annual incidence of venous thromboembolism in the general population is estimated to be 0.44 per 1,000 person-years in males and 0.55 per 1,000 person-years in females;³⁵ risk increases with age where TEE incidence varies between 1 per 10,000 person-years in childhood to 1% in the elderly.³⁶⁻³⁸

Risk factors for TEEs include increased FVIII levels and it is recommended to monitor FVIII:C in patients undergoing surgery or receiving multiple pdVWF/FVIII doses.²

Potential transmission of infectious agents is a known class effect of blood/plasma-derived products.³⁹ One report for transmission was received in post-marketing surveillance in addition to one reported in clinical trials. However, transmission of infectious agents was not confirmed in any case and there was no indication that viruses were transmitted via the product. One case of viral infection, presumed to be mumps, was considered attributable to an outbreak in the patient's local region. The manufacturing process for pdVWF/FVIII includes two dedicated virus inactivation steps: solvent detergent treatment and dry heat treatment.⁸ These steps are considered effective for enveloped viruses such as HIV, Hepatitis B and Hepatitis C, and the non-enveloped virus Hepatitis A, yet may have limited value against non-enveloped viruses such as parvovirus B19.⁴⁰

The authors have several reflections for further work to bridge literature gaps. Monitoring of factor levels following pdVWF/FVIII administration for surgery was not included in most studies. Adjunctive therapy was not reported according to VWD type; therefore, it was unclear whether these therapies were administered according to guidelines.² Intermittent prophylaxis was not studied as an outright treatment regimen and only one case was reported within an LTP cohort.⁶ Cases of HMB treated with an OD regimen reported moderate hemostatic efficacy in a separate study.⁸ The authors identify particular knowledge gaps in treatment of HMB with pdVWF/FVIII. The included studies did not report dosing per menstruation and no data were found on the use of adjunctive therapies such as TXA or hormonal therapies. This may be due to the search strategy employed, as pdVWF/FVIII is not a first-line therapy for women with HMB.²

The authors note several limitations of this review. First, only observational studies and non-randomized, non-controlled trials, mostly of single-arm design, were included. Second,

although pdVWF/FVIII is predominantly used for patients with inherited VWD, the product label also includes hemophilia A⁵ and limitations in pharmacovigilance reporting methods meant that the indication was not specified for the reported ADRs.

In conclusion, this systematic literature review constitutes a comprehensive summary of the interventional and non-interventional studies conducted to evaluate the use of pdVWF/FVIII. Hemostatic efficacy was rated as excellent/good in the majority of patients across all studies, in all treatment regimens, for all bleeding types and severity and across all VWD types and no treatment-related SAEs were reported. These results confirm the long-term efficacy and safety of pdVWF/FVIII when used for OD, LTP, and SP treatment regimens in adult and pediatric patients with VWD of all types.

Authorship Details

L. Rugeri, W. Thomas and G. Auerswald contributed to the concept and design of the systematic literature review, provided critical appraisal and interpretation of the data presented. L. Heyder and K. Schirner performed analysis and interpretation of the pharmacovigilance data. All authors provided critical appraisal and revisions of this document during its creation. All authors reviewed and approved the final version of this manuscript prior to submission. Medical writing assistance was provided by Lucy Craggs and Claire Crouchley of Meridian HealthComms, Plumley UK under the guidance of all authors.

Acknowledgments

The authors would like to thank Meridian HealthComms, Plumley, UK for providing medical writing support in accordance with Good Publication practice (GPP3), which was funded by CSL Behring GmbH, Hattersheim am Main, Germany.

Conflicts of Interest

LR has been a consultant for: CSL Behring and Octapharma and received honoraria from LFB for speeches at congresses. GA received honoraria from CSL Behring for speeches at congresses and travel expenses. WT has received speakers' fees from Takeda, Bayer, Sobi, Pfizer, NovoNordisk, CSL Behring, Alexion, Portola, Sanofi and participated in advisory boards for Pfizer, Takeda, Ablynx, Sanofi, Daiichi Sankyo, LFB, Grifols and Novo Nordisk. KS and LH are employees of CSL Behring.

References

1. Castaman G, Goodeve A, Eikenboom J, European Group on von Willebrand D. Principles of care for the diagnosis and treatment of von Willebrand disease. *Haematologica*. 2013;98(5):667–674. doi:10.3324/haematol.2012.077263
2. Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. *Blood Adv*. 2021;5(1):301–325. doi:10.1182/bloodadvances.2020003264
3. Heijdra JM, Cnossen MH, Leebeek FWG. Current and Emerging Options for the Management of Inherited von Willebrand Disease. *Drugs*. 2017;77(14):1531–1547. doi:10.1007/s40265-017-0793-2
4. Federici AB. Prophylaxis in Patients with von Willebrand disease: Who, when, how? *J Thromb Haemost*. 2015;13(9):1581–1584. doi:10.1111/jth.13036
5. European Medicines Agency. Summary of Products Characteristics - Voncento® . Accessed May 31, 2023. <https://www.ema.europa.eu/en/medicines/human/EPAR/voncento>
6. Lissitchkov TJ, Buevich E, Kuliczowski K, et al. Pharmacokinetics, efficacy, and safety of a plasma-derived VWF/FVIII concentrate (VONCENTO) for on-demand and prophylactic treatment in patients with von Willebrand disease (SWIFT-VWD study). *Blood Coagul Fibrinolysis*. 2017;28(2):152–162. doi:10.1097/mbc.0000000000000568
7. Gaasterland CMW, van der Weide MCJ, du Prie – Olthof MJ, et al. The patient's view on rare disease trial design – a qualitative study. *Orphanet J Rare Dis*. 2019;14(1):31. doi:10.1186/s13023-019-1002-z
8. Auerswald G, Djambas Khayat C, Stasyshyn O, et al. Pharmacokinetics, Efficacy and Safety of a Plasma-Derived VWF/FVIII Concentrate (Formulation V) in Pediatric Patients with von Willebrand Disease (SWIFTLY-VWD Study). *J Blood Med*. 2020;11:213–225. doi:10.2147/JBM.S236789
9. Lissitchkov T, Klukowska A, Buevich E, et al. An Open-Label Extension Study to Assess the Long-Term Efficacy and Safety of a Plasma-Derived von Willebrand Factor (VWF)/Factor VIII (FVIII) Concentrate in Patients with von Willebrand Disease (SWIFT-VWDext Study). *J Blood Med*. 2020;11:345–356. doi:10.2147/JBM.S268907
10. Dunkley S, Baker RI, Pidcock M, et al. Clinical efficacy and safety of the factor VIII/von Willebrand factor concentrate BIOSTATE (R) in patients with von Willebrand's disease: a prospective multi-centre study. *Haemophilia*. 2010;16(4):615–624. doi:10.1111/j.1365-2516.2010.02206.x
11. EU Clinical Trials Register. Identifier EUDRACT 2013-003305-25, An Open-label, Multi-centre Post-marketing Study to Assess the Efficacy and Safety of Voncento® in Subjects with Von Willebrand

Disease. Accessed May 31, 2023. <https://www.clinicaltrialsregister.eu/ctr-search/search?query=2013-003305-25>

12. d'Oiron R, Rugeri L, Harroche A, et al. Efficacy and safety of high ratio HVWF/FVIII concentrate (Voncento®) for the treatment of bleeding episodes in patients with Von Willebrand disease: The OPALE French Experience. *Haemophilia*. 2022;28(POSTER PRESENTATIONS):25–126. doi:<https://doi.org/10.1111/hae.14479>
13. Rugeri L, d'Oiron R, Harroche A, et al. Effectiveness and safety of hFVIII/VWF concentrate (Voncento®) in patients with inherited von Willebrand disease requiring surgical procedures: the OPALE multicentre observational study. *Blood Transfus*. 2021;19(2):152–157. doi:[10.2450/2020.0246-20](https://doi.org/10.2450/2020.0246-20)
14. Rugeri L, Harroche A, Repesse Y, et al. Effectiveness of long-term prophylaxis using pdFVIII/VWF concentrate in patients with inherited von Willebrand disease. *Eur J Haematol*. 2022;109(1):109–117. doi:[10.1111/ejh.13778](https://doi.org/10.1111/ejh.13778)
15. Harroche A, Rugeri L, D'Oiron R, et al. Efficacy and safety of HFVIII/VWF (Voncento®) concentrate in paediatric patients with Von Willebrand disease (VWD): The French experience. Abstract. *Haemophilia*. 2021;27(S2)(Virtual Congress of the European Association for Haemophilia and Allied Disorders 2021 3-5 February 2021):67. ABS090. doi:doi.org/10.1111/hae.14234
16. Howman R, Barnes C, Curtin J, et al. The clinical efficacy and safety of the FVIII/VWF concentrate, BIOSTATE (R), in children with von Willebrand disorder: a multi-centre retrospective review. *Haemophilia*. 2011;17(3):463–469. doi:[10.1111/j.1365-2516.2010.02445.x](https://doi.org/10.1111/j.1365-2516.2010.02445.x)
17. Shortt J, Dunkley S, Rickard K, Baker R, Street A. Efficacy and safety of a high purity, double virus inactivated factor VIII von Willebrand factor concentrate (Biostate (R)) in patients with von Willebrand disorder requiring invasive or surgical procedures. *Haemophilia*. 2007;13(2):144–148. doi:[10.1111/j.1365-2516.2006.01430.x](https://doi.org/10.1111/j.1365-2516.2006.01430.x)
18. EU Clinical Trials Register. Identifier EUDRACT 2009-017301-11, An Open-Label, Multi-Centre Extension Study to Assess the Efficacy and Safety of Biostate® in Paediatric, Adolescent, and Adult Subjects with Von Willebrand Disease who Completed Clinical Studies CSLCT-BIO-08-52 or CSLCTBIO-08-54. Accessed May 31, 2023. <https://www.clinicaltrialsregister.eu/ctr-search/search?query=2009-017301-11>
19. Djambas Khayat C, Iosava G, Romashevskaya I, et al. Efficacy, Safety and Pharmacokinetic Results of a Phase III, Open-Label, Multicenter Study with a Plasma-Derived Von Willebrand Factor (VWF)/Factor VIII (FVIII) Concentrate in Pediatric Patients <12 Years of Age with Hemophilia A (SWIFTLY-HA Study). *J Blood Med*. 2021;12:483–495. doi:[10.2147/JBM.S299130](https://doi.org/10.2147/JBM.S299130)
20. Skotnicki A, Lissitchkov TJ, Mamonov V, et al. Efficacy, safety and pharmacokinetic profiles of a plasma-derived VWF/FVIII concentrate (VONCENTO(R)) in subjects with haemophilia A (SWIFT-HA study). *Thromb Res*. 2016;137:119–125. doi:[10.1016/j.thromres.2015.10.014](https://doi.org/10.1016/j.thromres.2015.10.014)
21. Kershaw G, Barbaro P, Curtin J, Favaloro E, Shoemark R, Keegan A. High titre anti-VWF detectable by inhibition of collagen-binding activity in a patient with Type 3 von Willebrand Disease. *Haemophilia*. 2014;20(s3):1–186.
22. Committee for Medicinal Products for Human Use. Guideline on the clinical investigation of human plasma derived von Willebrand Factor products European Medicines Agency. Accessed May 31, 2023. <https://www.ema.europa.eu/en/clinical-investigation-human-plasma-derived-von-willebrand-factor-products>
23. James PD, Connell NT, Ameer B, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. *Blood Adv*. 2021;5(1):280–300. doi:[10.1182/bloodadvances.2020003265](https://doi.org/10.1182/bloodadvances.2020003265)
24. Windyga J, Dolan G, Altisent C, et al. Practical aspects of factor concentrate use in patients with von Willebrand disease undergoing invasive procedures: a European survey. *Haemophilia*. 2016;22(5):739–751. doi:[10.1111/hae.12955](https://doi.org/10.1111/hae.12955)
25. 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(2):171–232. doi:[10.1111/j.1365-2516.2007.01643.x](https://doi.org/10.1111/j.1365-2516.2007.01643.x)

26. Kouides P, Wawra-Hehenberger K, Sajan A, Mead H, Simon T. Safety of a pasteurized plasma-derived Factor VIII and von Willebrand factor concentrate: analysis of 33 years of pharmacovigilance data. *Transfusion*. 2017;57(10):2390–2403. doi:10.1111/trf.14241
27. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;26 Suppl 6:1–158. doi:10.1111/hae.14046
28. James PD, Lillicrap D, Mannucci PM. Alloantibodies in von Willebrand disease. *Blood*. 2013;122(5):636–640. doi:10.1182/blood-2012-10-462085
29. James PD, Lillicrap D. The molecular characterization of von Willebrand disease: good in parts. *Br J Haematol*. 2013;161(2):166–176. doi:10.1111/bjh.12249
30. Federici AB. The safety of plasma-derived von Willebrand/factor VIII concentrates in the management of inherited von Willebrand disease. *Expert Opin Drug Saf*. 2009;8(2):203–210. doi:10.1517/14740330902719481
31. Mannucci PM. How I treat patients with von Willebrand disease. *Blood*. 2001;97(7):1915–1919. doi:10.1182/blood.v97.7.1915
32. Coppola A, Santoro C, Tagliaferri A, Franchini M, G DIM. Understanding inhibitor development in haemophilia A: towards clinical prediction and prevention strategies. *Haemophilia*. 2010;16 Suppl 1:13–19. doi:10.1111/j.1365-2516.2009.02175.x
33. Chambost H. Assessing risk factors: prevention of inhibitors in haemophilia. *Haemophilia*. 2010;16 Suppl 2:10–15. doi:10.1111/j.1365-2516.2009.02197.x
34. Gouw SC, van den Berg HM. The multifactorial etiology of inhibitor development in hemophilia: genetics and environment. *Semin Thromb Hemost*. 2009;35(8):723–734. doi:10.1055/s-0029-1245105
35. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost*. 2007;5(4):692–699. doi:10.1111/j.1538-7836.2007.02450.x
36. Fowkes FJ, Price JF, Fowkes FG. Incidence of diagnosed deep vein thrombosis in the general population: systematic review. *Eur J Vasc Endovasc Surg*. 2003;25(1):1–5. doi:10.1053/ejvs.2002.1778
37. Rosendaal FR. Venous thrombosis: prevalence and interaction of risk factors. *Haemostasis*. 1999;29 Suppl S1:1–9. doi:10.1159/000054106
38. Isma N, Svensson PJ, Gottsater A, Lindblad B. Prospective analysis of risk factors and distribution of venous thromboembolism in the population-based Malmo Thrombophilia Study (MATS). *Thromb Res*. 2009;124(6):663–666. doi:10.1016/j.thromres.2009.04.022
39. Servey JT, Reamy BV, Hodge J. Clinical presentations of parvovirus B19 infection. *Am Fam Physician*. 2007;75(3):373–376.
40. Klamroth R, Groner A, Simon TL. Pathogen inactivation and removal methods for plasma-derived clotting factor concentrates. *Transfusion*. 2014;54(5):1406–1417. doi:10.1111/trf.12423
41. Part 2: General methods for Cochrane reviews: Chapter 7. Selecting studies and collection data. In: Higgins JP, Green S, eds. *Cochrane handbook for systematic reviews of interventions, version 5.1.0 (updated March 2011) The Cochrane Collaboration 2011* <https://handbook-5-1cochraneorg/Accessed December 2020>.

Figure 1. PRISMA flowchart presenting the results of the systematic literature review

Figure 2. Pooled hemostatic efficacy for on-demand treatment of bleeds (A), treatment of breakthrough bleeds during long-term prophylaxis (B) and during surgical prophylaxis (C) (N, %). A. Pooled data from 127 patients and 795 treated bleeds with haemostatic efficacy ratings across eight studies.^{6,8-10,12,15,16,18} B. Pooled data from 37 patients and 252 treated bleeds across nine studies.^{6,8-10,13-16,18} C. Pooled data from 202 patients undergoing a total of 266 procedures across eight studies (including moderate and mild severity).^{6,8,10,14-18} Data from included studies which did not report hemostatic efficacy are not represented in this figure.

Table 1. Population characteristics of studies reporting pdVWF/FVIII data

Study name and identifiers				SWIFT-VWD	SWIFTLY-VWD	SWIFT-VWDext	CSL-12-83	OPALE			
Primary reference	Dunkley et al. (2010) ¹⁷	Howman et al. (2011) ²²	Shorff et al. (2007) ²³	Lissitchkov et al. (2017) ¹¹	Auerswald et al. (2020) ⁵	Lissitchkov et al. (2020) ⁶	EudraCT 2013-003305-25 ¹⁸	Rugeri et al. (2021) ²⁰	Harroche et al. (2021) ¹⁴	Rugeri et al. (2022) ²¹	d'Oiron et al. (2022) ¹⁹
Substudy cohort	All ages, all regimens	Pediatric	Surgery	Adolescents and adults	Pediatric	Extension	Post-marketing	Surgery	Pediatric	Long-term Prophylaxis	On-demand
Patient number, N	20 ^a	43	43	22 ^c	17	19	25	66	19	23	29
Age, years	^b				NR	^e					
Mean (range) / (SD)	-	-	52.0 (19.0 - 80.0)	33.6 (15.2)	5.2 (3.4)	32.7 (18.5)	35.8 (19.1)	-	(1.0-12)	-	
Median (range)	-	10 (0.42-17.5)	-	30.5 (15.0-68.0)	5 (0.0-11.0)	30 (6.0-70.0)	-	45 (4.0-86)	-	16 (1.0-85)	43 (4.0-76.0)
Female sex, n (%)	9 (45)	18 (42)	22 (51)	12 (55)	10 (59)	7 (37)	12 (48)	44 (67)	5 (26)	12 (52)	11 (38)
VWD type, n (%)											
1	5 (25)	21 (49)	26 (60)	5 (23)	0	2 (11)	NR	23 (35)	(27)	-	6 (21)
2A	2 (10)	4 (9)	8 (19)	4 (18)	7 (41)	4 (21)		13 (20)	(17)	1 (4)	5 (17)
2B	0	6 (14)	4 (9)	0	-	-		5 (8)	(13)	6 (26)	2 (7)
2M	6 (30)	4 (9)	0	0	-	-		10 (15)	(14)	-	4 (14)
2N	0	1 (2)	0	0	-	-		6 (9)	(5)	-	1 (3)
3	6 (30)	7 (17)	5 (12)	13 (59)	10 (59)	13 (68)		6 (9)	(15)	16 (70)	6 (21)
NA	1 (5)	-	-	-	-	-		3 (4)	(9)	-	5 (17)
Severe VWD, n	NR	NR	NR	22 (100) ^d	17 (100)	19 (100)	25 (100) ^f	NR	NR	NR	NR

^f severe disease defined as VWF:RCo plasma levels <20%

On-Demand treatment of bleeds									
Study name and identifiers	N/A	N/A	SWIFT-VWD		SWIFTLY-VWD	SWIFT-VWDext	CSL-12-83	OPALE	
Primary reference	Dunkley et al. (2010)	Howman et al. (2011)	Lissitchkov et al. (2017)		Auerswald et al. 2020	Lissitchkov et al. (2020)	EudraCT 2013-003305-25	Harroche et al. (2021)	d'Oiron et al. (2022)
Substudy cohort	All ages	Pediatric	Adolescents and adults		Pediatric	Extension	Post-marketing	Pediatric	All ages
Patient number, N	5	24	20 ^b		12	7	11	19	29
Number of bleeds, n	9	72	407 ^c		80 ^c	77 ^c	69 ^c	23	62
Haemostatic efficacy, n (%)									
Overall	N=6 ^a		d		d	d	d		
Excellent	4 (66)	68 (94)	374 (92)		36 (45)	35 (46)	22 (32)	23 (100)	57 (92)
Good	-		25 (6)		44 (55)	41 (53)	36 (52)		
Moderate	1 (17)	4 (6)	7 (2)		-	1 (1)	11 (16)	-	-
NA	1 (17)	-	0		-	-	-	-	5 (8)
Long-term prophylaxis									
Study name and identifiers			SWIFT-VWD		SWIFTLY-VWD	SWIFT-VWDext	CSL-12-83	OPALE	
Primary reference	Dunkley et al. (2010)	Howman et al. (2011)	Lissitchkov et al. (2017)		Auerswald et al. 2020	Lissitchkov et al. (2020)	EudraCT 2013-003305-25	Harroche et al. (2021)	Rugieri et al. (2022)
			CP arm	CP-Switch arm					

Patient number, N	4	2	1	8	4	10	14	7	23
Prophylactic efficacy rating, n (%)	^e	NR	NR	NR	NR	NR	NR		
Excellent/Good	4 (100)							7 (100)	19 (100) ⁱ
Moderate/Poor	-							-	-
NA	-							-	-
Number of treated breakthrough bleeds, n	^f	NR	1	10	73 ^h	96 ^h	72 ^h	NR	NR
Haemostatic efficacy in breakthrough bleeds, n (%)				^g	^g	^g	^g		
Excellent/Good	^f		1 (100)	10 (100)	73 (100)	94 (98)	64 (89)		
Moderate/None	-		-	-	-	2 (2)	8 (11)		
Surgical prophylaxis									
Study name and identifiers				SWIFT-VWD		SWIFTLY-VWD	CSL-12-83		OPALE
Primary reference	Dunkley et al. (2010)	Howman et al. (2011)	Shortt et al. (2007)	Lissitchkov et al. (2017) [10]		Auerswald et al. 2020	Post-marketing		Harroche et al. (2021)
				OD arm	LTP-Switch arm	OD arm	OD arm	LTP arm	
Patient number, N	19	31	43	4	2	3	11	14	9
Number of procedures, n	29	42	58	4	2	8	9	4	10
Procedure type, n (%)	^j	^j		^j	^j	^q			
Major surgery	10 (34)	10 (24)	22 (38)	-	-	-	NR	NR	2 (20)
Minor surgery	19 (66)	32 (76)	23 (40)	4 (100)	2 (100)	8 (100)			7 (70)
Dental procedures	-	-	13 (22)	-	-	-			1 (10)
Prophylaxis haemostatic efficacy rating, n (%)									
Overall	N=25 ^k			^o	^p	^p			
Excellent	25 (100)	38 (90)	45 (78)	4 (100)	2 (100)	7 (87)	4 (44)	3 (75)	9 (100)
Good			13	-	-	1 (13)	5	-	65 (99)

			(22)				(56)			
Moderate	-	4 (10)	-	-	-	-	-	-	-	1 (1)
NA	-	-	-	-	-	-	-	1 (25)	-	-
Per procedure type (excellent/good rating, %)							NR	NR		
Major	10 (100)	9 (90)	22 (100)	-	-	-			"Good to excellent"	100
Minor	15 (100)	29 (91)	23 (100)	4 (100)	2 (100)	8 (100)				99 ^s
Dental procedure	-	-	13 (100)	-	-	-				
Blood loss during surgical procedures, n (%)	N=20 ^m	N=23 ⁿ	NR					N=3 ^r	NR	NR
Less than expected	17 (85)	20 (87)		1 (25)	1 (50)	-	1 (11)	1 (25)		
Equivalent to expected				3 (75)	1 (50)	8 (100)	8 (89)	2 (50)		
NA	-	-		-	-	-	-	1 (25)		

ABR: annualized bleeding rate; LTP: long-term prophylaxis; NA: not available; NR: not reported. Not all bleeding event details were reported or categorized, hence n numbers within categorized data may vary from total number of bleeds.

^a overall hemostatic efficacy was done by the investigator at the post-treatment visit 24h after the final dose. Only six of the nine non-surgical bleeds were assessed, although overall hemostatic efficacy rating was only reported for five bleeding events

^b on-demand efficacy population included 21 study participants. Exclusion of one patient due to the absence of evaluable non-surgical bleeding event

^c regarding number of treated bleeding events requiring pdVWF/FVIII administration as assessed by the investigator; all N are quoted directly from published papers.

^d investigator evaluated clinical response efficacy in every 3-month visit. Reported the overall hemostatic efficacy assessment according to investigator

^e hemostatic efficacy assessment was done each 3-months during the 12-month period. Data reports to the overall clinical response of investigator throughout the treatment period

^f reported 22 breakthrough bleeds during prophylaxis, although not explicit number of treated bleeds. Authors mention that overall efficacy in the management of bleeding events was excellent although all patients experienced at least one episode of spontaneous bleeding during the study period

^g reported investigator hemostatic efficacy assessment per treated non-surgical bleeding event

^h number of bleeding events assessed by the investigator

ⁱ data available for 19 patients

^j dental procedures/extractions were classified as minor surgery

^k overall hemostatic efficacy overall assessment at the post-treatment visit 24 hours after the final dose. Of the total 29 procedures, only 25 were assessed by the investigator

^l all major surgeries (n=10) were assessed for hemostatic efficacy, while only 15 minor surgeries were evaluated

^m approximately 85% of the surgery treatment events had assessments of blood loss by the surgeon: minor surgeries (n/N=10/12); major surgery (n/N=7/8)

ⁿ approximately 87% of the surgical events were assessed for blood loss by the surgeon - minor surgeries (n/N=15/16); major surgery (n/N=5/7)

^o post-surgery overall assessment

^p overall hemostatic efficacy assessment at the moment of discharge

^q minor surgical procedure was defined as surgery involving little risk to the life of the subject

^r assessment reported for only three procedures

^s one moderate outcome reported for minor surgery which included dental procedures

Table 3. Safety outcomes for on-demand treatment of bleedings, long-term prophylaxis, and surgical prophylaxis with pdVWF/FVIII

On-demand treatment of bleeds									
Study name and identifiers			SWIFT-VWD	SWIFTL Y-VWD	SWIFT-VWDext	CSL-12-83		OPALE	
Primary reference	Dunkl ey et al. (2010)	Howm an et al. (2011)	Lissitchkov et al. (2017)	Auersw ald et al. 2020	Lissitch kov et al. (2020)	EudraCT 2013-003305-25		Harroc he et al. (2021)	d'Oir on et al. (2022)
Patient number, N	5	24	21	12	7	11		3	29
Time of exposure, days	^a	NR	NR	8 (1-36)	NR	NR		NR	NR
Patients with any AE, n (%)	NR	NR	13 (62)	9 (69)	7 (100)	7 (64)		NR	0
Treatment-related			NR	1	NR	0			
Patients with any SAE, n (%)	NR	NR	NR	0	3 (43)	1 (9)		NR	0
Treatment-related			0	0	NR	0			
Patients with treatment discontinua tion due to AE, n (%)			0	0	0	NR		NR	0
Patients with AE of interest, n (%)						NR		NR	0
Severe hypersensiti vity reactions	NR	0	0	0	0				
Thrombotic events	0	0	0	0	0				
Long-term prophylaxis									
Study name and identifiers			SWIFT-VWD	SWIFTL Y-VWD	SWIFT-VWDext	CSL-12-83	OPALE		
Primary reference	Dunkl ey et al.	Howm an et al.	Lissitchkov et al. (2017)	Auersw ald et al. 2020	Lissitch kov et al.	Eudra CT 2013-	Rug eri et	Harroc he et al.	Ruge ri et al.

	(2010)	(2011)				(2020)	00330 5-25	<i>al.</i> (2020)	(2021)	(2022)
			LTP arm	LTP- Switch arm						
Patient number, N	4	2	1	8	4	10	14	12	7	23
Time of exposure, days (median (range))	^b	NR	NR	NR	129 (55–197)	NR	NR	NR	NR	NR
Patients with any AE, n (%)	NR	NR	1 (100)	3 (38)	3 (75)	7 (70)	12 (86)	1 (8)	NR	0
Treatment-related			17	2	1	NR	1 (7)	0		0
Patients with any SAE, n (%)			0	1 (12)	0	0	1 (7)	NR		0
Treatment-related			NR	0	NR	NR	NR			0
Patients with treatment discontinuation due to AE, n (%)	NR	NR	0	0	0	0	NR	NR	NR	0
Patients with AE of interest, n (%)	NR		NR	NR			NR	NR	NR	NR
Severe hypersensitivity reactions		0			0	0		NR	NR	0
Thrombotic events	0	0	0	0	0	0		0	NR	0
Surgical prophylaxis										
Study name and identifiers	N/A	N/A	N/A	SWIFT-VWD	OPALE					
Primary reference	Dunkley <i>et al.</i> (2010)	Howman <i>et al.</i> (2011)	Shortt <i>et al.</i> (2007)	Lissitchkov <i>et al.</i> (2017)	Harroche <i>et al.</i> (2021)	Rugeri <i>et al.</i> (2021)				
Patient number, N	19	31	43	4	9	66				
Time of exposure, days (median	^c	3 (1–24)	NR	NR	NR	1 (1–8)				

(range)										
Patients with any AE, n (%)	NR	NR	NR	NR	NR	6 ^d				
Treatment-related			0			NR				
Patients with any SAE, n (%)			NR							
Treatment-related			0							
Patients with treatment discontinuation due to AE, n (%)	NR	NR	NR	NR	NR	NR				
Patients with AE of interest, n (%)										
Severe hypersensitivity reactions		0								
Thrombotic events	0	0		0		1				

AE: adverse event; NR: not reported; SAE: serious adverse event

^a reported median exposure (range) – 2 (1;10) days

^b only reported median (range) treatment duration – 62 (53;197) days

^c reported median (range) exposure – 7.5 (3;24) and 2 (1;8) days in major and minor procedures, respectively

^d 6 AE's reported, not N patients

Table 4. Pooled safety data on-demand treatment of bleedings, long-term prophylaxis, and surgical prophylaxis with pdVWF/FVIII

Pooled safety data	On-demand	Long-term Prophylaxis	Surgical Prophylaxis
Patient number, N	109	78	163
Patients with any AE, n (%)	36 (33)	27 (35)	6 (4)
Treatment-related	1 (1)	21 (27)	0
Patients with any SAE, n (%)	4 (4)	2 (3)	0
Treatment-related	0	0	
Patients with AE of interest, n (%)	0	0	
Severe hypersensitivity reactions			0
Thrombotic events			1 (1) ^a

AE: adverse event; SAE: serious adverse event

^a DVT deemed unrelated to treatment, case report included in supplemental results

Table 5. Pharmacovigilance surveillance data

Pharmacovigilance data reported in clinical trials	
Total clinical trial population (N)^a	246

Reported cases (N)	24
Serious adverse events (N)	34
Anti-FVIII inhibitors (N)	5
Hemophilia A patients (n)	4
VWD patients (n)	1 ^b
Thromboembolic events (TEE; N)	1
Incidence TEEs in study population (%)	0.41
Ischemic stroke (n)	1 ^c
Hypersensitivity and/or anaphylaxis	0
Incidence hypersensitivity in study population (%)	0.00
Transmission of infectious agents (N)	2 ^d
Incidence transmission infectious agents in study population (%)	0.82
Pharmacovigilance data reported in post-marketing surveillance	
Doses pdVWF/FVIII administered	
IU VWF	3,300,753,000
IU FVIII	1,375,313,750
Single dose exposures	916,875
Patient years ^e	5,877
Reported cases (N)	241 ^f
Adverse drug responses (ADRs; N)	494
Case reports specific to Voncento®/Biostate® (n)	158
ADRs specific to Voncento®/Biostate® (n)	392
Anti-FVIII/VWF inhibitors	
Reported cases (N)^g	9
Anti-FVIII/VWF inhibitors ADRs (N)^h	11
Proportion inhibitor ADRs relative to total ADRs (%)	2.8
Non-serious ADRs (n)	1
Serious ADRs (n)	10
Anti-FVIII inhibitors (n)	10
Serious ADRs	9
Non-serious ADRs	1
Anti-VWF inhibitors (n)	1
Serious ADRs	1
Non-serious ADRs	0
Thromboembolic events (TEE)	
Reported cases (N)	5
TEE ADRs (N)	5
Proportion TEE ADRs relative to total ADRs (%)	1.28
Non-serious ADRs (n)	0
Serious ADRs (n)	5
Deep vein thrombosis	2
Pelvic venous thrombosis	1
Pulmonary embolism	2
Hypersensitivity reactions	
Reported cases (N)	34
Hypersensitivity ADRs (N)	62
Proportion hypersensitivity ADRs relative to total ADRs (%)	15.82

Non-serious ADRs (n)	28
Serious ADRs (n)	34
Anaphylaxis (n)	7
Transmission of infectious agents (TIA)	
Reported cases (N)	1
TIA ADRs (N)	1
Proportion TIA ADRs relative to total ADRs (%)	0.26
Viral infection (n)	1

ADR, adverse drug reaction; FVIII, factor VIII; VWD, von Willebrand disease VWF; von Willebrand factor.

^a Includes hemophilia A and VWD

^b Type 3 VWD

^c Not a case from a clinical trial within this SLR and not related to the use of pdVWF/FVIII

^d Epstein-Barr virus infection and comprised a total of 2 AEs in one patient, not confirmed to be associated with pdVWF/FVIII complex

^e Using 1500 IU FVIII/3600 IU VWF as standard dose per single administration

^f Includes remaining 83 cases with 102 ADRs pertaining to Human Factor VIII VWF (generic) that were excluded

^g Hemophilia A and VWD indication was not available

^h In one case, two serious ADRs of both FVIII inhibition and VWF inhibition were reported

Supplemental Materials

Supplemental methods

The search terms used for the online database searches in MEDLINE® and the Cochrane library are summarized in Supplemental Tables 1 and 2. All relevant systematic literature reviews and/or meta-analyses were reviewed, and any additional references identified from the bibliographies were included as grey literature. Grey literature also included relevant abstracts from the main scientific congress meetings in the therapeutic area of interest, restricted to the period of 2017–2022 (Supplemental table 3). The grey literature review was supplemented with a structured search of the main clinical trials registers (Supplemental table 4).

Reference selection

All publications retrieved were assessed against predefined inclusion/exclusion criteria to identify references of interest (Supplemental Table 5), following the Cochrane group recommendations.⁴¹ The criteria were selected to identify publications on studies including patients of any age (including pediatric) with mild, moderate, or severe inherited VWD,

receiving pdVWF/FVIII as either OD treatment, LTP or SP, and reported outcomes including efficacy, safety or consumption. Intermittent prophylaxis for menorrhagia was included in the inclusion criteria although this treatment regimen was not reported in the retrieved studies.

An initial screening was conducted on the title and abstract followed by a full-text screen of those articles that passed the initial screening. As cohort studies may be reported in more than one publication, the identified references were screened to link those reporting on the same study cohort, allowing duplicates or superseded study reports to be removed.

Data reported as mild, moderate or severe, such as classifications of bleeding episodes and surgical procedures, were as reported within each study. In one study where surgical procedures were not characterized into major or minor surgeries, the authors classified the procedures according to their own experience; consensus across all authors was agreed. This occurred in one instance of one study and did not affect the overall reported assessment of hemostatic efficacy for those procedures.¹⁵

Supplemental Table 1. Search strategy for MEDLINE®

#	Pubmed
1	"von Willebrand Diseases" [mh] OR "von Willebrand* Disease*" [tiab] OR "Von Willebrand Disorder*" [tiab] OR VWD [tiab] OR "Von Willebrand* Factor Deficiency" [tiab] OR "VWF deficiency" [tiab] OR "Von Willebrand* Deficiency" [tiab]
2	Voncento [tiab] OR Biostate [tiab] OR Aleviate [tiab]
3	von Willebrand Factor [mh]
4	#2 OR #3
5	#1 AND #4
6	clinical study [pt] OR observational study [pt] OR clinical trial [pt]
7	#5 AND #6
8	"animals" [mh] NOT "humans" [mh]
9	#7 NOT #8

Supplemental Table 2. Search strategy for the Cochrane Library

#	Cochrane Library
---	------------------

1	MeSH descriptor: [von Willebrand disease] explode all trees
2	"von Willebrand Diseases" OR "von Willebrand* Disease*" OR "Von Willebrand Disorder*" OR VWD OR "Von Willebrand* Factor Deficiency" OR "VWF deficiency" OR "Von Willebrand* Deficiency"
3	#1 AND #2
4	Voncento OR Biostate OR Aleviate
5	MeSH descriptor: [von Willebrand factor] explode all trees
6	#4 OR #5
7	#7 AND #3

To supplement the MEDLINE® and Cochrane database searches, a structured search was performed of abstract books of the main scientific congress/meetings in the therapeutic area of interest and restricted to the period of 2017–2022 (Supplemental Table 3). Each abstract was reviewed according to the pre-defined criteria and all references of interest were included as grey literature.

Supplemental Table 3. Main scientific congress in the therapeutic area of interested included in grey literature review

Scientific event	Period
World Federation of Hemophilia World Congress	2017-2023
International Society of Thrombosis and Haemostasis Congress	
American Society of Hematology Annual Meeting	
European Haematology Association Annual Meeting	

Additional grey literature was identified with a structured search of the main clinical trials registers (Supplemental 4).

Supplemental Table 4. Clinical trial registers included in grey literature review

Clinical trials registers	Search terms	Study type	Additional filter	Time filter
Clinicaltrials.gov	Von Willebrand Disease	All studies ^a	Studies with results	No time restriction
European Union Clinical Trial Register		NA		

NA: not applicable; ^a including interventional trials, observational studies and expanded access studies

The PICOS (Population, Intervention, Comparators, Outcomes and Study Design) criteria are summarized in Supplemental Table 5.

Supplemental Table 5. Study selection criteria

Inclusion criteria				Exclusion criteria	
Population		Adult and pediatric patients with mild, moderate and severe inherited VWD		<ul style="list-style-type: none">Acquired von Willebrand syndromeOther populations	
Intervention		Treatment with Human coagulation FVIII/human VWF (Voncento®/Biostate®/Aleviate®; CSL Behring, Marburg, Germany) in the following regimens: <ul style="list-style-type: none">On-demand treatment, including intermittent prophylaxis for non-surgical bleeds (NSBs)^aLong-term (continuous) prophylaxisSurgical prophylaxis		<ul style="list-style-type: none">Other pharmacological or non-pharmacological agentsOther treatment regimens	
Outcomes	Efficacy	Surgical prophylaxis	Prophylactic efficacy response assessment	Other outcomes	
			Blood loss during surgical procedures		
		On-demand treatment	Hemostatic efficacy assessment for total bleeds and per bleeding type, if available (spontaneous bleeding, traumatic bleeding, joint bleeding, mucosa bleeding, muscle bleeding)		
			Long-term prophylaxis		Prophylactic efficacy assessment
		ABR, AsBR and/or AjBR			
		Time to first bleeding event			
		Joint health status assessed by Haemophilia Joint Health Score			
		Bleeding assessment according to Tosetto Bleeding Score			
		Bleeding assessment according to International Society of Thrombosis and Haemostasis - Bleeding Assessment Tool			
		Intermittent prophylactic treatment (for menorrhagia)			Prophylactic efficacy of menstrual bleeding assessment according to the Pictorial Blood Assessment Chart
		Safety	Proportion of patients with (treatment related) adverse events		
			Proportion of patients with (treatment related) serious adverse events		
	Proportion of patients with thromboembolic events				
	Proportion of patients with serious hypersensitivity reactions				
	Proportion of patients who discontinued due to (treatment related) adverse events				
	Consumption	Surgical bleeding	VWF infusion number required to treat surgical bleedings, stratified by major or minor procedures (if possible)		
			VWF dose required to treat bleedings (preferable per infusion), if possible stratified by major or minor procedures		
		Surgical prophylaxis	VWF infusion number, stratified by major or minor procedures (if possible)		
			VWF dose (preferable per infusion), if possible stratified by major or minor procedures		
		On-demand treatment	VWF infusion number necessary to treat bleedings, stratified by major or minor non-surgical bleeding events (if possible)		
			VWF dose necessary to treat bleedings,		

				stratified by major or minor non-surgical bleeding events (if possible)	
		Long-term prophylactic treatment		Number of prophylactic infusions	
				VWF dose (preferable per infusion)	
		Intermittent prophylactic treatment (for menorrhagia)		Number of prophylactic infusions	
				VWF dose (preferable per infusion)	
		Other outcomes	LTP	PK	
	PROM				
			HRU and costs	Disease impact in self-perceived functional abilities assessed by Haemophilia Activities List	
	Number and duration of hospital admissions				
				Number of monitoring visits	
	Number and cost of transfused units of red blood cell concentrates				
Study design		<ul style="list-style-type: none">Interventional studies: controlled and non-controlled studies, including RCTs, non-RCT and single-arm trialsNon-interventional studies: observational studies, registries studies, PMS and PASS studies;			Pre-clinical studies, case reports, case series, reviews, comments, letters, editorials
Language		<ul style="list-style-type: none">No restriction during search and on abstract screening levelRestriction to English on full-text screening level			
Geographic		No restriction			
Time		No restriction			

^a non-surgical bleed (NSB) examples include epistaxis, gastrointestinal bleeds or menorrhagia. AsBR: annualized spontaneous bleeding rate; ABR: annualized bleeding rate; AjBR: annualized joint bleeding rate; LTP: long-term prophylaxis; FVIII: factor VIII; HRU: healthcare resource utilization; VWD: von Willebrand disease; VWF: von Willebrand Factor; PASS: post-authorization safety studies; pdVWF: plasma-derived von Willebrand factor; PK: pharmacokinetic parameters; PMS: post-marketing surveillance; PROM: patient reported outcome measures; RCT: randomized clinical trials; rVWF: recombinant von Willebrand factor

Classification of mild, moderate and severe bleeding events

Clinical efficacy parameters were assessed in studies using investigator rating scales and extracted data for this review retained the original published score. Most studies used assessed hemostatic efficacy was assessed using the following four-point grading scale: excellent (hemostasis achieved/cessation of bleeding), good (partial but adequate control of bleeding; did not require additional product for unplanned treatment), moderate (moderate control of bleeding; required additional product for unplanned treatment) and none (severe uncontrolled bleeding). Non-surgical bleeding events were assessed as 'major' or 'minor' by

the study investigators. 'Major' events included any bleeding into a joint or muscle or in the brain, or a mucosal bleeding of the gastrointestinal tract (excluding nasal or oral bleeding).

All other bleeding events were classified as 'minor' unless the investigator assessment noted otherwise.

Major and minor surgical bleeding events were reported as classified by the study investigators within each publication, except where these were unavailable in once study and the manuscript authors assigned major or minor ratings according to previous experience.

Classification of pharmacovigilance reporting

An adverse event is considered serious if it meets one or more of the following criteria:

1. results in death, or is life-threatening;
2. requires inpatient hospitalization or prolongation of existing hospitalization;
3. results in persistent or significant disability or incapacity;
4. results in a congenital anomaly (birth defect); or is otherwise "medically significant".

MedDRA Queries

Standardized MedDRA Queries (SMQs), High Level Group Terms (HLGT), High Level Terms (HLT) and Preferred Terms (PT) within the MedDRA dictionary were used as needed to identify events of special interest (important identified and potential risks) for analysis as follows:

- Anaphylaxis and hypersensitivity/allergic reactions were identified using MedDRA Hypersensitivity (SMQ) (narrow) and Anaphylactic reaction (SMQ) (narrow).
- Thromboembolic complications were identified using MedDRA Embolic and thrombotic events (SMQ).

- Development of factor VIII/von Willebrand factor inhibitors was identified using selection of PTs that specifically report formation of inhibitors (anti-factor VIII antibody positive, Factor VIII inhibition, inhibiting antibodies positive, von Willebrand factor activity decreased, von Willebrand factor antibody positive, von Willebrand factor antigen decreased, von Willebrand factor activity inhibition, and von Willebrand factor multimers abnormal).
- Suspicion of virus transmission was identified using terms associated with viral infection from the HLT of viral infectious disorders, and a selection of terms from the HLT of ancillary infectious topics, and HLT of sepsis, bacteremia, viraemia and fungaemia NEC; terms associated with Investigations relating to viral infection from the HLT of virus identification and serology, and a selection of terms from the HLT of microbiology and serology tests NEC; a selection of terms associated with procedures relating to viral infection from the HLT of anti-infective therapies.

Once identified, these cases were not reviewed to confirm that they met case definitions.

The cumulative quantity of pdVWF/FVIII distributed until 31st May 2023 was established from commercial records. As the actual total number of patients who received pdVWF/FVIII is not known, patient exposure is presented as number of estimated standard doses based on the units distributed.

Supplementary Results

Study cohorts included in systematic literature review

Of the five prospective interventional studies included, one was an early Phase II/III trial of pdVWF/FVIII in Australia of 23 patients with all ages with any type of inherited VWD.¹⁰ Three multi-national interventional studies were from the SWIFT program (Studies with von Willebrand factor/ Factor VIII) which includes the SWIFT-VWD Phase II study in adult and

adolescent patients (NCT00941616),⁶ the SWIFTLY-VWD Phase III study in pediatric patients (NCT01213446),⁸ and the SWIFT-VWDext Phase III extension study (NCT01224808) which includes patients from both the SWIFT-VWD and SWIFTLY-VWD studies.⁹ Finally, a post-marketing observational Phase IV study CSL-12-83 (NCT02552576) with 26 patients enrolled across 4 European countries was included.¹¹

Six observational studies assessed the use of pdVWF/FVIII including 4 prospective observational studies from the OPALE study cohort.¹²⁻¹⁵ The OPALE (Observatoire des patients présentant une Maladie de Willebrand et traités par Voncento®) study is a French multicenter observational study across 18 French bleeding disorder centers.¹⁴ It is designed to follow patients of all ages with any type of inherited VWD requiring treatment with Voncento® with currently 130 enrolled study patients.¹²⁻¹⁵ Two further non-interventional studies were retrospective observational studies, summarizing 43 pediatric patients from eighteen pediatric hemophilia treatment centers (HTCs) in Australia and New Zealand,¹⁶ and another study across three Australian HTCs of 43 adult patients undergoing surgical procedures.¹⁷

Hemostatic Efficacy Outcomes – Heavy Menstrual Bleeding/Intermittent Prophylaxis

This patient with severe type 1 VWD experienced 18 NSBs in 12 months whilst receiving OD treatment before switching to the LTP arm, following which the patient reported 1 bleed during the 12-month study period.⁶ Further menstrual bleedings were reported as NSBs within the OD treatment arm of the SWIFTLY-VWDext study. Treatment efficacy was assessed for 107 bleeding days by the patient/legal guardian, reported as moderate efficacy for 43.9% of bleeding days; these days were associated with menstrual bleedings and particularly associated with one individual patient (VWD type not reported).⁹

Safety Outcomes

Data regarding SAEs were reported in six publications, with only 2 cases reported: one case included three serious treatment-emergent adverse events (TEAEs) in the same patient within the SWIFT-VWD study, which were unrelated to pdVWF/FVIII treatment,⁶ and one in the CSL-12-83 trial.¹¹ In the SWIFT-VWD study, three serious TEAEs in a 68-year-old male patient were worsening of diabetes mellitus, a cataract in one eye and a mild increase in prostate antigen levels.⁶ The other SAE case was related to asthma in a subject receiving pdVWF/FVIII in the OD treatment group of the CSL-12-83 trial, however, no further details were available.¹¹

One case of deep vein thrombosis (DVT) was reported, occurring 10 days after the last infusion of pdVWF/FVIII and classified by the investigator as unrelated to treatment.¹³ This patient was a 53-year-old female with type 2N VWD, a body mass index of $>31\text{Kg/m}^2$ undergoing a total hip replacement. FVIII:C levels were $<150\text{ IU/dL}$ during the pdVWF/FVIII administration period where doses of 40, 26 and 26 IU VWF:RCO/Kg were given on days 0, 1 and 3, respectively. No information on the use of antithrombotic agents were reported for this patient.

Dosing and Consumption in Clinical Trials

On-demand dosing and consumption reporting varied between publications. The median (range) number of infusions was reported as 20 (3–92) infusions per patient during the SWIFT-VWD trial.⁶ In contrast, other studies reported the number of infusions per event, with a median (range) of 2 (1–12) reported by Dunkley *et al.*¹⁰ and a mean of 2.4 (significant difference [SD], 2.9) reported from the CSL-12-83 trial data.¹¹ The number of NSBs requiring OD treatment per patient per year was assessed in three studies, which reported medians of

19.5 (range 2–82),⁶ 12.7 (range 0.96–57.3),⁹ and 5.5 (range 1–22).⁸ Treatment duration ranged from a median (range) of 1 (1–13) to 2 (1–10) days per bleeding event.^{10,16}

Dosing and consumption data for LTP regimen were reported in six out of 8 studies reporting LTP treatment outcomes. In the SWIFT-VWD study, a median (range) prophylactic dose of 28.8 (25–35) IU VWF:RCo/Kg per infusion 1–3 times weekly was reported in the switch treatment arm.⁶ Comparatively, a dose of 37.9 IU VWF:RCo/Kg per infusion every 2–3 days was used to treat the single patient in the LTP treatment arm. This patient with type 1 VWD was administered two additional doses of 55.3 and 27.7 IU VWF:RCo/Kg to treat a major mucosal bleeding event.⁶ In the study from Dunkley *et al.*, an estimated median (range) dose of 56.2 (33.6–69.8) IU VWF:RCo/Kg (46.8 [28.0–58.2] FVIII:C IU/Kg) was reported per patient.¹⁰ In the SWIFT post-marketing study, a mean dose of 147.6 (\pm 171.8 SD) IU VWF:RCo/Kg was administered per NSB event in the OD arm and a mean dose of 167.2 (\pm 162 SD) IU VWF:RCo/Kg in the LTP arm.¹¹

Dunkley *et al.* reported a median (range) of 2 (1–14) and 10 (3–35) infusions administered in minor and major surgeries, respectively.¹⁰ The number of infusions required to treat a surgical bleeding event in the CSL-12-83 registry trial differed between study arms, with a mean (SD) of 15.8 (9.6) and 3.3 (2.6) administrations in the OD and LTP groups, respectively.¹¹ Howman *et al.* and Dunkley *et al.* both reported a median (range) of 3 (1–24) treatment days per procedure (median for major procedures 7–7.5 days and minor procedures 2–3 days).^{10,16} Shortt *et al.* reported a mean duration of 5, 3, and 2-day treatment duration for major, minor, and dental surgical procedures, respectively.¹⁷ In the

OPALE study, the median duration of treatment for minor surgeries was one day (range 1–8) whilst major surgeries required a median treatment duration of 4 days (range 1–26).¹³

Pre-operative loading doses were also reported in the surgical cohort of the OPALE study, where doses were similarly stratified according to surgical severity resulting in a median dose of 43.0 IU VWF:RCo/Kg (range 25.0–66.0) for major surgery and 41.0 IU VWF:RCo/Kg (range 18.0–147.0) for minor surgery.¹³ Four studies reported use of adjunctive therapies in 38.1–60.6% of surgical events,^{10,13,16,17} where tranexamic acid (TXA) or other antifibrinolytics were most frequently administered (Table 4).

Supplemental Table 6. Studies reporting pdVWF/FVIII data

Study name [clinical trials ID]	Primary reference	Study design	Study phase	Blinding	Centers	N	LT P	S P	O D
-	Dunkley <i>et al.</i> (2010)	Interventional (single-arm)	II/III	Open label	Multicentric (Australia/ New Zealand)	23	X	X	X
-	Howman <i>et al.</i> (2011)	Observational (retrospective)	-	-	Multicentric (Australia/ New Zealand)	43	X	X	X
-	Shortt <i>et al.</i> (2007)	Observational (retrospective)	-	-	Multicentric (Australia)	43		X	
SWIFT-VWD CSL-08-54 (NCT00941616)	Lissitchkov <i>et al.</i> (2017)	Interventional (multi-arm NRS)	II	Open label	Multicentric (Europe)	22	X	X	X
SWIFTLY-VWD CSL-08-52 (NCT01213446)	Auerswald <i>et al.</i> 2020	Interventional (multi-arm NRS)	III	Open label	Multicentric (Europe, Asia, America)	17	X	X	X

SWIFT-VWDext	Lissitchkov <i>et al.</i> (2020)	Interventional	III	Open label	Multicentric	18 ^a	X		X
CSL-09-64 (NCT01224808) (Includes patients from NCT00941616 and NCT01213446)		(multi-arm NRS)			(Europe)				
CSL-12-83 (NCT02552576)	EudraCT 2013-003305-25	PMS (single-arm)	IV	Open label	Multicentric (Europe)	25	X	X	X
OPALE (NCT04657887)	Rugeri <i>et al.</i> (2021)	Observational (prospective)	Post-marketing	-	Multicentric (France)	66		X	
	Harroche <i>et al.</i> (2021)					19	X	X	X
	Rugeri <i>et al.</i> (2022)					23	X		
	d'Oiron <i>et al.</i> (2022)					29			X

LTP: long-term prophylaxis; OD: on-demand; NRS: non-randomized study; PMS: post-marketing study; SP: surgical prophylaxis

^a subpopulations of interest

Supplemental Table 7. Efficacy outcomes for on-demand treatment of bleedings, long-term prophylaxis, and surgical prophylaxis with pdVWF/FVIII

On-demand treatment of bleeds										
Study name and identifiers	N/A	N/A	SWIFT-VWD	SWIFT LY-VWD	SWIFT - VWDext	CSL-12-83	OPALE			
Primary reference	Dunkley <i>et al.</i> (2010)	Howman <i>et al.</i> (2011)	Lissitchkov <i>et al.</i> (2017)	Auerswald <i>et al.</i> (2020)	Lissitchkov <i>et al.</i> (2020)	EudraCT 2013-003305-25	Harroche <i>et al.</i> (2021)	d'Oiron <i>et al.</i> (2022)		
Substudy cohort	All ages	Pediatric	Adolescents and adults	Pediatric	Extension	Post-marketing	Pediatric	All ages		
Patient number, N	5	24	20 ^c	12	7	11	19	29		
Number of	9	72	407 ^d	80 ^d	77 ^d	69 ^d	23	62		

bleeds, n										
Bleeding event type, n (%)	a	b				NR				
Mucosal	5 (56)	46 (64)	290 (71)	65 (81)	69 (90)		9 (39)	31 (50)		
Musculoskeletal/Soft tissue	-	26 (36)	17 (2)	12 (15)	8 (10)		2 (9)	7 (12) ^h		
Bleeding event severity, n (%)	NR	NR	e	f	g	NR	NR	NR		
Severe			125 (31)	26 (33)	9 (12)					
Mild			281 (69)	54 (67)	68 (88)					
Bleeding event cause, n (%)	NR	NR				NR	NR	NR		
Spontaneous			403 (99)	62 (78)	73 (95)					
Traumatic			3 (1)	18 (22)	1 (1)					
Bleed type	NR					NR	NR	NR		
(Excellent/Good rating, %)										
Joint		-	101 (100)	11 (100)	6 (100)					
Mucosal		45 (98)	283 (98)	65 (100)	68 (99)					
Bleeding severity (Excellent/Good rating, %)	NR	NR				NR	NR	NR		
Severe			119 (95)	26 (100)	9 (100)					
Mild			280 (100)	54 (100)	67 (99)					
Bleed cause	NR	NR				NR	NR	NR		
(Excellent/Good rating, %)										
Spontaneous			396 (98)	62 (100)	72 (99)					
Traumatic			3 (100)	18 (100)	1 (100)					
Long-term prophylaxis										
Study name and identifiers			SWIFT-VWD		SWIFT LY-VWD	SWIFT - VWDe xt	CSL-12-83	OPALE		
Primary reference	Dunkley <i>et al.</i> (2010)	Howman <i>et al.</i> (2011)	Lissitchkov <i>et al.</i> (2017)		Auerswald <i>et al.</i> 2020	Lissitchkov <i>et al.</i> (2020)	EudraCT 2013-003305-25	Rugeri <i>et al.</i> (2020)	Harroche <i>et al.</i> (2021)	Rugeri <i>et al.</i> (2022)
			CP arm	CP-Switch arm						

Patient number, N	4	2	1	8	4	10	14	12	7	23
Reasons for prophylactic treatment, n (%)	i		NR	NR	NR	NR	NR	NR	NR	
Joint bleeding	1 (25)	1 (50)								43
Epistaxis	-	1 (50)								39
ABR	NR	NR	NR		NR	NR		NR	NR	
Prior to prophylaxis, median (range)				26.5 (18.0; 52.0)			-			1 (0-6.0) ^k
After prophylaxis, median (range)				1.0 (1.0;6.0)			-			0.5 (0-7.2)
After prophylaxis, mean (SD)				-			6.2 (6.8) ^j			-
Surgical prophylaxis										
Study name and identifiers				SWIFT-VWD		SWIFT LY-VWD	CSL-12-83		OPALE	
Primary reference	Dunkley et al. (2010)	Howman et al. (2011)	Shortt et al. (2007)	Lissitchkov et al. (2017) [10]		Auerswald et al. 2020	Post-marketing		Harroche et al. (2021)	Rugeri et al. (2021)
				OD arm	LTP-Switch arm	OD arm	OD arm	LTP arm		
Patient number, N	19	31	43	4	2	NR	11	14	9	66
Number of procedures, n	29	42	58	4	2	8	9	4	10	100
Procedure type, n (%)						v	NR			
Major surgery	10 (34)	10 (24)	22 (38)	-	-	-			2 (20)	31 (31)
Minor surgery	19 (66)	32 (76)	23 (40)	4 (100)	2 (100)	8 (100)			7 (70)	42 (42)
Dental procedures	i	i	13 (22)	i	i	-			1 (10)	27 (27)
Pre-operative loading dose [IU FVIII:C/Kg], mean (range)				NR		NR	NR		NR	
Major surgery	43 (27.3 - 118.2)	50 (25.0 - 115)	29 (9.0-62.0)							43 (25.0-66.0)
Minor surgery	34.8 (22.6	40 (21.0	33 (19.0-							41 (18.0-147.0)

	- 72.3)	- 75.0)	54.0)							
Dental procedures	-	-	30 (15.0-49.0)							-
Procedures with adjuvant treatment, n (%)				NR	NR	NR	NR			
Anti-fibrinolytic (tranexamic or aminocaproic acid)	9 (31) ^m	15 (61) ^q	23 (38) ^s							60.6 ^x
DDAPV	-	0	2 (4) ^s							-
Prophylaxis haemostatic efficacy, n (%)										
Overall	N=25 ⁿ			t	u	u				
Excellent	25 (100)	38 (90)	45 (78)	4 (100)	2 (100)	7 (88)	4 (44)	3 (75)	9 (100)	99 (99)-
Good			13 (22)	-	-	1 (12)	5 (56)	-		
Moderate	-	4 (10)	-	-	-	-	-	-	-	1 (1)
NA	-	-	-	-	-	-	-	1 (25)	-	-
Per procedure type (excellent/good)	o						NR	NR		
Major	10 (100)	9 (90)	22 (100)	-	-	-			"Good to excellent"	100
Minor	15 (100)	29 (91)	23 (100)	4 (100)	2 (100)	8 (100)				99 ^y
Dental procedure	-	-	13 (100)	-	-	-				
Blood loss during surgical procedures, n (%)	N=17 ^p	N=23 ^r	NR					N=3 ^w	NR	NR
Less than expected	17 (100)	20 (87)		1 (25)	1 (50)	-	1 (11)	1 (25)		
Equivalent to expected				3 (75)	1 (50)	8 (100)	8 (89)	2 (50)		
NA	-	-		-	-	-	-	1 (25)		

LTP: Long-term prophylaxis; DDAPV: desmopressin; NR: not reported; OD: on-demand. Not all bleeding event details were reported or categorized, hence n numbers within categorized data may vary from total number of bleeds.

^a authors classified non-surgical bleeding events as mucosal (n=5) and non-mucosal (n=4)

^b authors classified non-surgical bleeding events as mucocutaneous (n=46) and musculoskeletal (n=26)

^c on-demand efficacy population included 21 study participants. Exclusion of one patient due to the absence of evaluable non-surgical bleeding event

^d regarding number of treated bleeding events requiring pdVWF/FVIII administration as assessed by the investigator

^e severe bleeds were classified as major and included any bleeding into a joint or muscle or in the brain, or a mucosal bleeding of the gastrointestinal tract (excluding nasal or oral bleeding). All other NSB events were classified as 'minor' unless the investigator assessment noted otherwise

^f severe bleeds were classified as major bleeding event and defined as one that involves any bleeding into a joint, muscle, or mucosal bleeds of the gastro-intestinal tract (excluding nasal or oral bleeding). All other bleeding events were classified as minor unless the Investigator assessment noted otherwise

^g 402 total bleeds of which 325 did not require treatment; remaining 77 bleeds required pdVFW/FVIII administration of which 9 were major and 68 were mild.

^h Value does not include bone fracture or soft tissue haematomas due to nature of reported data "treated bleeding events included epistaxis (n = 24), gastro-intestinal bleedings (n = 10), menorrhagia (n = 9), muscle haematoma (n = 7), and others such as haematuria, haematoma, and bone fracture (n = 12)".

ⁱ data available for only one patient

^j reported as ABR of treated events

^k ABR for 19 patients receiving prior long-term prophylaxis

^m tranexamic acid was used as adjuvant treatment in 30.0% (n=3) and 31.5% (n=6) of major and minor procedures, respectively

ⁿ overall hemostatic efficacy overall assessment at the post-treatment visit 24 hours after the final dose. Of the total 29 procedures, only 25 were assessed by the investigator

^o all major surgeries (n=10) were assessed for hemostatic efficacy, while only 15 minor surgeries were evaluated

^p approximately 85% of the surgery treatment events had assessments of blood loss by the surgeon: minor surgeries (n/N=10/12); major surgery (n/N=7/8)

^q tranexamic acid used in 20.0% (n=2) of major procedures, 40.6% (n=13) of minor procedures

^r approximately 87% of the surgical events were assessed for blood loss by the surgeon - minor surgeries (n/N=15/16); major surgery (n/N=5/7)

^s tranexamic acid used in 18% (n=4), 48% (n=11) and 62% (n=8) of major, minor and dental procedures, respectively, while DDAVP was limited to one major and one minor procedure

^t post-surgery overall assessment

^u overall hemostatic efficacy assessment at the moment of discharge

^v minor surgical procedure was defined as surgery involving little risk to the life of the subject

^w assessment reported for only three procedures

^x tranexamic acid used in 54.3% of procedures (55% minor surgery, 34% major surgery and 74% dental procedures), antithrombotic agent used in 10.3% of respective procedures (8.7% of orthopedic, 17.7% of digestive, 9.1% of gynecological procedures and 7.4% dental surgeries)

^y one moderate outcome reported for minor surgery which included dental procedures

Supplemental Table 8. Dosing and consumption for on-demand treatment of bleedings, long-term prophylaxis, and surgical prophylaxis with pdVWF/FVIII

On-demand treatment of bleeds									
Study name and identifiers	N/A	N/A	SWIFT-VWD	SWIFT LY-VWD	SWIFT-VWDe xt	CSL-12-83	OPALE		
Primary reference	Dunkley <i>et al.</i> (2010)	Howman <i>et al.</i> (2011)	Lissitchkov <i>et al.</i> (2017)	Auerswald <i>et al.</i> 2020	Lissitchkov <i>et al.</i> (2020)	Eudra CT 2013-00330 5-25	Harroche <i>et al.</i> (2021)	d'Oiron <i>et al.</i> (2022)	
Substudy cohort	All ages	Pediatric	Adolescents and adults	Pediatric	Extension	Post-marketing	Pediatric	All ages	
Patient number, N	5	24	20 ^b	12	7	11	19	29	
Number of bleeds, n	9	72	407 ^c	80 ^c	77 ^c	69 ^c	23	62	
vWF consumption (vWF:RCO)									
Median total consumption (range) IU	NR	NR	657.6 (105–64)	536 (80–2080)	NR	NR	NR	NR	

Median dose per patient (range), IU/kg			NR		43.6 (34.2–66.1)								
Mean dose per event (SD), IU/kg					NR						147.6 (171.8)		
Mean daily dose (range), IU/kg/day					65.76 (31.2–115.44) ^a						108 (38.4–460.8) ^a	NR	
Mean dose per infusion (range), IU/kg					NR						NR	36.1 (29.0–64.0) ‡	54.6 (40.0–86.0)
Mean total dose per treatment event (IU) (Range, or +/- SD)					19,080 (3,600–50,400)							NR	
Long-term prophylaxis													
Study name and identifiers			SWIFT-VWD		SWIFT LY-VWD	SWIFT-VWDe xt	CSL-12-83	OPALE					
Primary reference	Dunkle y et al. (2010)	Howm an et al. (2011)	Lissitchkov et al. (2017)		Auers wald et al. 2020	Lissitc hkov et al. (2020)	Eudra CT 2013-00330 5-25	Harro che et al. (2021)	Ruger i et al. (2022)				
			LTP arm	LTP-Swi tch arm									
Patient number, N	4	2	1	8	4	10	14	7	23				
vWF consumptio n (vWF:RCo)		NR	NR	NR	NR	NR	NR	NR	NR				
Mean total consumptio n (SD) IU	294,900 (279,931)												
Median total consumptio n (range) IU	200,400 (79,200 – 699,600)				8062 (3244–13,642)								
Mean per infusion (SD) IU/kg	NR				NR								
Median per infusion (range).	56.16 (33.6–69.8) ^{a,d}		35.9 (NA)	28.8 (25.0–	61.6 (46.0–66.1)	42.8 (28.5–85.8)			45.0 (33.0 –				

IU/kg				35.0)					109.0)	
Median weekly dose (range), IU/kg	NR		NR	NR	NR				96.0 (44.0 – 222.0)	
Median dose to treat NSB events (Range)		108.0 (38.4–460.8)		37.0 (25.0–66.0)	62.8 (45.5–74.6)	60.0 (37.1–79.8)	167.2 (+/- 161.98) ^e		NR	
Surgical prophylaxis										
Study name and identifiers				SWIFT-VWD		SWIFT LY-VWD	CSL-12-83		OPALE	
Primary reference	Dunkley et al. (2010)	Howman et al. (2011)	Shortt et al. (2007)	Lissitchkov et al. (2017) [10]		Auerswald et al. 2020	Post-marketing		Harroche et al. (2021)	Rugeri et al. (2021)
				OD arm	LTP-Switch arm	OD arm	OD arm	LTP arm		
Patient number, N	19	31	43	4	2	NR	11	14	9	66
Number of procedures, n	29	42	58	4	2	8	9	4	10	100
Procedure type, n (%)	^f	^f		^f	^f	^g				
Major surgery	10 (34)	10 (24)	22 (38)	-	-	-	NR	NR	2 (20)	31 (31)
Minor surgery	19 (66)	32 (76)	23 (40)	4 (100)	2 (100)	8 (100)	NR	NR	7 (70)	42 (42)
Dental procedures	-	-	13 (22)	-	-	-	NR	NR	1 (10)	27 (27)
vWF consumption (vWF:RCo)										
Total mean vWF:RCo consumption (IU)	36,994 (4,800–206,400)	NR	NR	NR		NR	NR	NR	NR	NR
Major surgery	81,180 (21,600 – 206,400)									
Minor surgery	13,737.6 (4,800–82,800)									

y									
Median total dose (range), IU/kg	NR								
Maj or surgery									155 (40–575)
Min or surgery									63 (18–594)
Mean dose per infusion to treat surgical bleeding event (SD), IU/kg						58.5 (37.7) ‡	104.5 (87.1) ‡		NR
Mean dose (range), IU/kg	114.7 (54.2;283.7) ^a	96.0 (50.4;276.0) ^a	74.4(21.6;148.8) ^a	NR	NR	NR	NR	NR	NR
Maj or surgery	175.2 (65.5;283.7) ^a	120.0 (60.0;276.0) ^a	69.6 (21.6;148.8) ^a						
Min or surgery	83.5 (54.2;173.5) ^a	96.0 (50.4;180.0) ^a	79.2 (36.0;117.6) ^a						
Dental procedures	-	-	72.0 (36.0;117.6) ^a						
Maintenance dose				NR	NR	NR	NR	NR	NR
Mean daily dose (range), IU/kg/day	86.9 (30.2–179.8) ^a	112.8 (31.2–362.4) ^a	69.6 (21.6–156.0) ^a						
Maj or surgery	99.1 (30.2–179.8) ^a	122.4 (31.2–362.4) ^a	69.6 (21.6–146.4) ^a						
Min or surgery	80.4 (47.3–173.5) ^a	108.0 (60.0–276.0) ^a	72.0 (21.6–156.0) ^a						

y									
Dental procedures	-	-	67.2 (36.0–105.6) ^a						

IU: international unit; Kg: kilogram; NR: not reported; SD: standard deviation; vWF: von Willebrand concentrate factor; vWF:RCo: von Willebrand factor ristocetin cofactor activity

a dose values estimated in accordance to FVIII:C/vWF:RCo ratio in Voncento of 1:2.4

b on-demand efficacy population included 21 study participants. Exclusion of one patient due to the absence of evaluable non-surgical bleeding event^c

c regarding number of treated bleeding events requiring pdVWF/FVIII administration as assessed by the investigator

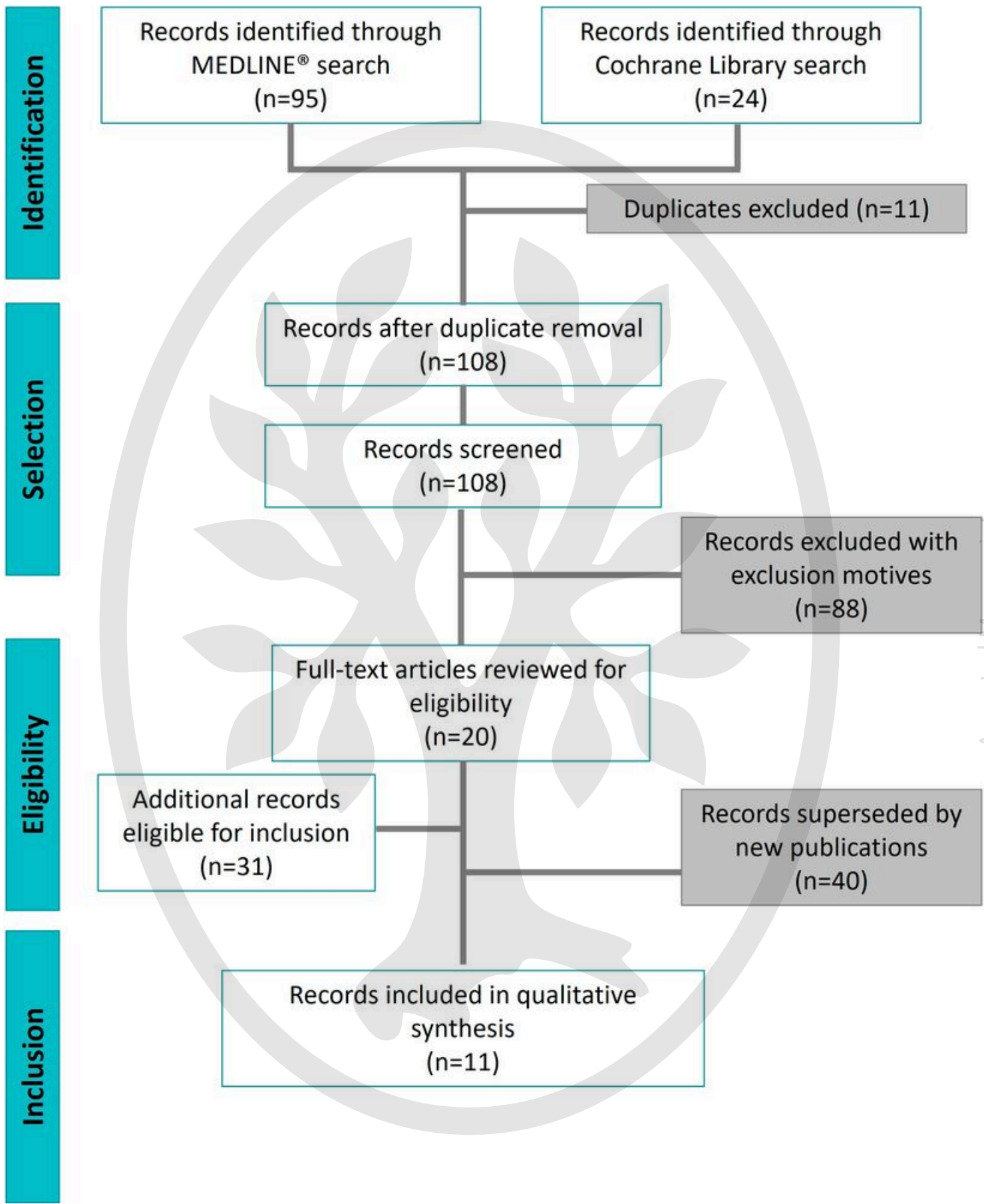
d estimated according to individual patient data reported by authors

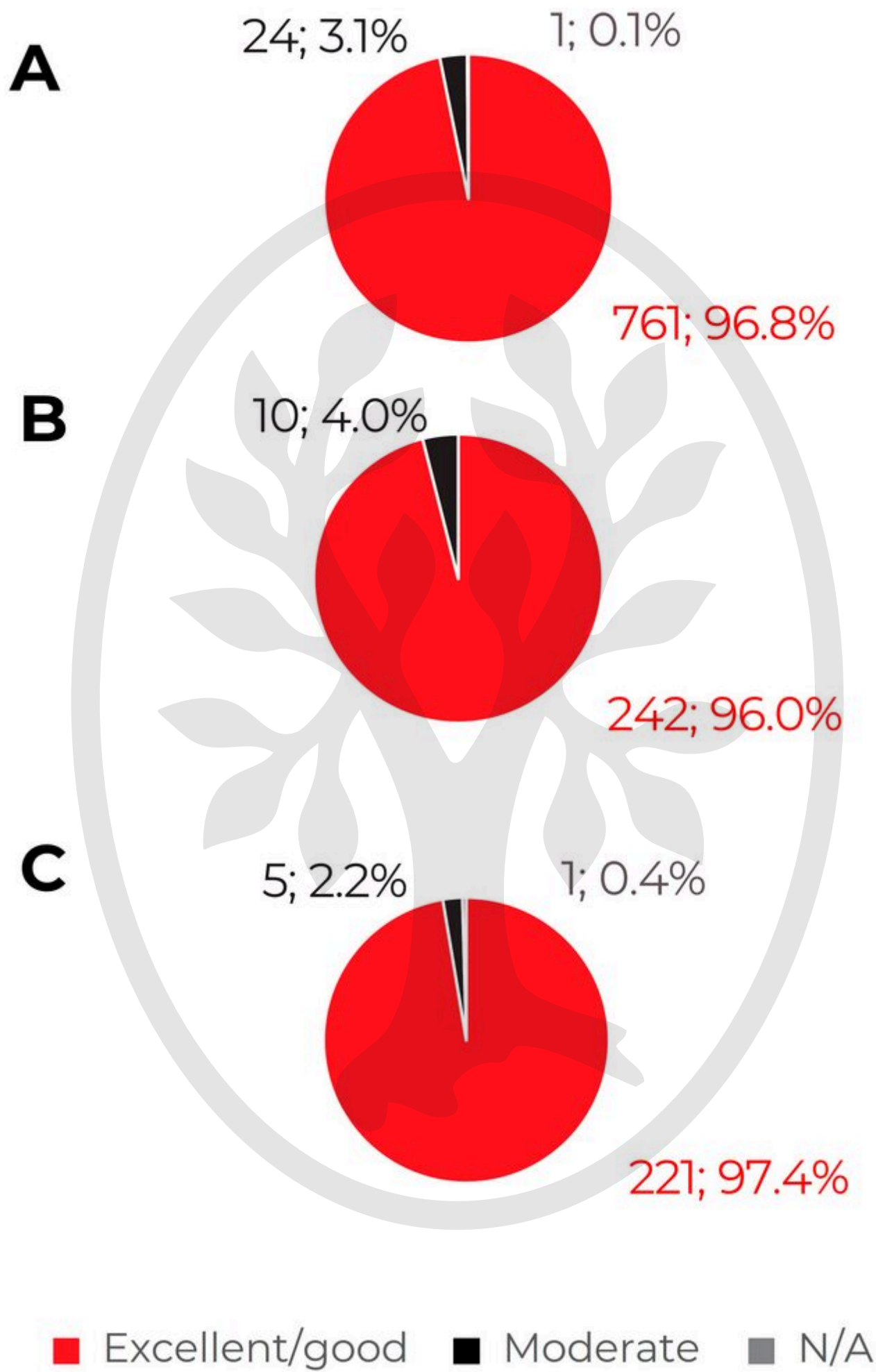
e mean value (+/- SD)

f dental procedures/extractions were classified as minor surgery

g minor surgical procedure was defined as surgery involving little risk to the life of the subject

h consumption data reported for only four patients, in each study arm, with surgical bleeding events







TITLE: A systematic review of efficacy and safety of plasma-derived von Willebrand factor/Factor VIII concentrate (Voncento®) in von Willebrand Disease



SUMMARY: This review demonstrates the long-term effectiveness and safety of this plasma-derived VWF/FVIII across all ages, types of VWD and treatment settings

STUDY DESIGN – SYSTEMATIC LITERATURE REVIEW

DATABASES:

- MEDLINE®: 1946–1 June 2023
- Cochrane Library: up to 1 June 2023
- Grey literature: congress abstracts 2017–2023

INCLUSION CRITERIA:

- Patient of any age with mild, moderate or severe inherited VWD
- Administration of pdVWF/FVIII as either on-demand treatment, long-term prophylaxis or surgical prophylaxis
- Reported outcomes including efficacy, safety or consumption

11
original
publications from
8 VWD study
cohorts

PHARMACOVIGILANCE

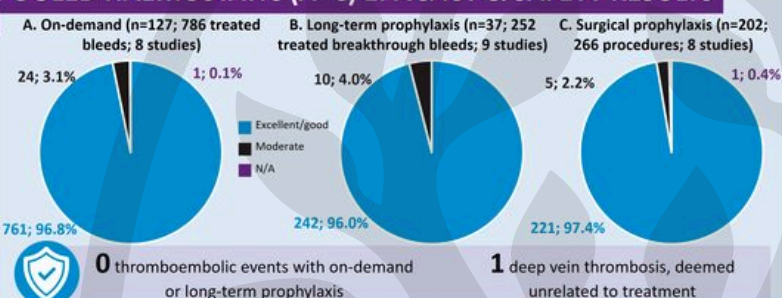
Cases reported from first marketing authorisation (2000–31 May 2023)

DATA SOURCES:

- Spontaneous reports
- Post-marketing trials
- Regulatory agencies
- Case reports in published literature and clinical trials



POOLED HAEMOSTATIC (A–C) EFFICACY & SAFETY RESULTS



POST-MARKETING SURVEILLANCE RESULTS

- 3,300,753,000 IU VWF** of plasma-derived VWF/FVIII
- 241 cases** with **494** adverse drug reactions
- 10 cases** of FVIII inhibitors
- 1 case** von Willebrand Factor inhibitor
- 5 cases** of thromboembolic events