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CADTH DRUG REIMBURSEMENT REVIEW

Clinical Review Report

von Willebrand Factor (Recombinant)

(VONVENDI)

(Shire Pharma Canada ULC, now part of Takeda Canada Inc.)

Indication: For the treatment and control of bleeding episodes in adults diagnosed with von Willebrand disease (aged ≥ 18), and perioperative management of bleeding in adults diagnosed with von Willebrand disease (aged ≥ 18)

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Abbreviations

AE	adverse event
CHS	Canadian Hemophilia Society
CI	confidence interval
DDAVP	desmopressin
DVT	deep vein thrombosis
EU	European Union
FAS	full analysis set
FVIII	factor VIII
FVIII:C	factor VIII coagulant
GI	gastrointestinal
HRQoL	health-related quality of life
MID	minimal important difference
PK	pharmacokinetics
PP	per-protocol
rFVIII	recombinant factor VIII
rVWF	recombinant von Willebrand factor
SAE	serious adverse event
SD	standard deviation
$T_{1/2}$	half-life
VWD	von Willebrand disease
VWF	von Willebrand factor
VWF:Ag	von Willebrand factor antigen
VWF:GPIbM	von Willebrand factor glycoprotein Ib-IX-V containing gain-of-function mutations
VWF:GPIbR	von Willebrand factor glycoprotein Ib-IX-V and ristocetin
VWF:RCo	von Willebrand factor: ristocetin cofactor

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Recombinant von Willebrand factor (Vonvendi), lyophilized powder for solution, 650 IU VWF:RCo/vial and 1,300 IU VWF:RCo/vial for intravenous injection
Indication	For the treatment and control of bleeding episodes in adults diagnosed with VWD (aged ≥ 18), and the perioperative management of bleeding in adults diagnosed with VWD (aged ≥ 18)
Reimbursement request	• Adults (aged ≥ 18) diagnosed with severe VWD • Adults (aged ≥ 18) diagnosed with mild or moderate VWD who do not respond or are intolerant to DDAVP
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	January 10, 2019
Sponsor	Shire Pharma Canada ULC, now part of Takeda Canada Inc.

DDAVP = desmopressin; NOC = Notice of Compliance; VWD = von Willebrand disease; VWF:RCo = von Willebrand factor ristocetin cofactor.

Introduction

von Willebrand disease (VWD) is the most common inherited bleeding disorder caused by deficiencies or defects in von Willebrand factor (VWF), a glycoprotein that is crucial for primary hemostasis and coagulation.[1-5] Many patients with VWD are asymptomatic, with hemorrhage presenting only after trauma or surgery, or mild spontaneous bleeding. Typical clinical manifestations of VWD are mild to severe mucosal bleeding, including epistaxis, menorrhagia, gingival bleeding, bruising, and gastrointestinal (GI) bleeding. Life-threatening bleeding can occur in patients with certain subtypes of VWD.[5-7]

VWD is classified to 3 subtypes. Type 1 VWD is the most common, accounting for 70% to 80% of cases. Patients with type 1 VWD have a decreased plasma concentration of functionally normal VWF. Type 2 VWD represents qualitative VWF defects and/or deficiencies and can be further classified to type 2A, type 2B, type 2M, and type 2N. Type 3 VWD is the most severe form of VWD (< 5% of VWD cases), where patients generally have an undetectable plasma VWF concentration.[1,3,5,6] Decreases in VWF concentration and VWF activities, as well as the pattern of such changes, help define VWD and its type, and the need for further testing.[3]

The prevalence of VWD has been reported as 1% in the general population while the estimated prevalence of symptomatic patients who require treatment is 0.01%, approximately 1 per 10,000 people in the community.[2,4] According to the sponsor, in Canada, the number of symptomatic patients was estimated to be [redacted], and an estimated [redacted] of these patients are anticipated to receive therapy.[8]

The treatment strategies for VWD vary depending on the type and severity of disease, the location of bleeding for on-demand treatment, and the invasiveness of the surgical procedure. Treatment for bleeding episodes in patients with VWD or perioperative management for surgical patients with VWD is achieved by increasing the level of VWF in the circulation and stabilizing the clot that is formed at the site of injury.[1,4]

For on-demand treatment of bleeding episodes or perioperative management for surgical patients, the 2 main treatment options for VWD are desmopressin (DDAVP) and replacement therapy with VWF-containing product. DDAVP promotes the release of endogenous VWF from storage sites in endothelial cells into circulation. In general, DDAVP is considered more appropriate for treatment of minor bleeding and perioperative management of minor surgery. Adverse effects associated with the use of DDAVP are tachyphylaxis, hyponatremia, vasodilatation, and hypotension.[1,3,5,9] For patients with bleeding associated with severe VWD (all types), for those with mild to moderate VWD planning major surgeries, and when DDAVP is not an appropriate treatment option, VWF replacement therapy is required.[1,3,5] The VWF concentrates increase the VWF activity level into the normal range by providing a source of VWF intravenously. This is the primary treatment for severe or life-threatening bleeding or major surgery in most patients with VWD. Two VWF concentrates are currently available in Canada, Humate-P and Wilate. Both are derived from human plasma and contain factor VIII (FVIII) in addition to VWF. The use of plasma-derived products may be associated with increased risk of transmission of blood-borne viral agents. In addition, repeated doses of such products may lead to FVIII accumulation, which increases the risk of thrombosis.[1,10,11]

Recombinant VWF (rVWF, brand name Vonvendi) is produced and formulated without the addition of any exogenous human- or animal-derived plasma proteins. In January 2019, rVWF was approved by Health Canada for the treatment and control of bleeding episodes in adults diagnosed with VWD (aged ≥ 18), and for the perioperative management of bleeding in adults diagnosed with VWD (aged ≥ 18).[12] Dose and frequency of rVWF administration must be personalized according to clinical judgment and based on the patient's weight, VWD type, and severity of bleeding episodes and surgical intervention, and also based on monitoring of appropriate clinical and laboratory measures. Co-administration of FVIII concentrate may also be required in some patients.[13]

The objective of the current review was to perform a systematic review of the beneficial and harmful effects of rVWF (650 IU VWF ristocetin cofactor [VWF:RCo]/vial and 1,300 IU VWF:RCo/vial) for the treatment and control of bleeding episodes in adults diagnosed with VWD, and for the perioperative management of bleeding in adults diagnosed with VWD.

Stakeholder Engagement

The information in this section is a summary of input provided by the patient group that responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

One patient group submitted patient input. The Canadian Hemophilia Society (CHS) is a national voluntary health charity whose mission is to improve the health and quality of life of all people in Canada with inherited bleeding disorders and ultimately find cures. For this patient input submission, the CHS conducted an online survey in January 2020 that was advertised via the organization's website, email, and Facebook and Twitter platforms. Seven responses were collected representing 4 provinces and all respondents were individuals affected by VWD. The CHS also consulted leading physicians' opinion with respect to the treatment of VWD.

In Canada, 4,321 people (1,542 males and 2,776 females) were identified with VWD, of whom 96 individuals were diagnosed with type 3 VWD. The CHS indicated that patients with milder forms of VWD may be under-diagnosed.

Different types of VWD require different treatments that may include hormone therapy, DDAVP, antifibrinolytics, and factor replacement (plasma-derived VWF-FVIII), sometimes in combination. The respondents reported that their current treatments were effective in stopping and preventing bleeding, but they can be associated with various side effects. The CHS was not aware of any Canadian patients who had experience with rVWF through a clinical trial. Having easier accessibility and administration, longer lasting benefits, and fewer side effects are deemed important by patients with VWD. Patients are also willing to try recombinant VWD therapy when it is related to a lower risk of viral contamination, which is seen in plasma-derived factor concentrates. In addition, it was noted that given that rVWF is the first therapeutic to contain only VWF without FVIII, it may have the potential to fill an unmet need, where additional FVIII is not needed or is even contraindicated.

Clinician Input

The experts indicated that the mechanism of action of rVWF is the same as the plasma-derived VWF concentrates in the treatment and control of bleeding episodes or perioperative management of patients with VWD, while the absence of FVIII in rVWF is an important distinction. In situations where VWF concentrate is required, rVWF would be an alternative to donor plasma–derived VWF replacement such as Humate-P or Wilate. The experts did not anticipate that rVWF would fundamentally shift the current treatment paradigm. Meanwhile, the role of DDAVP or antifibrinolytics in the management of bleeding episodes or perioperative management of patients with VWD is not anticipated to change with rVWF.

The clinical experts consulted by CADTH thought that rVWF would be used in patients currently being treated with plasma-derived factor concentrates. The characteristics of adult patients best suited for treatment with rVWF are similar for the treatment of bleeding episodes and for perioperative management: those with major or prolonged bleeding episodes or undergoing moderate or major surgery, those with non–type 1 VWD or non–type 2A VWD, or type 1 VWD or type 2A VWD with historic inadequate response to DDAVP for controlling the bleeding episode, or those who are intolerant or at risk of adverse effects of DDAVP.

These patients would be identified by clinical judgment, subtype of VWD, and a review of laboratory response. Diagnosis of VWD is generally straightforward but classifying the severity of bleeding episodes and deciding on the most appropriate treatment can be challenging. Determining which situations require factor replacement versus DDAVP requires clinical experience.

For the treatment and control of bleeding episodes in patients with VWD, achieving hemostasis or control of the acute bleeding is the main outcome of interest. A cessation of bleeding, stable hemoglobin concentration, reduction in blood transfusion requirement, reduced need for intervention, reduction in length of hospital stay, and reduction in emergency room visits would be considered clinically meaningful responses to treatment.

For perioperative management in patients with VWD, the reduction of perioperative blood loss would be the main outcome of interest. Achieving intraoperative hemostasis, reduced estimated surgical blood loss, stable post-operative hemoglobin, reduced blood transfusion

requirements, a decreased need for post-operative interventions such as a return to the operating room or packing, and a decreased length of hospital stay post-operatively would be considered clinically meaningful responses to treatment.

In both populations, treatment response should be assessed using clinical bleeding assessment and achieving targeted VWF activity and antigen levels.

The following must be considered for the treatment and control of bleeding episodes. First, minor bleeding is often managed as an outpatient with clinical assessment of bleeding cessation done by phone assessment or clinic visit; when factor concentrate is given to patients with minor bleeding events, VWF is often measured before and after the first infusion. Second, for patients with moderate or major bleeding, admission to hospital is required. Visible bleeding would be monitored continuously while internal bleeding would be monitored radiologically every few days until bleeding ceases. Change in hemoglobin would be examined once or twice a day initially. The measurement of VWF and FVIII levels would occur before and after the first and second doses of factor replacement, and pre- and post-infusion levels repeated with any dose change or increase in bleeding despite factor replacement.

For the treatment and control of bleeding episodes or perioperative management in patients with VWD, a hematologist with expertise in inherited bleeding disorders is required in the diagnosis and management of patients who require VWF concentrate. rVWF is for intravenous administration; however, due to the chronic nature of inherited bleeding disorders, patients may be taught how to administer to themselves at home. rVWF is suitable for inpatient settings, outpatient clinics, or home self-administration.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two phase III trials submitted by the sponsor (Study 071001, N = 37, and Study 071101, N = 15) are included in this systematic review. The trials included adult patients with severe VWD (aged ≥ 18 years).

Study 071001[14] was a phase III, parallel-group, open-label, non-controlled, multi-centre trial that assessed the efficacy, safety, and pharmacokinetics (PK) of rVWF, with or without rFVIII, in the treatment of bleeding episodes in adult patients diagnosed with severe type 3 VWD and severe non–type 3 VWD. Eligible study participants were assigned to 1 of 4 treatment groups at the discretion of the investigator:

1. PK50 (50 IU/kg VWF: ristocetin cofactor [RCo] rVWF with 38.5 IU/kg rFVIII or 50 IU/kg VWF:RCo rVWF with placebo) and treatment for bleeding episodes (n = 9)
2. PK50 only (PK assessment with 50 IU/kg VWF:RCo rVWF) (n = 9)
3. PK80 (PK assessment with 80 IU/kg VWF:RCo rVWF) and treatment for bleeding episodes (n = 16)
4. Assessment of treatment for bleeding episodes only (n = 6)

The study's primary end point was the number of patients with treatment success for treated bleeding episodes at the end of the study. Treatment success was defined as a mean efficacy rating score of less than 2.5, taking into account all bleeding episodes, and

was measured using a physician-completed hemostatic efficacy rating scale. The mean efficacy score was based on a 4-point rating scale defined using the prospectively estimated number of infusions needed to treat the bleeding episodes as assessed by the investigator versus the actual number of infusions administered: excellent = 1, good = 2, moderate = 3, and none = 4. Secondary efficacy end points included the number of study drug–treated bleeding episodes with an efficacy rating of "excellent" or "good," and the number of infusions and number of units of rVWF plus rFVIII and/or rVWF alone per bleeding episode. In this study, the mean age of patients was 37 years and most were White ([redacted]). The majority of the study participants (78%) had type 3 VWD and were receiving on-demand treatment exclusively in the 24 months prior to and at study enrolment ([redacted] and [redacted], respectively).

Study 071101 was an open-label, non-randomized, non-controlled, phase III trial conducted to evaluate the efficacy and safety of rVWF, with or without rFVIII, in major or minor elective surgeries in adult patients with severe VWD. A priming dose with rVWF 40 IU/kg to 60 IU/kg was given to patients 12 hours to 24 hours prior to surgery to allow the endogenous FVIII levels to increase to target levels before the loading dose of rVWF, with or without rFVIII, was administered. Within 1 hour prior to surgery, an rVWF loading dose with or without rFVIII was administered, depending on the FVIII coagulant (FVIII:C) assay levels. Intraoperative and post-operative dosing were individualized according to the PK results, the intensity and duration of the hemostatic challenge, and the institution's standard of care. Doses were either rVWF alone or rVWF plus rFVIII, depending on the respective VWF and FVIII levels. [redacted]

[redacted]. The primary efficacy outcome measure was the percentage of patients in each overall investigator-assessed hemostatic efficacy category (i.e., "excellent," "good," "moderate," or "none") 24 hours after the last perioperative infusion or at completion of the study, whichever occurred earlier. Secondary efficacy end points included intraoperative and post-operative blood loss, and the dose of rVWF required for perioperative management in the study population. The PK profile of rVWF was also examined. In this study, the mean age of patients was 39 years. More than half of the study participants (53%) had type 3 VWD. Ten out of 15 patients underwent major surgeries.

Efficacy Results

Treatment and Control of Bleeding Episodes

In Study 071001, all patients achieved treatment success (primary efficacy end point) when they were treated with rVWF, with or without rFVIII, during the study period. The proportion of patients with treatment success was 100% (18 out of 18 patients with on-demand treatment for bleeding episodes; Clopper-Pearson exact 90% confidence interval [CI], 84.7% to 100%). Results of sensitivity analyses were aligned with the primary analysis. The results also showed that hemostatic efficacy of the study drug was rated as "excellent" or "good" (secondary efficacy outcome) for 100% of all treated bleeding episodes (126 out of 126 treated bleeding episodes; Clopper-Pearson exact 90% CI, 97.7% to 100%). The clinical experts consulted for this review indicated that the primary efficacy outcome of this study was based on a subjective, physician-completed rating scale, and the accuracy of this scale is unclear as compared to the other more objective measurements, such as the actual number of infusions given. Although the study drug demonstrated a potential hemostatic effect for acute bleeding episodes in patients with VWD, the results should be interpreted

with caution due to limitations associated with the non-randomized, non-controlled nature of the study design and small number of participants in each group.

Subgroup analyses by VWD subtypes or severity of bleeding were reported in this study. The results of the subgroup analyses suggested that hemostatic efficacy was "excellent" or "good" for all treated bleeding episodes, regardless of VWD subtypes or severity of bleeding. However, given the small sample size in each subgroup and that no formal statistical comparisons were conducted, no conclusions can be made pertaining to hemostatic efficacy for the subgroup analyses.

The mean total dose of rVWF plus rFVIII or rVWF alone was 57.4 IU/kg per bleeding episode (standard deviation [SD] = 30.27). The mean actual dose for co-infusion of rVWF plus rFVIII was 48.6 IU/kg rVWF per bleeding episode (SD = 15.3) and 35.9 IU/kg rFVIII per bleeding episode (SD = 13.90), and 64.1 IU/kg rVWF for rVWF infused alone per bleeding episode (SD = 31.24). In the subgroup analyses based on severity of bleeding episodes, the mean total dose of rVWF plus rFVIII or rVWF was 103.5 IU/kg per major bleeding episode (SD = 28.46), 66.8 IU/kg per moderate bleeding episode (SD = 39.40), and 49.4 IU/kg per minor bleeding episode (SD = 18.08).

In 192 bleeding episodes, the mean number of infusions was 1.2 infusions (SD = 0.56) for treatment of a bleeding episode, and the median number of infusions was 1.0 (range = 1 to 6). More than 80% of the bleeding episodes were controlled by 1 infusion of rVWF plus rFVIII or rVWF alone during the study. Of these, 94.8% of the bleeding episodes were controlled with 1 infusion of rVWF plus rFVIII.

In this study, [redacted] and [redacted].

Perioperative Management

In Study 071101, the overall hemostatic efficacy was rated as "excellent" or "good" for all 15 treated patients (100%; Clopper-Pearson exact 90% CI, 81.9% to 100%), including 10 patients with major surgery, 4 patients with minor surgery, and 1 patient with oral surgery. The intraoperative hemostatic efficacy was also rated as "excellent" or "good" in all 15 patients. Similar results were reported for the subgroups by surgery classification and VWD subtypes. As in study 071001, the primary efficacy outcome of this study was based on a subjective, unvalidated, physician-completed rating scale; therefore, the accuracy of this scale is unclear.

Hemostatic efficacy was also measured by actual to predicted intraoperative blood loss. The mean ratings for actual intraoperative blood loss relative to predicted blood loss and intraoperative hemostatic efficacy at completion of surgery were rated as "excellent" or "good" for intraoperative actual versus predicted blood loss (100%; Clopper-Pearson exact 90% CI, 81.9% to 100%) and for intraoperative hemostatic efficacy (100%; Clopper-Pearson exact 90% CI, 81.9% to 100%). During the surgery, the actual blood loss assessed by the operating surgeon was numerically less than predicted blood loss in the study population (actual blood loss of 94.3 mL versus predicted blood loss of 106.1 mL). The experts did not consider this difference clinically important, given the challenges of accurately measuring intraoperative blood loss and the small sample size of this study.

The median total dose (IU/kg) administered per patient (including doses for PK assessments, during surgery, treatment of bleeds, and maintenance of hemostasis) was [redacted] rVWF in patients treated with rVWF alone, [redacted] rVWF and [redacted] rFVIII in patients treated with rVWF plus rFVIII, and 306.4 rVWF (range = 63.8 to 701.6) for all patients treated with rVWF, with or without rFVIII.

[redacted] was also identified as an outcome of importance to patients and was measured using [redacted] and [redacted] in Study 071101. [redacted] (Figure 6).

Harms Results

Treatment and Control of Bleeding Episodes

During the overall study period, [redacted] patients ([redacted]%) experienced at least 1 adverse event (AE). The majority of AEs were of mild or moderate severity. Commonly reported AEs included iron deficiency anemia ([redacted]%), vomiting ([redacted]%), upper respiratory tract infection ([redacted]%), arthralgia ([redacted]%), and headache ([redacted]%). [redacted] patients ([redacted]%) reported serious AEs (SAEs), including osteomyelitis, constipation, uterine polyp, spontaneous abortion, GI hemorrhage, mesenteric hematoma, hemorrhoids, chest discomfort, and increased heart rate. None of these SAEs occurred in any more than 1 patient. One patient discontinued treatment due to an AE of chest discomfort and increased heart rate. For the AEs of special interest, 1 patient reported a hypersensitivity reaction and 1 patient reported an infusion-related reaction of tachycardia.

Perioperative Management

In Study 071101, a total of 12 AEs were reported by 6 patients ([redacted]%) during or after infusion with the study drug, including acne, dry skin, iron deficiency anemia, peripheral swelling, nasopharyngitis, joint swelling, dizziness, headache, pelvic pain, and deep vein thrombosis (DVT). These AEs were mild to moderate in severity. Two patients reported SAEs (DVT and diverticulitis were each reported by 1 patient). No patient withdrew from the study due to AEs and no deaths were reported during the study. For AEs of special interest, 1 patient had thrombotic events and another patient developed anti-VWF binding antibodies.

Table 2: Summary of Key Results From Study 071001 — Treatment and Control of Bleeding Episodes

Study 071001, N = 37	
Efficacy results	
Proportion of patients with treatment success (excluding GI bleeding)	
n of N (%), 90% CI	18/18 (100); 90% CI, 84.7% to 100%
Proportion of study drug–treated BEs with an "excellent" or "good" efficacy rating (excluding GI bleeding)	
n of N (%), 90% CI	126/126 (100); 90% CI, 97.7% to 100%
Total dose of rVWF + rFVIII or rVWF alone per BE	
IU/kg, mean (SD)	57.4 (30.27)
Number of infusions required for treatment of a BE	
Number of BEs	192
Number of infusions required, mean (SD)	1.2 (0.56)
Harms results	
Patients with ≥ 1 AE, n (%)	[redacted]
Patients with ≥ 1 SAE, n (%)	[redacted]
Patients with ≥ 1 WDAE, n (%)	[redacted]
Notable harms, n (%)	
Hypersensitivity reactions	[redacted]
Infusion-related reactions	[redacted]

AE = adverse event; BE = bleeding episode; CI = confidence interval; GI = gastrointestinal; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

Source: Clinical Study Report for Study 071001.[14]

Table 3: Summary of Key Results From Study 071101 — Perioperative Management

Study 071101, N = 15	
Efficacy results	
Overall hemostatic efficacy, n (%)	
Excellent	11 (73.3)
Good	4 (26.7)
Moderate	0
None	0
Intraoperative hemostatic efficacy, n (%)	
Excellent/good	15 (100)
Moderate/none	0 (0)
Intraoperative blood loss, mL, mean (SD)	
Actual blood loss	94.3 (177.88)
Predicted blood loss	106.1 (161.82)
Actual blood loss relative to predicted blood loss, %, mean (SD)	69.6 (44.77)
Total dose of rVWF ± rFVIII	
IU/kg, median (range)	306.4 (63.8 to 701.6)
Harms results	
Patients with ≥ 1 AE, n (%)	[redacted]

Study 071101, N = 15	
Patients with ≥ 1 SAE, n (%)	[redacted]
Patients with ≥ 1 WDAE, n (%)	[redacted]
Notable harms, n (%)	
Thrombotic events	[redacted]
Anti-VWF antibodies	[redacted]

AE = adverse event; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; SAE = serious adverse event; SD = standard deviation; VWF = von Willebrand factor; WDAE = withdrawal due to adverse event.

Source: Clinical Study Report for Study 071101.[15]

Critical Appraisal

The major limitations of the included trials are the non-randomized, non-controlled study design and a lack of statistical comparison between the study drug and other active treatments. In addition, the small number of study participants makes data interpretation difficult when the observed treatment effect could be due to chance, or alternatively, a true effect may not be detected due to insufficient power of the trial. In both studies, patients and the attending physicians were not blinded to the treatment. Therefore, when a subjective rating scale was used to measure the treatment effect, results of the assessment can be biased.

Several efficacy outcomes in both trials were descriptively reported without performing formal statistical testing — specifically, the dose of infused study drug required for treatment of bleeding episodes and the number of infusions required per bleeding episode in Study 071001, the actual intraoperative blood loss and dose of study drug in Study 071101, and health-related quality of life (HRQoL) results and all subgroup analyses in the 2 trials. In the absence of formal statistical testing, no inferences can be made regarding the results of the aforementioned outcomes.

Patients with significant comorbid conditions or poor performance status were excluded from the trials, resulting in a highly selected patient population. Based on the study population, the treatment effect of rVWF may not be generalized to patients with comorbid conditions who may be eligible to receive treatment with a VWF replacement therapy.

The indication for rVWF approved by Health Canada does not restrict use to any specific VWD subtype or severity. According to the experts consulted for this review, the study populations in these 2 trials are reflective of typical Canadian patients diagnosed with severe VWD, according to baseline patient characteristics. This is consistent with the anticipated place in therapy for rVWF.

The approved indication for perioperative management does not restrict the use of rVWF to severity of surgical procedure, although most patients enrolled in Study 071101 were undergoing major surgery. Further, in Study 071101, only patients undergoing planned surgical procedures were included in the study, which allowed for pre-operative loading doses to be carefully managed. It is uncertain whether the results of this study would be generalizable to patients with VWD undergoing emergency surgery.

Indirect Evidence

No indirect evidence was submitted by the sponsor for this review. CADTH conducted a literature search to identify potentially relevant indirect treatment comparisons in patients with VWD. No relevant indirect comparisons were identified in the literature search.

Other Relevant Evidence

No other studies submitted by the sponsor were considered to fill any evidence gaps relevant to this review.

Conclusions

Two phase III, non-randomized, non-controlled, open-label clinical trials were included in this review to provide evidence on the efficacy and safety of rVWF in adult patients (aged ≥ 18 years) with VWD for 1) the treatment and control of acute bleeding episodes (Study 071001) and 2) perioperative management (Study 071101). rVWF administered according to the Health Canada–approved dose was associated with high treatment success rates in terms of hemostatic efficacy in both studies. The hemostatic effect of rVWF in on-demand and surgical bleed management was rated as “excellent” or “good” in all study participants. [redacted]. The majority of the reported AEs were mild to moderate in intensity. Isolated cases of thrombotic events, hypersensitivity reaction, infusion-related reactions, and development of anti-VWF binding antibodies were reported in the study population. There were no deaths during either study. The main limitations of the included trials were the small sample size, non-randomized design, lack of control groups, use of subjective rating scale in measuring hemostatic efficacy of the study drug, lack of statistical testing, and lack of comparative evidence. Overall, there is uncertainty associated with the potential benefit of rVWF compared to treatments already available in Canada, due to the low quality of the evidence supporting the efficacy and safety of rVWF to control bleeding episodes and for perioperative management.

Introduction

Disease Background

VWD is the most common inherited bleeding disorder caused by deficiencies or defects in VWF. VWF is a glycoprotein that is crucial for primary hemostasis (it is involved in platelet adhesion to the subendothelium after vascular injury and in platelet aggregation at high shear rates of blood flow) and coagulation (it is the carrier protein for coagulation FVIII and prolongs the half-life [$T_{1/2}$] of FVIII).[1-5]

All genders can be affected by VWD. Many patients with VWD are asymptomatic, with hemorrhage presenting only after trauma or surgery, or mild spontaneous bleeding. Typical clinical manifestations of VWD are mild to severe mucosal bleeding, including epistaxis, menorrhagia, gingival bleeding, bruising, and GI bleeding. Life-threatening bleeding can occur in patients with certain subtypes of VWD.[5-7] The age of symptom onset is variable, but severe VWF deficiency usually manifests in childhood with joint bleeds on crawling or ambulating or with minimal trauma, mirroring the clinical presentation of hemophilia.[5]

VWD is classified by 3 subtypes. Patients with type 1 VWD have a decreased plasma concentration of functionally normal VWF. Type 3 VWD is the most severe form of VWD; patients with this subtype generally have an undetectable plasma VWF concentration. Type 2 VWD represents qualitative VWF defects and/or deficiencies.[1,3,5,6] Decreases in VWF concentration and VWF activities, as well as the pattern of such changes, help define VWD and its type, and the need for further testing.[3]

Here are the subtypes of VWD:

- Type 1: Most patients with type 1 VWD present with mildly reduced levels of VWF; this is the most common presentation of VWD (70% to 80% of VWD cases).
- Type 2: These are various forms of dysfunctional VWF (25% of VWD cases).
  - Type 2A: It has decreased VWF-dependent platelet adhesion and a selective deficiency of high-molecular weight VWF multimers; this is the most common presentation of type 2 VWD.
  - Type 2B: It has increased affinity of VWF for platelet glycoprotein Ib; generally, it comprises 10% to 20% of type 2 VWD.
  - Type 2M: It has decreased VWF-dependent platelet adhesion without a selective deficiency of high-molecular weight VWF multimers; this is an under-recognized form of type 2 VWD and may be as common as type 2A VWD.
  - Type 2N: It has markedly decreased binding affinity for FVIII; it is a rare form of type 2 VWD (generally < 10%).
- Type 3: This features a virtually complete deficiency of VWF; it is a rare form of VWD in developed countries (< 5% of VWD cases).

The diagnosis of VWD is based on clinical presentation, a patient's personal and family history of bleeding, and laboratory findings. In addition to preliminary hematology tests such as complete blood count, prothrombin time, and partial thromboplastin time, specific laboratory tests for VWD are needed to establish the diagnosis. These include the assessment of VWF protein level in plasma based on VWF antigen (VWF:Ag), and VWF activity using various assays to measure the ability of VWF to bind to platelets. These commonly used assays measure the affinity of VWF for collagen, the binding capacity of

VWF to glycoprotein Ib, with or without the use of ristocetin (e.g., VWF:RCo, VWF: Glycoprotein Ib-IX-V and ristocetin [VWF:GPIbR]), VWF: Glycoprotein Ib-IX-V containing gain-of-function mutations [VWF:GPIbM]), and the binding capacity of VWF to exogenous FVIII. The VWF:RCo assay determines the capacity of VWF to agglutinate exogenous platelets in the presence of ristocetin and has been the gold standard for measuring VWF activity. Due to the imprecision and poor sensitivity of the classic VWF:RCo assay, new assays such as VWF:GPIbR and VWF:GPIbM have been developed. The VWF activity is expressed as a percentage of normal VWF activity.[16] In addition, the plasma concentration of FVIII measured by FVIII:C assay is needed in the diagnosis and treatment of VWD.[1,3,5,6] According to the clinical experts consulted for this review, diagnostic tests related to VWD and subtype determination are standard of care and widely available in Canada. Diagnosis of VWD is generally straightforward and misdiagnosis is uncommon. Also, according to the experts, there is no generally accepted definition of mild, moderate, or severe VWD.

The prevalence of VWD has been reported as 1% in the general population while the prevalence of symptomatic patients with VWD who require treatment has been reported as 0.01%, or approximately 1 per 10,000 people in the community.[2,4] According to the sponsor, in Canada, the number of symptomatic patients was estimated to be [redacted], and an estimated [redacted] of these patients are anticipated to receive therapy.[8]

Standards of Therapy

The treatment strategies for VWD vary depending on the type and severity of disease, the location of bleeding for on-demand treatment, and the invasiveness of the surgical procedure. Treatment for bleeding episodes in patients with VWD or perioperative management for surgical patients with VWD is achieved by increasing the level of VWF in the circulation and stabilizing the clot that is formed at the site of injury.[1,4]

For on-demand treatment of bleeding episodes or perioperative management for surgical patients, the 2 main treatment options for VWD are DDAVP and replacement therapy with VWF-containing product. They are used to directly increase the VWF levels. DDAVP is a synthetic analogue of human antidiuretic hormone and promotes the release of endogenous VWF from storage sites in endothelial cells into circulation. In general, DDAVP is considered more appropriate for the treatment of minor bleeding and perioperative management of minor surgery; for example, it can be used to maintain hemostasis in surgical procedures and post-operatively when administered 45 minutes prior to the scheduled procedure. Adverse effects associated with the use of DDAVP are tachyphylaxis, hyponatremia, vasodilatation, and hypotension.[1,9] According to the clinical experts consulted for this review, the use of DDAVP is made on a situational basis. It depends on the target VWF and FVIII required for the clinical situation and the level that the patient has previously achieved with DDAVP test challenge. In Canada, a test of VWF and FVIII would be organized through the hemostasis centre taking care of the patient, with levels of VWF activity and antigen as well as FVIII measured at baseline, 1 hour post DDAVP, and 4 hours post DDAVP. According to the clinical experts, an increase of more than 30% sustained activity would be considered a good response.

For patients with bleeding associated with severe VWD (all types), for those with mild to moderate VWD planning major surgeries, and when DDAVP is not an appropriate treatment option, VWF replacement therapy is required.[1,3,5] The VWF concentrates increase the VWF activity level into the normal range by providing a source of VWF intravenously. This is the primary treatment for severe or life-threatening bleeding or major surgery in most patients

with VWD. Two VWF concentrates are currently available in Canada, Humate-P and Wilate. Both are derived from human plasma and contain FVIII in addition to VWF. The ratio of VWF to FVIII is 2.4:1 for Humate-P and 1:1 for Wilate.[10,11] In the Warnings and Precautions section of the product monographs of Humate-P and Wilate, it is noted that the use of plasma-derived products may be associated with the increased risk of transmission of blood-borne viral agents such as hepatitis or other viral diseases.[10,11] In addition, repeated doses of such products may lead to FVIII accumulation, which increases the risk of thrombosis. Serious thrombotic and/or thromboembolic events have been reported in patients with VWD receiving VWF/FVIII replacement therapy, especially in patients with known risk factors for thrombosis, such as perioperative periods without thromboprophylaxis or obesity. Pulmonary embolism occurred in patients who received Humate-P while no thromboembolic events were observed in clinical trials with Wilate.[1,10,11]

Treatment with VWF replacement therapy or DDAVP may be accompanied by additional pharmacologic agents for indirect hemostatic effect, such as fibrinolysis inhibitors (e.g., tranexamic acid) and hormonal treatment (e.g., estrogen-progesterone combined oral contraceptives).[5]

Drug

rVWF (brand name: Vonvendi) is a factor replacement therapy produced and formulated without the addition of any exogenous human- or animal-derived plasma proteins. It shares the same mechanism of action as plasma-derived VWF products. It contains ultra-large multimers that are effective in supporting interactions with collagen and platelet receptors, in addition to all of the multimers found in plasma.[13] The binding capacity and affinity of rVWF to FVIII in plasma is comparable to that of endogenous VWF, allowing for rVWF to reduce FVIII clearance. rVWF is available as lyophilized powder for intravenous injection of 650 IU VWF:RCo/vial and 1,300 IU VWF:RCo/vial.[13]

In January 2019, rVWF was approved by Health Canada for the treatment and control of bleeding episodes in adults diagnosed with VWD (aged ≥ 18), and for the perioperative management of bleeding in adults diagnosed with VWD (aged ≥ 18).[12]

Dose and frequency of rVWF administration must be personalized according to clinical judgment and based on the patient's weight, VWD type, and severity of bleeding episodes and surgical intervention, and also based on monitoring of appropriate clinical and laboratory measures.[13]

Treatment of Bleeding Episodes

The dosing of rVWF recommended by Health Canada for the treatment of bleeding episodes is provided in Figure 2. The first dose of rVWF should be 40 IU/kg to 80 IU/kg body weight. Depending on the patient's baseline FVIII:C level, a single infusion of rVWF is expected in a majority of patients to lead to an increase in endogenous FVIII:C activity above 40% within 6 hours. However, if the patient's baseline plasma FVIII:C level is less than 40% or is unknown, a recombinant FVIII (rFVIII) product should be administered with the first infusion of rVWF to achieve a hemostatic plasma FVIII:C level. Subsequent doses of 40 IU/kg to 60 IU/kg of rVWF every 8 hours to 24 hours is needed to maintain the hemostatic effect, depending on the severity of bleeding.

Figure 1: Dosing Recommendations for the Treatment of Minor and Major Bleeding

Type of Bleeding	Initial Dose[a] (IU VWF:RCo/kg body weight)	Subsequent Dose
Minor (e.g. epistaxis, oral bleeding, menorrhagia)	40 to 50 IU/kg	40 to 50 IU/kg every 8 to 24 hours (or as long as deemed clinically necessary)
Major[b] (e.g. severe or refractory epistaxis, menorrhagia, gastrointestinal bleeding, central nervous system trauma, hemarthrosis, or traumatic hemorrhage)	50 to 80 IU/kg	40 to 60 IU/kg every 8 to 24 hours for approximately 2-3 days (or as long as deemed clinically necessary)

VWF:RCo = von Willebrand factor ristocetin cofactor.

Source: Vonvendi product monograph.[13]

Perioperative Management

The dosing of rVWF recommended by Health Canada for perioperative management is provided in Figure 2. Prior to the initiation of any surgical procedure, baseline VWF:RCo and FVIII:C levels should be assessed. The recommended minimum FVIII:C target levels prior to initiating the surgery are 30 IU/dL for minor surgery and 60 IU/dL for major surgery. In case of major bleeding events or major surgeries requiring repeated, frequent infusions, the monitoring of FVIII levels is recommended to decide if rFVIII is required for subsequent infusions and to avoid an excessive rise of FVIII levels.[13]

Figure 2: Recommended VWF:RCo and FVIII:C Target Peak Plasma Levels for the Prevention of Excessive Bleeding During and After Surgery

Type of Surgery	VWF:RCo Target Peak Plasma Level	FVIII:C Target Peak Plasma Level[a]	Calculation of rVWF Dose (to be administered within 1 hour prior to surgery) (IU VWF:RCo required)
Minor	50 - 60 IU/dL	40 - 50 IU/dL	Δ[b] VWF:RCo x BW (kg) /IR[c]
Major	100 IU/dL	80 - 100 IU/dL	

BW = body weight; FVIII:C = factor VIII coagulant; rFVIII = recombinant factor VIII; IR = incremental recovery; rVWF = recombinant von Willebrand factor; VWF:RCo = von Willebrand factor ristocetin cofactor.

[a] Additional rFVIII may be required to attain the recommended FVIII:C target peak plasma levels. Dosing calculation should be done based on the IR and product monograph.
[b] Δ = Target peak plasma VWF:RCo – baseline plasma VWF:RCo.
[c] IR = [Plasma VWF:RCo at 30 minutes post-infusion (IU/dL) – Plasma VWF:RCo at baseline (IU/dL)] / Dose (IU/kg)

Source: Vonvendi product monograph.[13]

Table 4: Key Characteristics of VWF Replacement Therapies

	Vonvendi	Humate-P	Wilate
Mechanism of action	This is a purified rVWF. It increases VWF concentration, but does not contain FVIII.	Human VWF and human coagulation FVIII complex Both Humate-P and Wilate increase VWF concentration.	
Indication[a, b]	Treatment and control of bleeding episodes in adults diagnosed with VWD (aged ≥ 18) Perioperative management of bleeding in adults diagnosed with VWD (aged ≥ 18)	**VWD** • In adult and pediatric patients for treatment of spontaneous and trauma-induced bleeding episodes in severe VWD • In mild and moderate VWD where use of DDAVP is known or suspected to be inadequate and to prevent excessive bleeding (i.e., bleeding that exceeds the expected blood loss under a given condition) during and after surgery in adult and pediatric patients	**VWD** • Treatment and prophylaxis of spontaneous and trauma-induced bleeding episodes in patients with all types of VWD where DDAVP is ineffective or contraindicated • Prevention and treatment of bleeding during and after surgical procedures
Route of administration	IV	IV	IV
Recommended dose for VWD	**Minor hemorrhage** Initial dose of 40 IU/kg to 50 IU/kg, subsequent dose of 40 IU/kg to 50 IU/kg, every 8 hours to 24 hours **Major hemorrhage** Initial dose of 50 IU/kg to 80 IU/kg, subsequent dose of 40 IU/kg to 60 IU/kg, every 8 hours to 24 hours for 2 to 3 days **Perioperative management prior to surgery** rVWF dose of 40 IU/kg to 60 IU/kg may be administered 12 hours to 24 hours prior to surgery to raise endogenous FVIII:C levels	**Type 1, mild if DDAVP is inappropriate, major hemorrhage** 40 IU/kg to 50 IU/kg every 8 hours to 12 hours for 3 days to keep the nadir level of VWF:RCo > 50%, then 40 IU/kg to 50 IU/kg daily for up to 7 days of treatment **Type 1, moderate or severe, minor hemorrhage** 40 IU/kg to 50 IU/kg (1 or 2 doses) **Type 1, moderate or severe, major hemorrhage** 40 IU/kg to 60 IU/kg every 8 hours to 12 hours for 3 days to keep the nadir level	**Minor hemorrhage** Loading dose of 20 IU/kg to 40 IU/kg, maintenance dose of 20 IU/kg to 30 IU/kg, every 12 hours to 24 hours **Major hemorrhage** Loading dose of 40 IU/kg to 60 IU/kg, maintenance dose of 20 IU/kg to 40 IU/kg, every 12 hours to 24 hours **Minor surgery** Loading dose of 30 IU/kg to 60 IU/kg, maintenance dose of 20 IU/kg to 40 IU/kg, every 12 hours to 24 hours

	Vonvendi	Humate-P	Wilate
	to minimum target levels: 30 IU/dL for minor surgery, 60 IU/dL for major surgery. **During and after surgery** The rVWF dose is calculated based on baseline and target peak plasma VWF:RCo, surgery type, body weight, and IR. **Subsequent maintenance doses after surgery** The rVWF dose is calculated based on target trough plasma level of VWF:RCo and FVIII:C and the surgery type.	of VWF:RCo > 50%, then 40 IU/kg to 60 IU/kg daily for up to 7 days of treatment **Type 2 and type 3, minor hemorrhage** 40 IU/kg to 50 IU/kg (1 or 2 doses) **Type 2 and type 3, major hemorrhage** 40 IU/kg to 80 IU/kg every 8 hours to 12 hours for 3 days to keep the nadir level of VWF:RCo > 50%, then 40 IU/kg to 60 IU/kg daily for up to 7 days of treatment **Major surgery** Loading dose: Calculated based on target peak plasma VWF:RCo level (100 IU/dL), baseline VWF:RCo level, body weight, and IVR. Maintenance doses: Calculated based on target trough plasma levels (VWF:RCo > 50 IU/dL up to 3 days following surgery, > 30 IU/dL after Day 3; FVIII:C > 50 IU/dL up to 3 days following surgery, > 30 IU/dL after Day 3) and minimum duration of treatment for subsequent maintenance doses **Minor/oral surgery** Loading dose: Calculated based on target peak plasma VWF:RCo level (50 IU/dL to 60 IU/dL), baseline VWF:RCo level, body weight, and IVR. Maintenance doses: Calculated based on target trough plasma levels (VWF:RCo ≥ 30 IU/dL, FVIII:C ≥ 30 IU/dL) and minimum duration of treatment for subsequent maintenance doses	**Major surgery** Loading dose of 40 IU/kg to 60 IU/kg, maintenance dose of 20 IU/kg to 40 IU/kg, every 12 hours to 24 hours

	Vonvendi	Humate-P	Wilate
Serious adverse effects or safety issues	• Risk of occurrence of thrombotic events, particularly in patients with known risk factors for thrombosis. Patients who are at risk for thrombosis should be monitored for early signs of thrombosis and prophylaxis measures against thromboembolism should be instituted. • In patients requiring frequent doses of rVWF in combination with rFVIII, plasma levels for FVIII:C activity should be monitored to avoid sustained excessive FVIII:C plasma levels, which may increase the risk of thrombotic complications. • Hypersensitivity reactions • Inhibitors of VWF and/or FVIII can occur, especially in patients with type 3 VWD.	• Serious thromboembolic events have been reported in patients with VWD who are treated with coagulation factor replacement therapy. • There is a risk for transmission of infectious agents. • When very large or frequently repeated doses are needed, patients in blood group A, B, or AB should be monitored for signs of intravascular hemolysis and decreasing hematocrit values and be treated appropriately as required. • Inhibitors of FVIII or VWF may occur.	• Allergic and anaphylactic reactions • Inhibitors of FVIII may occur. • There is a risk for transmission of blood-borne viral agents. • Thromboembolic events may occur in patients with VWD receiving VWF/FVIII replacement therapy, especially in patients at risk for thrombosis.
Other	Recombinant product without FVIII. A dose of FVIII is given with the first infusion of rVWF in emergency settings.	Plasma-derived product, contains FVIII	Plasma-derived product, contains FVIII

DDAVP = desmopressin; FVIII = factor VIII; FVIII:C = factor VIII coagulant; IR = incremental recovery; IVR = in vivo recovery; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; VWD = von Willebrand disease; VWF = von Willebrand factor; VWF:RCo = von Willebrand factor ristocetin cofactor.

[a] Health Canada–approved indication.

[b] Humate-P and Wilate carry additional indications.

Source: Product monographs of Vonvendi, Humate-P, and Wilate.[10,11,13]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

About the Patient Groups and Information Gathered

CADTH received 1 patient input submission from the CHS. The CHS is a national voluntary health charity whose mission is to improve the health and quality of life of all people in Canada with inherited bleeding disorders and to ultimately find cures. The organization works at the national, provincial, and local levels with chapters in 10 provinces. Its approximately 300 volunteers are made up of individuals affected by bleeding disorders, family members, and health care providers who work in bleeding disorder treatment centres. The CHS is also affiliated with the World Federation of Hemophilia and works in collaboration with the 26 inherited bleeding disorder treatment centres across Canada, blood system operators (the Canadian Blood Services and Héma-Québec), the Network of Rare Blood Disorder Organizations, the Canadian Organization for Rare Diseases, and others that share their common interests.

During the past 2 years, the CHS received funding in excess of $50,000 from the sponsor. The patient group declared no conflicts of interest in the preparation of this submission. A disclosure of any conflicts of interest for the organization is available on the CADTH website.

For this patient input submission, the CHS conducted an online survey in January 2020 that was advertised via the organization's website, email, and Facebook and Twitter platforms. Seven responses were collected representing 4 provinces and all respondents were individuals affected by VWD. The CHS also consulted leading physicians' opinion with respect to the treatment of VWD.

Disease Experience

There are many types of VWD: type 1, type 2A, type 2B, type 2M, type 2N, and type 3. They differ in the severity of disease. Type 3 VWD is the most severe form and these patients sometimes require prophylactic or preventive therapy. In a survey conducted by the World Federation of Hemophilia in 2018, 4,321 people (1,542 males and 2,776 females) were identified with VWD in Canada, of whom 96 individuals were diagnosed with type 3 VWD. The CHS indicated that patients with milder forms of VWD are significantly under-diagnosed.

Respondents of the CHS survey described VWD as being "*a huge, negative factor in life, affecting everything*," "*very disabling*," "*has caused swelling from stressed limbs, muscles, ligaments, joints which is difficult to manage*," "*causes pain*," and "*causes frequent nosebleeds, bruises, and joint bleeds. The joint pain and menstrual issues have increased with age.*" As a result, many patients suffer lost time at work and school and their quality of life is significantly reduced.

Experience With Treatment

Different types of VWD require different treatments; these may include hormone therapy, DDAVP, antifibrinolytics, and factor replacement (plasma-derived VWF-FVIII such as Humate-P), sometimes in combination. The respondents reported that their current treatments were effective in stopping and preventing bleeding, though these therapies can be burdensome and are associated with various side effects. Some patients stated that current treatments for VWD stop or temporarily stop the bleeding while others were interested in better treatment

options. One patient stated that the condition is "*managed at a satisfactory level*" and they are "*always willing to try something better or more effective*." Others described how treatment was not always easily accessible: "*I take Humate P and it works awesome but when I'm bleeding, I can't get to [the] hospital to get it.*" Another patient using Humate-P was concerned with how "*the cost for travel to [the] hospital is increasing.*" And still other patients described treatment side effects such as "*flu-like symptoms*" or "*prickly feeling, headaches, fatigue after infusions.*" VWD treatment and symptoms interrupt daily life and 1 individual reported having to infuse multiple times per week while another mentioned having to take time off school.

The CHS noted that the aforementioned concerns "*would not be ameliorated by Vonvendi in comparison to other clotting factor concentrates currently available to treat VWD*" as the efficacy, $T_{1/2}$, and treatment schedules are similar between these 2 types of treatments.

The CHS was not aware of any Canadian patients who had experience with Vonvendi through a clinical trial.

Improved Outcomes

When asked what improvements they would like to see with future VWD treatments, patients responded with having easier accessibility and administration, longer lasting benefits, and fewer side effects. One individual stated that having a treatment with "*a longer half-life, less side effects, and easier administration would be ideal*" and particularly with the last point, that "*while self-infusion is usually easy for [them], some days are hard.*" Another patient suggested that a "*daily dose of something majorly anti-inflammatory would help significantly, allowing less missed days from work.*"

In the past, there have also been concerns raised over the risk of viral contamination in plasma-derived clotting factor concentrates, causing some patients with VWD to refuse these types of treatments. The CHS added that patients may be more willing to accept a recombinant VWD therapy if it were available.

Given that rVWF is the first therapeutic to contain only VWF without FVIII, the CHS noted that it may have the potential to fill an unmet need, where additional FVIII is not needed or is even contraindicated. For example, this could be in a prophylaxis setting where exogenous FVIII is not required, but VWF is, or for instances where the infusion of conventional VWF-FVIII concentrates over longer periods can cause FVIII to accumulate and increase the risk of thrombosis.

Clinician Input

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results and providing guidance on a potential place in therapy). The following input was provided by 3 clinical specialists with expertise in the diagnosis and management of VWD.

Unmet Needs

The experts indicated that the current treatment options for the control of bleeding episodes or perioperative management in patients with VWD include antifibrinolytic agents, DDAVP, and plasma-derived factor replacement therapy. Antifibrinolytic agents can be used alone for the control of very minor bleeding or very low-bleeding risk procedures (e.g., tooth

extraction) in patients with type 1 VWD with only mildly reduced VWF levels. Antifibrinolytics are often used in combination with other treatments such as DDAVP or factor concentrate for minor bleeding, major bleeding, prolonged bleeding, or for other procedures. DDAVP is used in type 1 or type 2A patients who have had a documented increase in VWF levels following the administration of a test dose of DDAVP. Factor concentrates are reserved for major bleeding episodes regardless of VWD type, for minor bleeding episodes in non–type 1 or non–type 2A or type 1 DDAVP–non-responders, or prolonged bleeding episodes in DDAVP-responders. One clinical expert provided the following information: after considering these factors, if a patient with VWD presents with an acute bleeding event, has no contraindication to DDAVP, and has a documented prior response to DDAVP with VWF activity to the threshold required for the management of the bleeding event, then DDAVP is generally preferred over factor replacement. In all other patients, a factor replacement product is chosen (currently Humate-P or Wilate). Additionally, because of the tachyphylaxis, bleeding events that require treatment beyond 2 doses are typically managed with a factor replacement product.

For the treatment and control of bleeding episodes in patients with VWD, the most important goals of an ideal treatment are to achieve hemostasis with as few treatment administrations as possible without increasing the risk of thromboembolic events or possibly transmitting infections. Similarly, for perioperative management in patients with VWD, the ideal treatment would be to reduce intraoperative and post-operative blood loss with as few treatment administrations as possible without increasing the risk of thromboembolic events or possibly transmitting infections.

Humate-P and Wilate are plasma-derived VWF concentrates that are currently available in Canada. Both of them are derived from donor plasma; therefore, they may carry the risk of transmitting infections such as HIV, hepatitis B, or hepatitis C. In addition, both Humate-P and Wilate contain FVIII. In circumstances when FVIII levels are increasing with repeated VWF administration and subsequently are associated with higher risk of thromboembolic events, it would be desirable to have a product without FVIII.

Place in Therapy

The experts indicated that the mechanism of action of rVWF is the same as the plasma-derived VWF concentrates in the treatment and control of bleeding episodes or perioperative management of patients with VWD, while the absence of FVIII in rVWF is an important distinction. In situations when VWF concentrate is required, rVWF would be an alternative to donor plasma–derived VWF replacement such as Humate-P or Wilate. In other words, for patients for whom a VWF concentrate is required, it is not appropriate to try other treatments first. In most cases when rVWF is given, co-administration with a FVIII concentrate would be needed.

The experts consulted by CADTH did not anticipate that rVWF would fundamentally shift the current treatment paradigm. The role of DDAVP or antifibrinolytics in the management of bleeding episodes or perioperative management of patients with VWD is not anticipated to change with rVWF.

Patient Population

The clinical experts consulted by CADTH thought that rVWF would be used in patients who would be currently treated with plasma-derived factor concentrates. The characteristics of adult patients best suited for treatment with rVWF are similar for the treatment of bleeding episodes and for perioperative management: those with major or prolonged bleeding

episodes or undergoing moderate or major surgery, those with non–type 1 VWD or non–type 2A VWD, or type 1 VWD or type 2A VWD with historic inadequate response to DDAVP, or those who are intolerant or at risk of adverse effects of DDAVP.

These patients would be identified by clinical judgment, subtype of VWD, and the review of laboratory response (e.g., 1-hour and 4-hour VWF activity levels with a test dose of DDAVP when appropriate). Note that diagnostic tests related to VWD and subtype determination are standard of care and widely available in Canada. Patient care is coordinated through bleeding disorder treatment centres and health care practitioners experienced in the management of VWD. The diagnosis of VWD is generally straightforward but classifying the severity of bleeding episodes and deciding on the most appropriate treatment can be challenging. All patients in Canada with VWD are provided with a treatment recommendation card that is completed by their bleeding disorder treatment centre; it outlines a patient's specific treatment plan with the exact choice of therapy and dosing for various indications. Similarly, classifying bleeding risk with intermediate risk surgeries and deciding on most appropriate treatment can be challenging. Determining which situations require factor replacement versus DDAVP requires clinical experience.

Patients who would not require a plasma-derived factor concentrate would be least suitable for rVWF (i.e., those who can be treated with DDAVP) for the treatment and control of bleeding episodes or perioperative management.

Assessing Response to Treatment

The clinical experts stated that for the treatment and control of bleeding episodes in patients with VWD, achieving hemostasis or control of the acute bleeding is the main outcome of interest. This can be assessed by the measurement of blood loss, the serial measurement of hemoglobin concentration, the need for blood transfusion, the need for local interventions (such as surgery or packing), the length of stay in hospital, visits to the emergency department or hospital, or other health care services provided for ongoing bleeding. A cessation of bleeding, stable hemoglobin concentration, reduction in blood transfusion requirement, reduced need for intervention, reduction in length of hospital stay, and reduction in emergency room visits would be considered clinically meaningful responses to treatment.

For perioperative management in patients with VWD, the clinical experts stated that the reduction of perioperative blood loss would be the main outcome of interest. This can be assessed by surgical assessment of estimated blood loss and the adequacy of achieved hemostasis, change in hemoglobin concentration perioperatively, the need for perioperative blood transfusions, the need for local interventions to achieve hemostasis (such as repeat surgeries, re-suturing, or packing), the length of post-operative stay in hospital, re-admission to hospital, or visits to the emergency department for recurrent bleeding. Achieving intraoperative hemostasis, reduced estimated surgical blood loss, stable post-operative hemoglobin, reduced blood transfusion requirements, a decreased need for post-operative interventions such as a return to the operating room or packing, and a decreased length of hospital stay post-operatively would be considered clinically meaningful responses to treatment.

Treatment response should be assessed using clinical bleeding assessment and achieving targeted VWF activity and antigen levels.

The following must be considered for the treatment and control of bleeding episodes. First, minor bleeding is often managed as an outpatient with clinical assessment of bleeding

cessation done by phone assessment or clinic visit; when factor concentrate is given to patients with minor bleeding events, VWF is often measured before and after the first infusion. Second, for patients with moderate or major bleeding, admission to hospital is required. Visible bleeding would be monitored continuously while internal bleeding would be monitored using changes in hemoglobin concentration as well as radiologic assessments until bleeding ceases. Change in hemoglobin would be examined once or twice a day initially. The measurement of VWF and FVIII levels would occur before and after the first and second doses of factor replacement, and pre- and post-infusion levels repeated with any dose change or increase in bleeding despite factor replacement.

For perioperative management in patients with VWD, it is recommended that admission to hospital is necessary for surgeries where factor concentrate therapy is required. Assessing the degree of bleeding and monitoring hemoglobin concentration would occur continuously intraoperatively and every 8 hours to 24 hours post-operatively. Hemoglobin concentration would be monitored more frequently for major surgery. The measurement of VWF activity and antigen levels and FVIII activity would be monitored before and after each dose given in the first 24 hours to 48 hours and would be measured again with any clinical changes such as an increase in bleeding or a fall in hemoglobin. Administering factor replacement would continue for a period, dependent on the type of surgery and patient response. Upon discharge, patients would continue to be monitored with telephone consultation until it is deemed that no post-operative bleeding complications are present.

Discontinuing Treatment

The experts indicated that the duration of factor replacement therapy depends on the severity and location of bleeding, or the type of surgery. Major bleeding or major surgeries would require maintaining a trough VWF level of more than 0.5 for 5 days to 14 days; for minor bleeding or surgeries, this would be for 1 day to 5 days. A patient who is having ongoing bleeding will be maintained with a higher trough VWF level for a longer duration.

Prescribing Conditions

In practice, major bleeding episodes would be managed in hospital while minor bleeding episodes could be managed in a hemostasis clinic or in a hospital.

Clinical practice guidelines recommend that the surgical management of patients with VWD should be carried out at centres with experience treating bleeding disorders. These centres are usually tertiary care centres. Day surgery or an inpatient setting would be appropriate depending on the type of surgery.

For the treatment and control of bleeding episodes or perioperative management in patients with VWD, a hematologist with expertise in inherited bleeding disorders is required in the diagnosis and management of patients who require VWF concentrate. Specialist nurses with expertise in bleeding disorders are also required. In addition, specialized medical laboratories that are able to measure VWF activity and antigen and FVIII activity are required. The study drug is an intravenous medication, however. Due to the chronic nature of inherited bleeding disorders, patients may be taught how to administer to themselves at home. rVWF is suitable for inpatient settings, outpatient clinics, or home self-administration.

Clinical Evidence

The clinical evidence included in the review of rVWF is a systematic review of pivotal studies provided in the sponsor's submission to CADTH and Health Canada as well as those studies that were selected according to an a priori protocol. No indirect evidence was submitted by the sponsor or identified from the literature that met the selection criteria specified in the review. No sponsor-submitted long-term extension studies or additional relevant studies were considered to address important gaps in the evidence; therefore, no additional evidence was included in this review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of rVWF (650 IU VWF:RCo/vial and 1,300 IU VWF:RCo/vial) for the treatment and control of bleeding episodes in adults diagnosed with VWD, or perioperative management of bleeding in adults diagnosed with VWD

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 5.

Table 5: Inclusion Criteria for the Systematic Review

Patient population	Control of bleeding episodes	Perioperative management
	Adults diagnosed with VWD (aged ≥ 18 years) Potential subgroups have: • severity of bleeding • response to previous treatment with DDAVP • intolerance to previous treatment with DDAVP • VWD types • FVIII levels	Adults diagnosed with VWD (aged ≥ 18 years) Potential subgroups have: • severity of bleeding • response to previous treatment with DDAVP • intolerance to previous treatment with DDAVP • types of surgery • VWD types • FVIII levels
Intervention	Dosing recommendations for rVWF according to type of bleeding: • minor — initial dose of 40 IU/kg to 50 IU/kg, subsequent dose of 40 IU/kg to 50 IU/kg every 8 hours to 24 hours • major — initial dose of 50 IU/kg to 80 IU/kg, subsequent dose of 40 IU/kg to 60 IU/kg every 8 hours to 24 hours for approximately 2 days to 3 days Co-administration of rFVIII is required if the FVIII:C level is < 40% or unknown	**12 hours to 24 hours prior to initiating surgery** A dose of 40 IU/kg to 60 IU/kg may be administered to raise endogenous FVIII:C levels to the recommended minimum target levels: • minor — 30 IU/dL • major — 60 IU/dL **Within 3 hours prior to the procedure** If FVIII:C levels are at the recommended minimum target levels, 1 dose of rVWF alone within 1 hour prior to the procedure is given; if FVIII:C levels are below the recommended minimum target levels, administer rVWF in addition to rFVIII to raise VWF:RCo and FVIII:C levels. **During and after surgery** The VWF:RCo and FVIII:C levels should be monitored and the intraoperative and post-operative substitution regimen should be individualized according to the PK results, intensity and duration of hemostatic challenge, and the institution's standard of care.
	IV infusion, up to a maximum of 4 mL/minute	

Comparators	DDAVP Plasma-derived VWF replacement concentrates (containing FVIII concentrates)	
Outcomes	• Hemostatic efficacy (e.g., bleeding control)[a] • Dose of infused study drug • Survival • HRQoL[a] • Number of transfusions needed • Use of rescue therapy for uncontrolled bleeding • Hospitalization due to uncontrolled bleeding • Productivity (e.g., return to school/work, return to normal functioning)[a] • Change from baseline in level of VWF • Change from baseline in activity of VWF • Change from baseline in level of FVIII • PK outcomes (e.g., half-life of study drug)	• Hemostatic efficacy (e.g., number of bleeding events during and after surgery, intraoperative blood loss) • Dose of infused study drug • Survival • HRQoL[a] • Number of transfusions needed • Use of rescue therapy for uncontrolled bleeding • Hospitalization due to uncontrolled bleeding • Change from baseline in level of VWF • Change from baseline in activity of VWF • Change from baseline in level of FVIII • PK outcomes (e.g., half-life of study drug)
	Harms outcomes AEs, SAEs, WDAEs, mortality Notable harms/harms of special interest are: • thrombotic events (e.g., stroke, DVT) • hypersensitivity reaction (e.g., skin rash, angioedema, anaphylaxis) • injection site reaction • infusion-related reaction (e.g., tachycardia, flushing, dyspnea, blurred vision) • blood-borne infections • anti-VWF antibodies	
Study design	Published and unpublished phase III and phase IV RCTs	

AE = adverse event; DDAVP = desmopressin; DVT = deep venous thrombosis; FVIII = factor VIII; FVIII:C = factor VIII coagulant; HRQoL= health-related quality of life; IV = intravenous; PK = pharmacokinetics; RCT = randomized controlled trial; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; SAE = serious adverse event; VWD = von Willebrand disease; VWF = von Willebrand factor; VWF:RCo = von Willebrand factor ristocetin cofactor; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[17]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the U.S. National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was the drug name, Vonvendi. Clinical trial registries were searched: the U.S. National Institutes of Health's ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on May 29, 2020. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee in September 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist:[18] Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trial Registries, and Databases (Free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Findings From the Literature

A total of 2 studies were identified from the literature for inclusion in the systematic review (Figure 3). The included studies are summarized in Table 6.

Figure 3: Flow Diagram for Inclusion and Exclusion of Studies

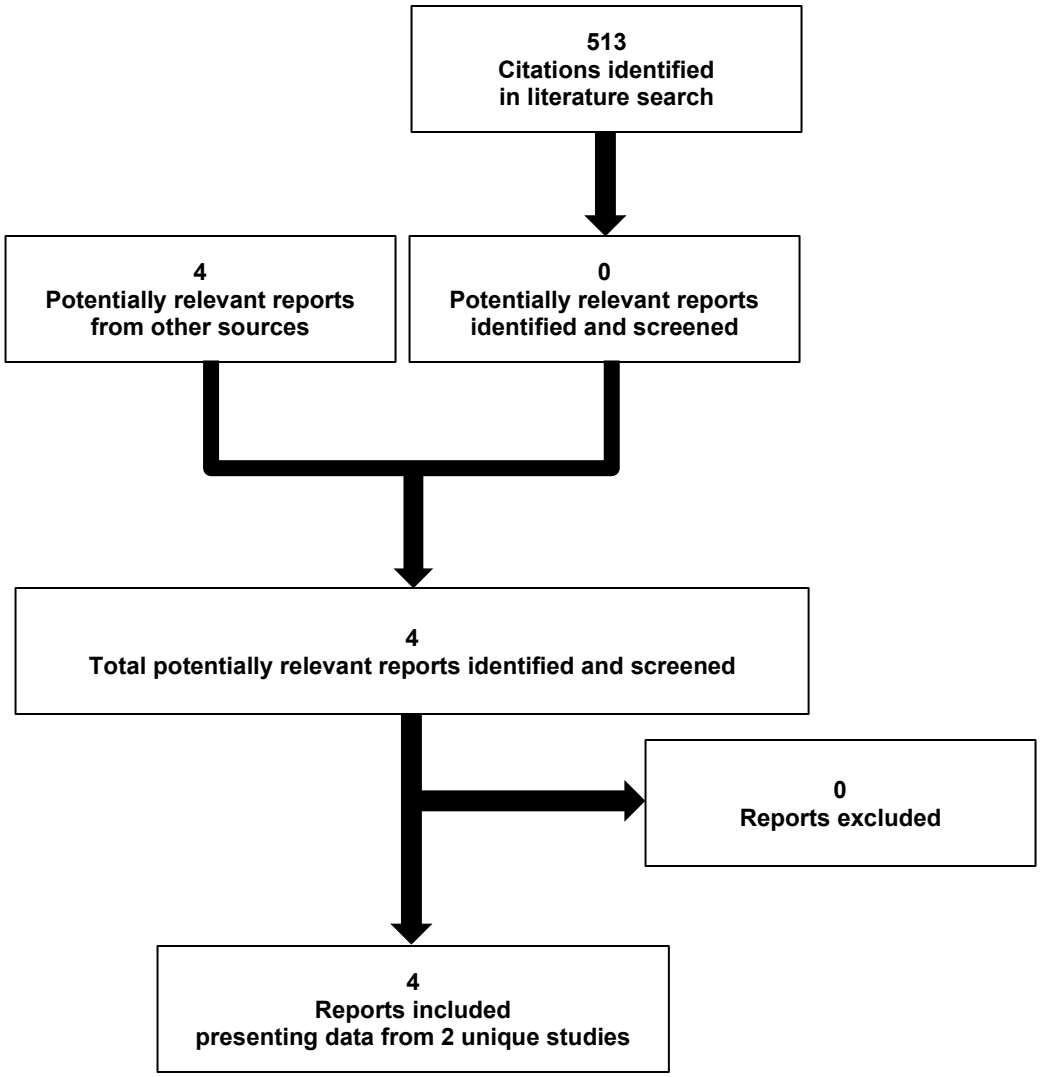


Table 6: Details of Included Studies

		Study 071001 for treatment and control of bleeding episodes	Study 071101 for perioperative management
DESIGNS AND POPULATIONS	**Study design**	Phase III, OL, non-controlled, multi-centre, part-RCT[a]	Phase III, OL, non-randomized, non-controlled, multi-centre trial
	Locations	30 sites in the US, England, Europe, Australia, and Asia	14 sites in the US, England, Europe, Australia, and Asia
	Enrolled (N)	49	24
	Inclusion criteria	Adult patients (aged ≥ 18 and < 65 years) diagnosed with: • type 1 (VWF:RCo < 20 IU/dL) or • type 2A (VWF:RCo < 20 IU/dL), type 2B (diagnosed by genotype), type 2N (FVIII:C < 10% and historically documented genetics), type 2M or • type 3 (VWF:Ag ≤ 3 IU/dL) or • severe VWD with a history of requiring substitution therapy with VWF concentrate to control bleeding. Patients who participated in treatment for bleeding episodes were required to have ≥ 1 documented bleed requiring VWF replacement therapy in the previous 12 months prior to enrolment. Karnofsky score ≥ 60%	Adult patients (aged ≥ 18 years) with severe VWD and elective surgical procedure planned VWD with a history of requiring substitution therapy with VWF concentrate to control bleeding: • type 1 (VWF:RCo < 20 IU/dL) or • type 2A (as verified by multimer pattern), type 2B (diagnosed by genotype), type 2N (FVIII:C < 10% and historically documented genetics), type 2M or • type 3 (VWF:Ag ≤ 3 IU/dL). If type 3 VWD, patient had a medical history of ≥ 20 exposure days to VWF/FVIII coagulation factor concentrates. If type 1 or type 2 VWD, patient had a medical history of 5 exposure days or a past major surgery requiring VWF/FVIII coagulation factor concentrates.
	Exclusion criteria	Pseudo VWD or another hereditary or acquired coagulation disorder other than VWD A documented history of a VWF:RCo half-life < 6 hours History or presence of a VWF inhibitor or FVIII inhibitor (with a titer ≥ 0.4 BU or 0.6 BU based on various assays) at screening Hypersensitivity to any components of the study drugs Medical history of immunological disorders/thromboembolic event/HIV positive with absolute CD4 count < 200/mm^3 Patients with CV disease, an acute illness at screening, significant liver disease, renal disease with serum creatinine level ≥ 2 mg/dL, or another clinically significant concomitant disease that may pose additional risks for the patient	Pseudo VWD or another hereditary or acquired coagulation disorder History or presence of a VWF inhibitor or FVIII inhibitor (with a titer ≥ 0.4 BU or 0.6 BU based on various assays) at screening Hypersensitivity to any components of the study drugs Medical history of immunological disorders/thromboembolic event/HIV positive with absolute CD4 count < 200/mm^3 Platelet count < 100,000/mL Patients with significant liver disease or renal disease with serum creatinine level ≥ 2.5 mg/dL Patients who had been treated with an immunomodulatory drug < 30 days prior to signing the informed consent Patients who participated in another clinical study involving the study drug < 30 days prior to

		Study 071001 for treatment and control of bleeding episodes	Study 071101 for perioperative management
		Patients who had been treated with an immunomodulatory drug < 30 days prior to signing the informed consent Patients who participated in another clinical study involving the study drug < 30 days prior to enrolment or were scheduled to participate in another study involving the study drug during the course of Study 071001 Patients with a history of drug or alcohol abuse < 2 years prior to enrolment Patients with progressive fatal disease and/or life expectancy of < 3 months	enrolment or were scheduled to participate in another study involving the study drug during the course of Study 071101 Patients with progressive fatal disease and/or life expectancy of < 3 months
Drugs	**Intervention**	**Arm 1: PK50 + treatment of BEs** Initially randomized to: • 50 IU/kg rVWF + 38.5 IU/kg rFVIII • 50 IU/kg rVWF + placebo After a washout period of 18 days (± 10 days), patients were crossed over to receive the alternative treatment. This was followed by 12 months of on-demand treatment for BEs. **Arm 2: PK50 only** Randomized to: • 50 IU/kg rVWF + 38.5 IU/kg rFVIII • 50 IU/kg rVWF + placebo After a washout period of 18 days (± 10 days), patients were crossed over to receive the alternative treatment. No on-demand treatment of BEs **Arm 3: PK80 + treatment of BEs** • first 80 IU/kg rVWF followed by 6 months of on-demand treatment for BEs • second 80 IU/kg rVWF followed by additional 6 months of on-demand treatment for BEs **Arm 4: Treatment of BEs** rVWF for 12 months of on-demand treatment for BEs Study drug was administered intravenously.	rVWF intravenously administered. Dose and dosage frequency were determined by type of surgery, PK results, and VWF and FVIII levels. A priming dose with rVWF of 40 IU/kg to 60 IU/kg was given to patients 12 hours to 24 hours prior to surgery to allow the endogenous FVIII levels to increase to at least 30 IU/dL (for minor and oral surgery) or 60 IU/dL (for major surgery), before the loading dose of rVWF ± rFVIII was administered. An rVWF loading dose ± rFVIII was administered within 1 hour prior to surgery. If the target FVIII:C levels were achieved, rVWF alone was administered to achieve the peak levels; if target FVIII:C levels were not achieved, rVWF was co-administered with rFVIII to meet recommended peak levels.
	Comparator(s)	No comparator	No comparator

		Study 071001 for treatment and control of bleeding episodes	Study 071101 for perioperative management
DURATION	**Phase**	**Screening** Treatment allocation: • PK assessment, followed by • on-demand treatment The study consisted of 2 parts (Part A and Part B). *Part A* • PK assessments alone (Arm 2: PK50 only without treatment of bleeding episodes), or • PK assessments (Arm 1: PK50 and Arm 3: PK80) plus on-demand treatment period(s) of 6 months for bleeding episodes; for Arm 4, there was on-demand treatment for bleeding episodes only *Part B* Patients receiving treatment for PK assessments and/or bleeding episodes in Part A were to be entered into Part B to continue on-demand treatment for bleeding episodes for 6 additional months for a total of 12 months in the study.	Treatment started from the date of signing informed consent until a follow-up period of 14 days post surgery, and was expected to last [redacted]: **Screening** PK assessment: • for major surgery (not required for minor surgery) Pre-operative priming infusion with rVWF only, 12 hours to 24 hours prior to surgery Pre-operative loading infusion, 1 hour to 2 hours prior to surgery *Surgical procedure, with further infusions as necessary:* Intraoperative assessments performed *Post-operative infusions:* Assessments performed until discharge *Post-operative follow-up:* Study completion visit at day 14 (± 2 days) post surgery
OUTCOMES	**Primary end point**	Number of patients with treatment success for treated bleeding episodes ("success" defined as a mean efficacy rating score of < 2.5 for a patient's study drug–treated BEs during the study period)	Overall hemostatic efficacy 24 hours after last perioperative study drug infusion or at completion of day 14 visit, whichever occurs earlier
	Secondary and exploratory end points	**Secondary efficacy** • Number of BEs with an efficacy rating of "excellent" or "good" • Number of treated BEs with an efficacy rating of "excellent" or "good" • Number of infusions of rVWF + rFVIII and/or rVWF per BE • Number of units of rVWF + rFVIII and/or rVWF per BE **Secondary safety** • AEs, SAEs, WDAEs, death • Notable harms (e.g., thrombotic events) **Secondary PK** • AUC of VWF:RCo, VWF:Ag, and FVIII • Half-life of VWF:RCo, VWF:Ag, and FVIII • Intra-patient PK of VWF:RCo, VWF:Ag at baseline and after 6 months in a subset of patients with severe VWD **Exploratory** • HRQoL	**Secondary** • Intraoperative actual vs. predicted blood loss at surgery completion • Intraoperative hemostatic efficacy score on a scale of "excellent," "good," "moderate," or "none" at completion of surgery • Daily intraoperative and post-operative weight-adjusted dose of rVWF ± rFVIII through post-operative day 14 **PK** • AUC, half-life, clearance of the study drug **Safety** • AEs, SAEs, WDAEs • Notable harm (e.g., thrombotic events, severe allergic reactions) **Exploratory** • HRQoL

		Study 071001 for treatment and control of bleeding episodes	Study 071101 for perioperative management
Notes	**Publications**	Gill et al. (2015)[19]	Peyvandi (2019)[20]

AE = adverse event; AUC = area under the curve; BE = bleeding episode; BU = Bethesda unit; CV = cardiovascular; FVIII = factor VIII; FVIII:C = factor VIII coagulant; HRQoL = health-related quality of life; OL = open label; PK = pharmacokinetics; RCT = randomized controlled trial; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; SAE = serious adverse event; vs. = versus; VWD = von Willebrand disease; VWF = von Willebrand factor; VWF:Ag = von Willebrand factor antigen; VWF:RCo = von Willebrand factor ristocetin cofactor; WDAE = withdrawal due to adverse event.

[a] In Study 071001, once eligibility was confirmed by the sponsor, a patient entered Arm 1, Arm 2, Arm 3, or Arm 4, per discussions with the study investigator; patients were randomized to 1 of the 2 treatments during PK assessment period, while no randomization was conducted during the on-demand treatment period.

Note: Two additional reports were included: CADTH's submission[8] and Health Canada's reviewer's report.[21]

Source: Clinical Study Reports for Study 071001[14] and Study 071101.[15]

Description of Studies

Treatment and Control of Bleeding Episodes

Study 071001 was a phase III, parallel-group, open-label, non-controlled, multi-centre trial submitted by the sponsor[14] to assess the efficacy, safety, and PK of rVWF, with or without rFVIII, in the treatment of bleeding episodes in adult patients (aged ≥ 18 years) diagnosed with severe type 3 VWD and severe non–type 3 VWD. This study was conducted in 30 sites in the US, England, Europe, Australia, and Asia. It was initiated in November 2011 and completed in February 2014.

After screening, eligible patients were assigned to 1 of the following 4 treatment arms at the investigator's discretion (Figure 4):

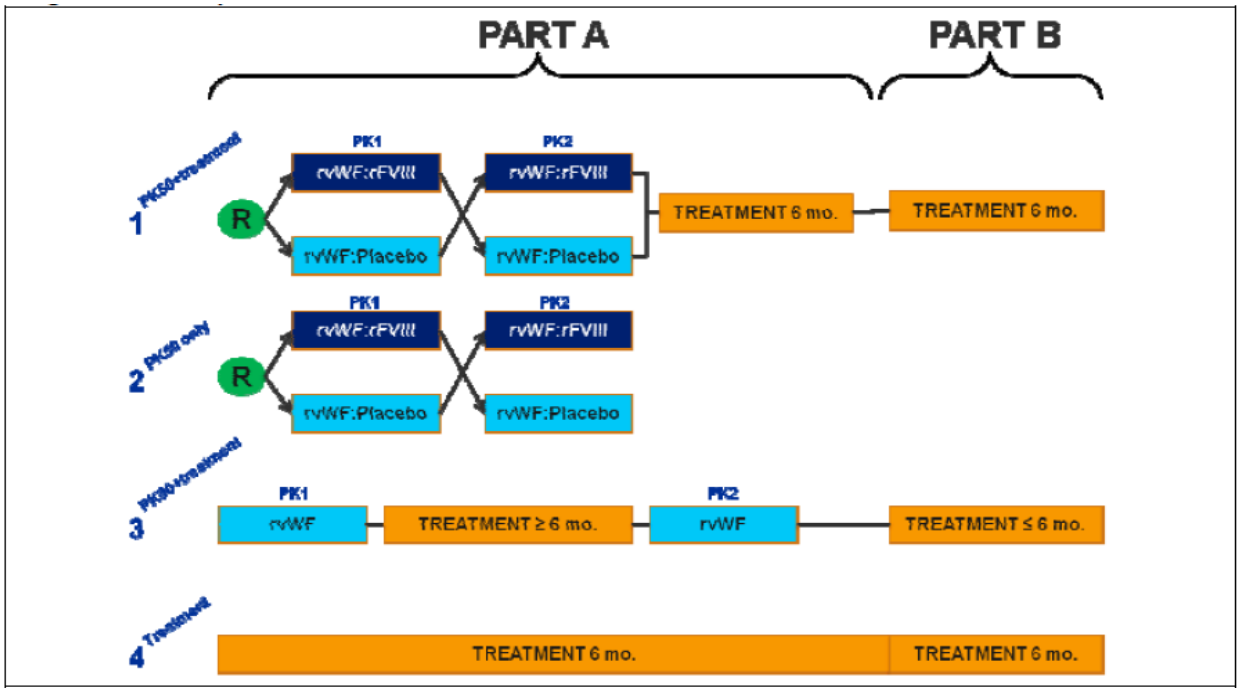
1. PK50 (50 IU/kg VWF:RCo rVWF with 38.5 IU/kg rFVIII or 50 IU/kg VWF:RCo rVWF with placebo) and treatment for bleeding episodes (n = 9)
2. PK50 only (PK assessment with 50 IU/kg VWF:RCo rVWF) (n = 9)
3. PK80 (PK assessment with 80 IU/kg VWF:RCo rVWF) and treatment for bleeding episodes (n = 16)
4. Assessment of treatment for bleeding episodes only (n = 6)

The study consisted of 2 parts (Part A and Part B). Part A consisted of PK assessments only (Arm 2: PK50 only without treatment of bleeding episodes), or PK assessments (Arm 1: PK50 and Arm 3: PK80) plus an on-demand treatment period of 6 months for bleeding episodes, or Arm 4: on-demand treatment for bleeding episodes only. Patients who received treatment for PK assessments and/or bleeding episodes in Part A were to be entered into Part B to continue on-demand treatment for bleeding episodes for 6 additional months for a total of 12 months in the study.

For the PK assessments in arms 1 and 2, patients were crossed over to the other treatment after a washout period of 18 days, plus or minus 10 days. The sequence of treatment regimens was randomized and blinded to site personnel. The randomization was conducted using a predetermined central randomization list. The total period of on-demand treatment was 12 months. The primary efficacy end point of this study was the number of patients with treatment success for treated bleeding episodes at the end of the study.

A central laboratory was used for all protocol-required laboratory tests. In addition, tests for complete blood count, serum chemistry, and/or coagulation parameters could be performed in the local lab. No inter-laboratory standardization methods were used.

Figure 4: Study 071001 Flow Chart



mo. = month; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor.

Source: Protocol of Study 071001.[14]

Perioperative Management

Study 071101 was a phase III, open-label, non-controlled, non-randomized, multi-centre trial to evaluate the efficacy and safety of rVWF, with or without rFVIII, as prophylactic treatment for major or minor elective surgical procedures in adult patients (aged ≥ 18 years) with severe VWD (N = 15, consisting of 10 major surgeries, 4 minor surgeries, and 1 oral surgery).[15] The study was conducted in 14 sites in the US, England, Europe, Australia, and Asia. It was initiated in April 2015 and completed in July 2016. Major surgeries referred to major orthopedic surgery, major abdominal surgery, major gynecological surgery, major head and neck surgery, any intracranial, cardiovascular, or spinal surgery, and any other surgery that has a significant risk of large-volume blood loss or blood loss into a confined anatomical space. Minor surgeries referred to interventions such as the placement of intravenous access devices, the removal of small skin lesions, arthroscopy, gastroscopy, colonoscopy, or conization. Oral surgeries comprised extractions of fewer than 3 teeth, if the teeth were non-molars and had no bony involvement.

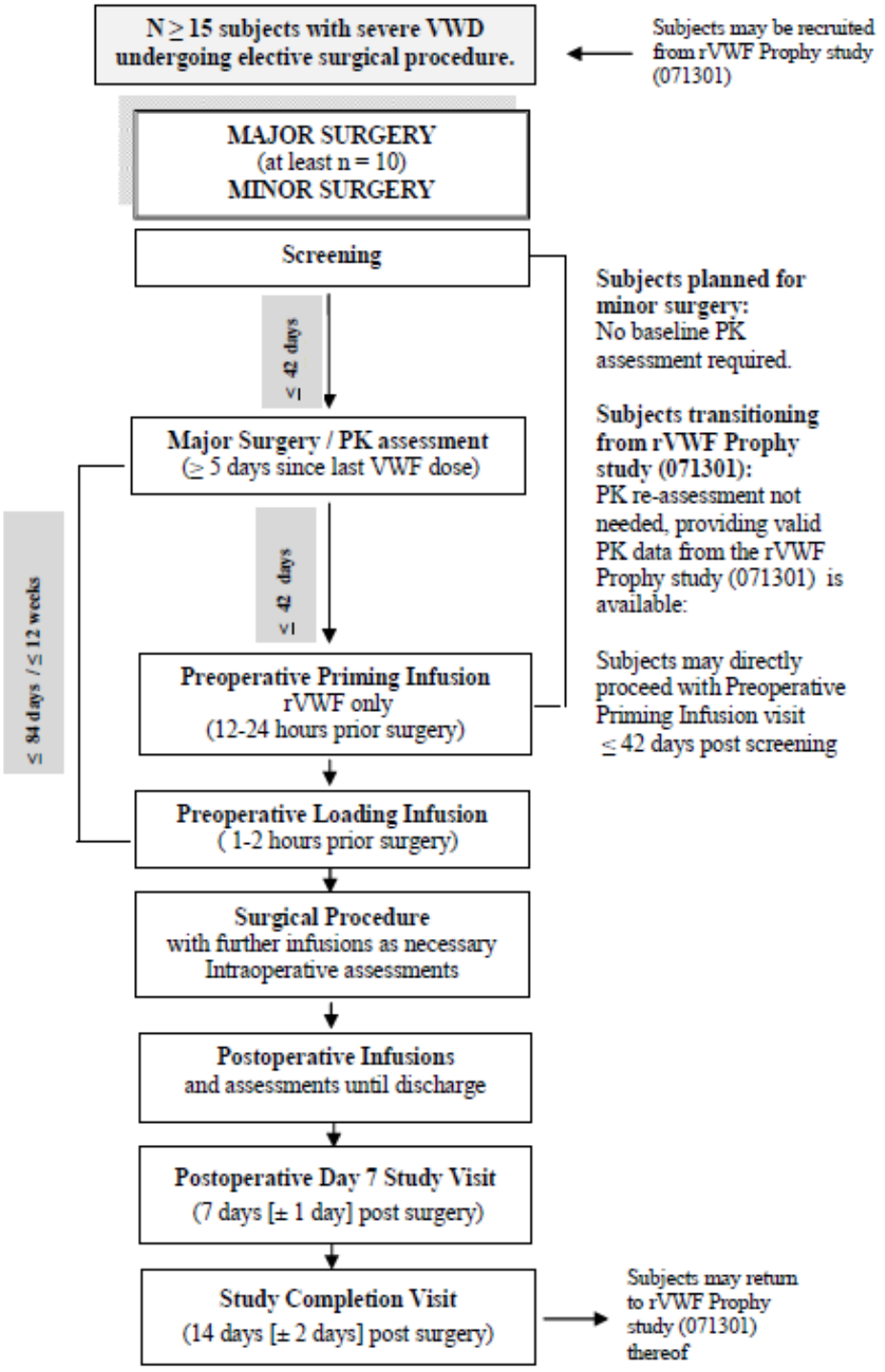
The treatment duration was expected to last [redacted] weeks from screening to the study completion visit, including a 14-day follow-up period after the surgery, unless prematurely discontinued. Eligible study participants who planned for major surgery had an initial PK evaluation on rVWF over a 72-hour period within 42 days before surgery. The PK data were

used to guide pre-operative dosing for the study drug. Patients who planned minor or oral surgery were not required to undergo a PK assessment. At 12 hours to 24 hours before surgery, rVWF 40 IU/kg to 60 IU/kg VWF:RCo was given intravenously to allow endogenous FVIII:C levels to rise to 30 IU/dL or more for minor or oral surgery or 60 IU/dL or more for major surgery. If the target FVIII:C levels were achieved, rVWF alone was administered within 1 hour before surgery to achieve the peak levels as advised in the product monograph. If target FVIII:C levels were not achieved, rVWF was co-administered with rFVIII within 1 hour before surgery to meet recommended peak levels. Intraoperative and post-operative dosing were individualized to maintain target trough levels according to PK results, as well as the intensity and duration of the hemostatic challenge. After surgery, patients were monitored for 14 days and target trough plasma levels of VWF:RCo and FVIII:C were maintained. Details of the study design are presented in Figure 5.

The primary efficacy outcome measure was the percentage of patients in each overall investigator-assessed hemostatic efficacy category (i.e., “excellent,” “good,” “moderate,” “none”) at 24 hours after the last perioperative infusion or at completion of the study, whichever occurred earlier.

All laboratory assessments were undertaken at the central laboratory unless otherwise stated. Additional local laboratory tests could be performed for clinical management of the patient as deemed necessary by the investigator.

Figure 5: Study 071101 Flow Chart



PK = pharmacokinetics; rVWF = recombinant von Willebrand factor; VWD = von Willebrand disease; VWF = von Willebrand factor.

Source: Clinical Study Report for Study 071101.[15]

Populations

Inclusion and Exclusion Criteria

Treatment and Control of Bleeding Episodes

Adult patients with severe non–type 3 VWD and type 3 VWD were included in Study 071001. Patients who participated in treatment for bleeding episodes were required to have at least 1 documented bleed requiring VWF replacement therapy during the previous 12 months prior to enrolment. Patients were also required to have a Karnofsky score of 60% or greater. A Karnofsky score of 60% was defined as "requires occasional assistance, but is able to care for most of his needs."[14] Patients were excluded if they had a coagulation disorder other than VWD, a history or presence of a VWF inhibitor or FVIII inhibitor at screening, a history of immunologic disorders or thromboembolic events, or any clinically significant concomitant disease that could pose additional risks for the patients. Details of the inclusion and exclusion criteria are provided in Table 6.

Perioperative Management

Patients aged 18 years or older with severe VWD as specified in Table 6 who had planned elective surgery were eligible for participation in the study. Patients with type 3 VWD had to have a history of 20 exposure days or more to VWF/FVIII concentrates. For patients with type 1 or type 2 VWD, a minimum of 5 exposure days or a post–major surgery treatment requiring VWF/FVIII-containing products was required. Patients were excluded if they had a history or presence of a VWF inhibitor or FVIII inhibitor at screening, had a history of a thromboembolic event, were hypersensitive to VWF, had a platelet count of less than 100,000/mL, or had any clinically significant concomitant disease that could pose additional risks for the patients. Details of the inclusion and exclusion criteria are provided in Table 6.

Baseline Characteristics

Treatment and Control of Bleeding Episodes

In Study 071001, the mean age of patients was 37 years (range = 19 years to 64 years). Sex was evenly distributed (male 46% versus female 54%). Most patients were White ([redacted]). The majority of the study participants ([redacted]) had type 3 VWD (Table 7).

Table 7: Summary of Baseline Characteristics — Treatment and Control of BEs, Safety Analysis Set

Characteristics	Study 071001 N = 37
Age, years, mean (SD)	36.9 ([redacted])
Sex, n (%)	
Male	17 (45.9)
Female	20 (54.1)
Race, n (%)	
White	[redacted]
Black or African American	0
Asian	[redacted]
American Indian or Alaska Native	0
Native Hawaiian or other Pacific Islander	0

Characteristics	Study 071001 N = 37
VWD subtype, n (%)	
1	2 (5.4)
2A	5 (13.5)
2B	0
2M	0
2N	1 (2.7)
3	29 (78.4)
Patient has prothrombotic risk factors, n (%)	[redacted]
Patient has CVD risk factors, n (%)	[redacted]
Family history of VWF inhibitors, n (%)	[redacted]
Family history of FVIII inhibitors, n (%)	[redacted]
Family history of CVD or thrombosis, n (%)	[redacted]
Family history of TTP, n (%)	[redacted]
Treatment that patient received during the 24-month period prior to study enrolment, n (%)	
On-demand exclusively	[redacted]
Prophylaxis exclusively	[redacted]
Both	[redacted]
Treatment that patient was receiving prior to study entry, n (%)	
On demand exclusively	[redacted]
Prophylaxis exclusively	[redacted]
Both	[redacted]
Regimen that was followed, n/N (%)[a]	
1 infusion per week	[redacted]
2 infusions per week	[redacted]
3 infusions per week	[redacted]

BE = bleeding episode; CVD = cardiovascular disease; FVIII = factor VIII; SD = standard deviation; TTP = thrombotic thrombocytopenic purpura; VWD = von Willebrand disease; VWF = von Willebrand factor.

[a] Only applicable for "prophylaxis exclusively" and for "combination of both."

Source: Clinical Study Report for Study 071001.[14]

Perioperative Management

In Study 071101, the mean age of patients was 39 years (range = 20 years to 70 years). Sex was evenly distributed in this study (male 47% versus female 53%). Most patients were White (80%). More than half of the study participants (53%) had type 3 VWD. The majority of the patients received previous coagulation concentrates therapy. Most patients enrolled in this study underwent a major surgical procedure (66.7%). Details of patient characteristics at baseline are provided in Table 8.

Table 8: Summary of Baseline Characteristics — Perioperative Management, Safety Analysis Set

Characteristics	Study 071101 N = 15
Age, years, mean (SD)	39.3 ([redacted])
Sex, n (%)	
Male	7 (46.7)
Female	8 (53.3)
Race, n (%)	
White	12 (80)
Asian	3 (20)
VWD type, n (%)	
1	3 (20)
2A	2 (13.3)
2B	1 (6.7)
2M	1 (6.7)
3	8 (53.3)
Surgical classification, n (%)	
Major	10 (66.7)
Minor	4 (26.6)
Oral surgery	1 (6.7)
VWF:Ag, IU/dL, mean (SD)	[redacted]
VWF:RCo, IU/dL, mean (SD)	[redacted]
FVIII:C, IU/dL, mean (SD)	[redacted]
Surgical procedure classification, n (%)	
Major	10 (66.7)
Minor	4 (26.7)
Oral	1 (6.7)
Coagulation concentrates treatment history	
Lifetime exposure, days, mean (SD)	[redacted]
Coagulation factor product, n (%)	
Haemate P	[redacted]
Humate-P	[redacted]
Wilate	[redacted]
Other	[redacted]

FVIII:C = factor VIII coagulant; SD = standard deviation; VWD = von Willebrand disease; VWF:Ag = von Willebrand factor antigen; VWF:RCo = von Willebrand factor ristocetin cofactor.

Source: Clinical Study Report for Study 071101.[15]

Interventions

Treatment and Control of Bleeding Episodes

In Study 071001, after screening, eligible study participants were assigned to the following treatment arms at the investigator's discretion:

- **Arm 1** (*PK50 and treatment of bleeding episodes*; N = 9): Patients were randomized to 1 of 2 treatment groups within Arm 1 to initially receive either 1) 50 IU/kg VWF:RCo rVWF plus 38.5 IU/kg rFVIII or 2) 50 IU/kg VWF:RCo rVWF plus placebo. After a washout period of 18 days, plus or minus 10 days, patients in each dose group crossed over to receive the alternative treatment to the initial infusion. PK was assessed after each infusion. Patients then received on-demand treatment of bleeding episodes for 12 months after initial exposure to rVWF.
- **Arm 2** (*PK50 only*; N = 9): Patients were randomized to 1 of 2 treatment groups within Arm 2 to initially receive either 1) 50 IU/kg VWF:RCo rVWF plus 38.5 IU/kg rFVIII or 2) 50 IU/kg VWF:RCo rVWF plus placebo. After a washout period of 18 days, plus or minus 10 days, patients in each dose group crossed over to receive the alternative treatment of the initial infusion. PK was assessed after each infusion. There was no on-demand treatment for bleeding episodes. Thereafter, patients either exited the study after the second dose of study drug or could undergo new informed consent for on-demand treatment of bleeding episodes at home for 12 months after initial exposure to rVWF; these patients were considered to be in Arm 1.
- **Arm 3** (*PK80 and treatment of bleeding episodes*; N = 16): Patients received 80 IU/kg VWF:RCo rVWF followed by 6 months of on-demand treatment for bleeding episodes. They then received a second dose of 80 IU/kg VWF:RCo rVWF followed by a second 6-month treatment for bleeding episodes for a total of 12 months after initial exposure to rVWF. PK was assessed with each of the 2 infusions of 80 IU/kg VWF:RCo rVWF.
- **Arm 4** (*treatment of bleeding episodes only*; N = 6): Patients received on-demand treatment for bleeding episodes only over an initial period of 6 months, followed by a second period of 6 months for a total of 12 months. No PK assessments were performed. Patients in this arm who were suitable for home treatment of bleeds had to receive 2 infusions of rVWF at the clinic before initiating home treatment.

All infusions for PK assessments were performed in the clinic. In Arm 1, Arm 3, and Arm 4, patients experiencing a bleeding episode were able to receive the study drug at any time for treatment.

When a bleeding episode occurred during the study, patients were initially treated with an infusion of rVWF together with rFVIII at a ratio of 1.3:1 (± 0.2 VWF:RCo/FVIII:C) to ensure an immediate hemostatic level of FVIII:C, and subsequently with rVWF, with or without rFVIII, based on FVIII levels if available. When there was no information for FVIII levels, the patient's PK data were used to determine the rFVIII dose, at the discretion of the investigator. In order to avoid an excessive rise in FVIII:C, reduced doses and/or prolongation of the dose interval were considered. Dose recommendations for the treatment of bleedings in Study 071001 are provided in Figure 6.

Figure 6: Dosing Recommendations in Study 071001

rVWF:RCo Dosing Recommendations for the Treatment of Bleedings in VWD		
Classification of VWD	**Hemorrhage**	**Dosage (IU VWF:RCo/kg body weight)**
Type 1 • severe (Baseline VWF:RCo activity typically <20%)	Minor (e.g. epistaxis, oral bleeding, menorrhagia)	40 to 50 IU/kg (1 or 2 doses)
	Major (e.g. severe or refractory epistaxis, menorrhagia, gastrointestinal (GI) bleeding, CNS trauma, hemarthrosis, or traumatic hemorrhage)	Initial dose 50 to 75 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment.
Type 2 (all variants) and Type 3	Minor (clinical indications above)	40 to 50 IU/kg (1 or 2 doses)
	Major (clinical indications above)	Initial dose of 60 to 80 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the trough level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment.

CNS = central nervous system; VWD = von Willebrand disease; VWF:RCo = von Willebrand factor ristocetin cofactor.

Source: Clinical Study Report for Study 071001.[14]

When treatment for controlling bleeding episodes was needed, patients were considered suitable for home treatment of minor and moderate bleeds without the need for follow-up visits only after the patient had received at least 2 infusions of the study drug in the clinic (either via PK or treatment for a bleeding episode), at the discretion of the investigator. If a bleeding episode occurred between PK infusion 1 and PK infusion 2 in Arm 1, Arm 2, or Arm 3, and the patient had not received any additional rVWF infusion in between, the patient was treated with rVWF, with or without rFVIII, at the clinic. Alternatively, bleeding episodes were treated with the patient's standard care such as a plasma-derived VWF/FVIII product.

Perioperative Management

In Study 071101, a priming dose with rVWF 40 IU/kg to 60 IU/kg was given to patients 12 hours to 24 hours prior to surgery to allow the endogenous FVIII levels to increase to at least 30 IU/dL (for minor or oral surgery) or 60 IU/dL (for major surgery) before the loading dose of rVWF, with or without rFVIII, was administered. An rVWF loading dose with or without rFVIII was administered within 1 hour prior to surgery. If the target FVIII:C levels were achieved, rVWF alone was administered to achieve the peak levels; if target FVIII:C levels were not achieved, rVWF was co-administered with rFVIII to meet recommended peak levels (see Figure 7 and Figure 8). Intraoperative and post-operative dosing were individualized according to the PK results, the intensity and duration of the hemostatic challenge, and the institution's standard of care. Post-operatively, patients with minor surgery were infused with rVWF every 12 hours to 24 hours or every other day, targeting 30 IU/dL or more (VWF and FVIII) at least for the first 48 hours; patients with oral surgery were infused with rVWF at least once within the first 8 hours to 12 hours, targeting 30 IU/dL or more (VWF and FVIII); patients with major surgery were infused with rVWF every 12 hours to 24 hours or every other day, targeting more than 50 IU/dL (VWF and FVIII) at least for the first 72 hours followed by 30 IU/dL or more (VWF and FVIII) as long as deemed

necessary by the investigator. Doses were either rVWF alone or rVWF plus rFVIII, depending on the respective VWF and FVIII levels.

Figure 7: Recommendations for Loading Dose in Study 071101

VWF:RCo and FVIII:C
Loading Dose Recommendations for the Prevention of Excessive Bleeding During and After Surgery

Type of Surgery	VWF:RCo Target Peak Plasma Level	FVIII:C Target Peak Plasma Level[a]	Calculation of Loading Dose rVWF (Administered Within 1 Hour Prior to Surgery) (IU VWF:RCo Required)
Minor/oral[a]	50-60 IU/dL	40 - 50 IU/dL	Δ^{b}VWF:RCo x BW (kg) /IR[c]
Major	100 IU/dL	80-100 IU/dL	Δ^{b}VWF:RCo x BW (kg) /IR[c]

Δ = Target peak plasma VWF:RCo – baseline plasma VWF:RCo; BW = body weight; FVIII:C = factor VIII coagulant; IR = incremental recovery; VWF:RCo = von Willebrand factor ristocetin cofactor.

Source: Clinical Study Report for Study 071101.[15]

Figure 8: Recommendations for Subsequent Maintenance Doses in Study 071101

VWF:RCo and FVIII:C Target Trough Plasma Level and Minimum Duration of Treatment Recommendations for Subsequent Maintenance Doses for the Prevention of Excessive Bleeding During and After Surgery

Type of Surgery	VWF:RCo Target Trough Plasma Level		FVIII:C Target Trough Plasma Level		Minimum Duration of Treatment/ Frequency of Dosing
	Up to 72 Hours Post Surgery	After 72 Hours Post Surgery	Up to 72 Hours Post Surgery	After 72 Hours Post Surgery	
Major	> 50 IU/dL	> 30 IU/dL	> 50 IU/dL	> 30 IU/dL	72 h every 12-24 h/ every other day
Minor	≥ 30 IU/dL	-	-	> 30 IU/dL	48 h every 12-24 h/ every other day
Oral	≥ 30 IU/dL	-	-	> 30 IU/dL	8 – 12 h every 12-24 h/ every other day

FVIII:C = factor VIII coagulant; VWF:RCo = von Willebrand factor ristocetin cofactor.

Source: Clinical Study Report for Study 071101.[15]

After surgery, patients were monitored for 14 days and target trough plasma levels of VWF:RCo and FVIII:C were maintained.

Study participants were not taking concomitant hemostatic products. (Concomitant medications were defined as medications that started prior to, on, or after the first dose of investigational product administration and started before the completion visit plus 30 days and ended on or after the date of first investigational product administration.)

Outcomes

Treatment and Control of Bleeding Episodes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 9. End points related to hemostatic efficacy and HRQoL are further summarized as follows. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 3.

Table 9: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	Study 071001	Study 071101
Treatment success	Primary	—
Overall hemostatic efficacy 24 hours after last perioperative study drug infusion or at completion of day 14 visit	—	Primary
Intraoperative hemostatic efficacy	—	Secondary
Number of study drug–treated BEs with efficacy rating of “excellent” or “good”	Secondary	—
Number of infusions	Secondary	Secondary
Operative blood loss	—	Secondary
Number of units of rVWF + rFVIII and/or rVWF alone per BE	Secondary	Secondary
Intraoperative hemostatic efficacy	—	Secondary
Number of transfusions	—	Secondary
HRQoL	[redacted]	[redacted]

BE = bleeding episode; HRQoL = health-related quality of life; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor.

Hemostatic Efficacy

In Study 071001, hemostatic efficacy was used as an indicator of treatment success, which was the primary efficacy end point. Hemostatic efficacy was examined using a 4-point rating scale rated by the attending physician as “excellent,” “good,” “moderate,” or “none.” The hemostatic efficacy rating was based on the actual number of infusions administered to control the bleed versus the treating physician’s estimate of the number of infusions required. No literature was identified that tested the hemostatic efficacy rating scale for reliability, validity, or responsiveness in patients with VWD. No minimal important difference (MID) was identified in the literature for this rating scale (details provided in Appendix 3).

Health-Related Quality of Life

[redacted]

- [redacted]
- [redacted]

[redacted]

Perioperative Management

Table 9 provides a list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review. End points related to hemostatic efficacy are summarized as follows. End points related to HRQoL included the [redacted] and [redacted] as previously described.

Hemostatic Efficacy

In Study 071101, hemostatic efficacy was the primary end point. It was examined using a physician-rated rating scale with assessments of "excellent," "good," "moderate," or "none." No literature was identified that tested the hemostatic efficacy rating scale for reliability, validity, or responsiveness in patients with VWD. No MID was identified in the literature for this rating scale. It was used as guidance to assess the overall hemostatic efficacy of the study drug (details provided in Appendix 3 of this review).

The results of hemostatic efficacy were presented as follows:

- Overall hemostatic efficacy 24 hours after the last perioperative study drug infusion or at the completion of day 14 visit, whichever occurred earlier as assessed by the physician, was a key result. The proportion of patients rated as "excellent" or "good" was reported. This was the primary end point in Study 071101. Also note that, for the overall primary efficacy assessment rating, the following were considered: the severity of bleedings observed during surgery, the need for additional hemostatic medications, blood loss during surgery, and post-operative bleedings.
- Intraoperative actual versus predicted blood loss (assessed by the operating surgeon) at completion of surgery was another key result. This was the secondary efficacy end point in Study 071101.

Statistical Analysis

Treatment and Control of Bleeding Episodes

In Study 071001, the null hypothesis of the rate of patients with a treatment success of 0.65 or less (pertaining to the primary efficacy end point) versus an alternative hypothesis of more than 0.65 was tested at the 5% level of significance. The proportion of patients with treatment success under the alternative hypothesis was expected to be approximately 0.90. If 20 patients were treated, the study would provide 86% power to reject the null hypothesis. [redacted]

[redacted]

[redacted].

The primary efficacy analysis was based on the full analysis set (FAS). Point estimates and corresponding 2-sided exact CIs according to Clopper-Pearson at the 90% CI were calculated for the proportion of patients with a treatment success, considering all study drug–treated bleeding episodes during the overall study period. If a bleed occurred more than 24 hours following the resolution of a current bleed, or at a different anatomical location, it was considered to be a new bleed. The primary efficacy analysis was carried out based on all treated bleeding episodes excluding GI bleeds and for bleeds where the assessments were made prospectively.

For the secondary efficacy outcomes, point estimates and corresponding 2-sided exact CIs at the 90% CI were calculated for the rate of study drug–treated bleeding episodes with excellent or good treatment outcome according to the efficacy rating scale. Descriptive statistics such as means, medians, and ranges were used to summarize the number of infusions per bleeding episode. Sensitivity analyses of the primary and secondary efficacy outcomes of the proportion of bleeding episodes were conducted based on all treated bleeding events including GI bleeds (prospective estimates only) and those bleeding episodes for which the investigator estimated the number of infusions required either prospectively or retrospectively.

Subgroup analyses based on VWD subtypes and the severity of bleeding episodes were conducted, and the results were descriptively summarized. It was unclear whether the subgroup analyses were predefined.

No adjustments for covariates were required in data analysis. No interim analyses were required for this study. No statistical techniques were used to identify and exclude any observations as outliers from the analyses. When data were considered spurious, the reason for their exclusion and the analyses from which the data were excluded were documented. Methods for imputing missing data were not applied. Multiplicity was not applicable in this study, according to the sponsor.

PK parameters were summarized using descriptive statistics.

Perioperative Management

In Study 071101, sample size was determined by the number of patients requiring elective major, minor, and oral surgical procedures and was not based on statistical considerations. The sample size of at least 15 patients with VWD undergoing surgery, 10 of whom were having surgery considered major surgeries, was based on the *Guideline on the Clinical Investigation of Human Plasma Derived Von Willebrand Factor Products*.[22]

The overall assessment of hemostatic efficacy 24 hours after the last perioperative study drug infusion or at completion of the day 14 visit were summarized by the proportion of patients in each efficacy category (“excellent,” “good,” “moderate,” or “none”) carried out on the FAS. Point estimates and corresponding 2-sided exact CIs determined by the Clopper-Pearson test at the 90% CI were calculated for the primary and secondary efficacy outcomes and the proportion of patients with an overall assessment of hemostatic efficacy of “excellent” or “good” 24 hours after the last perioperative study drug infusion or at

completion of the day 14 visit, whichever occurred earlier. The efficacy of rVWF alone and rVWF plus rFVIII was not compared in this study.

Intraoperative actual versus predicted blood loss and intraoperative hemostatic efficacy at completion of the surgery by the surgeon were summarized using a similar approach. The actual blood loss (expressed as a percentage of the estimated blood loss) and the average daily and total weight-adjusted doses of rVWF, with or without rFVIII, per patient were summarized using descriptive statistics.

Subgroup analyses of overall primary hemostatic efficacy, intraoperative hemostatic efficacy, intraoperative blood loss, and HRQoL were performed by surgery classification and VWD subtypes. The results were descriptively summarized.

No adjustments for covariates were required in data analysis. No interim analyses were required for this study. No statistical techniques were used to identify and exclude any observations as outliers from the analyses. When data were considered spurious, the reason for their exclusion and the analyses from which the data were excluded were documented. There was no imputation of missing values in general. Patients with partial data were to be evaluated on a case-by-case basis to determine if sufficient data were available for meaningful analysis.

The safety of rVWF was monitored by an independent data monitoring committee as well as by the sponsor's medical director at predefined time points, and on an as-needed basis until completion of the study.

PK parameters were summarized using descriptive statistics in this study.

Analysis Populations

Treatment and Control of Bleeding Episodes

The FAS comprised all patients for whom at least 1 efficacy rating scale assessment was available for a bleeding episode treated with the study drug. This was the primary population for efficacy analyses.

The per-protocol (PP) analysis set was defined as a subset of the FAS; only patients who met all study inclusion criteria and who had no major protocol violations that might impact efficacy assessments for study drug–treated bleeding episodes were included in the PP analysis set.

The safety analysis set comprised all patients who received any amount of the study drug (rVWF + rFVIII or rVWF alone).

Full PK dataset:

- The crossover full PK analysis set consisted of all patients in the crossover PK subgroup (patients in Arm 1 and Arm 2 of Study 071001) who were randomized and received both infusions, and who provided data suitable for PK analysis.
- The repeated full PK analysis set consisted of all patients in the repeated PK subgroup (patients in Arm 3 of Study 071001) who received both infusions and who provided data suitable for PK analysis.

Perioperative Management

The FAS comprised all patients with at least 1 hemostatic assessment (overall assessment 24 hours after the last infusion of the study drug or at completion visit, intraoperative actual

versus predicted blood loss at completion of surgery, or intraoperative hemostatic efficacy at completion of surgery). This was the primary analysis set for efficacy evaluations.

The safety analysis set consisted of all patients who received any amount of the study drug — rVWF, with or without rFVIII.

The PK analysis set consisted of all patients who underwent a PK assessment and provided data suitable for PK analysis.

Results

Patient Disposition

Treatment and Control of Bleeding Episodes

In Study 071001, a total of 49 patients were enrolled and screened, of whom 18 patients were randomized in Arm 1 and Arm 2. Thirty-seven patients were treated with the study drug (all treatment arms) and 30 patients completed the study. [redacted] patients discontinued after treatment started. Details of patients' disposition for Study 071001 are presented in Table 10.

Table 10: Patient Disposition — Treatment and Control of BEs

	PK50 + treatment	PK50	PK80 + treatment	Treatment only	No arm assigned	Total
Screened, N	49					
Enrolled, n (%)	9 (100)	9 (100)	16 (100)	6 (100)	9 (100)	49
Randomized, n (%)	9 (100)	9 (100)	NA	NA	NA	18
Treated with study drug, n (%)	8 (88.9)	8 (88.9)	15 (93.8)	6 (100)	NA	37
Discontinued study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]			[redacted]
Completed study, n (%)	4 (44.4)	8 (88.9)	13 (81.3)	5 (83.3)	NA	30
FAS	22					
PP	17					
SAS	37					
Full PK analysis set, crossover	16					
Full PK analysis set, repeated	15					

BE = bleeding episode; FAS = full analysis set; NA = not applicable; PK = pharmacokinetics; PP = per-protocol; SAS = safety analysis set.

Source: Clinical Study Report for Study 071001.[14]

Perioperative Management

In Study 071101, a total of 24 patients were enrolled and screened. Among them, 15 patients were treated with the study drug, 14 patients completed the study without

discontinuation of treatment, and 1 patient withdrew consent on day 17 after treatment with the study drug. There were [redacted] patients who discontinued the study.

Details of patients' disposition for Study 071101 are presented in Table 11.

Table 11: Patient Disposition — Perioperative Management

	Study 071101
Screened, N	24
Enrolled, n (%)	24
Patients treated with study drug, n (%)	15 (62.5)
Patients who completed without discontinuation of treatment, n (%)	14 (58.3)
Patients who completed with discontinuation of treatment, n (%)	0
Patients who discontinued, n (%)	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FAS, N	15
PP, N	15
SAS, N	15
PK analysis set	11

FAS = full analysis set; PK = pharmacokinetics; PP = per-protocol; SAS = safety analysis set.

Source: Clinical Study Report for Study 071101.[15]

Exposure to Study Treatments

Data regarding exposure to study treatments are provided in the dose of infused study drug section, which follows shortly.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported as follows.

Hemostatic Efficacy

Treatment and Control of Bleeding Episodes

In Study 071001, a total of 193 bleeding episodes occurred in 22 patients (17 with type 3 VWD, 4 with type 2A VWD, and 1 with type 2N VWD) and were treated with the study drug. The majority of bleeds were mucosal (107), followed by joint bleeds (59). There were 6 GI bleeds. Thirty-seven bleeds occurred in other locations (e.g., superficial, body cavity, soft tissue, muscle). Of the 193 bleeding episodes, 166 were spontaneous (86.0%), 26 were traumatic (13.5%), and 1 was of unknown cause (0.5%). There were 122 minor bleeding episodes (63.2%), 62 moderate bleeding episodes (32.1%), and 7 major or severe bleeding episodes (3.6%). The 7 major or severe bleeding episodes occurred in 5 unique patients.

The proportion of patients with treatment success was 100% for bleeding episodes (18 out of 18 patients with on-demand treatment for bleeding episodes; Clopper-Pearson exact 90% CI, 84.7% to 100%). Results of sensitivity analyses were aligned with the primary analysis. The results from the PP analysis set ([redacted]patients with on-demand treatment for bleeding episodes; [redacted], Clopper-Pearson exact 90% CI, 81.9% to 100%) confirmed those from the primary analysis in the FAS.

The results also showed that hemostatic efficacy of the study drug was rated as "excellent" or "good" (secondary efficacy outcome) for 100% of all treated bleeding episodes (126 out of 126 treated bleeding episodes; Clopper-Pearson exact 90% CI, 97.7% to 100%). Hemostatic efficacy was rated as "excellent" in [redacted]bleeding episodes ([redacted]) and "good" in [redacted] bleeding episodes ([redacted]) for bleeding events, including GI bleeds for both prospective and retrospective estimates from the investigator. Similar results were obtained when the Clopper-Pearson exact 95% CIs were used.

Details of hemostatic efficacy of the study drug for bleeding episodes are provided in Table 12.

Table 12: Hemostatic Efficacy — Treatment and Control of BEs, Full Analysis Set

	Patients with on-demand treatment for BE N = 22
Proportion of patients with treatment success (excluding GI bleeding)	
n of N (%), 90% CI[a]	18/18 (100); 90% CI, 84.7% to 100%
Proportion of patients with treatment success (including GI bleeding)[b]	
n of N (%), 90% CI[a]	[redacted]
Proportion of study drug–treated BEs with an "excellent" or "good" efficacy rating (excluding GI bleeding)	
n of N (%), 90% CI[a]	126/126 (100); 90% CI, 97.7% to 100%
Proportion of study drug–treated BEs with an "excellent" or "good" efficacy rating (including GI bleeding)[b]	
n of N (%), 90% CI[a]	[redacted]

BE = bleeding episode; CI = confidence interval; GI = gastrointestinal; SD = standard deviation.

[a] Clopper-Pearson exact CI.

[b] Sensitivity analyses were based on all treated bleeding episodes, including GI bleeds and those bleeding episodes for which the investigator had to make retrospective estimates of the number of infusions required.

Source: Clinical Study Report for Study 071001.[14]

Subgroup analyses based on VWD subtype were performed. There were [redacted] bleeding episodes in 4 patients of type 2A VWD, 1 bleeding episode in [redacted] of type 2N VWD and [redacted] bleeding episodes in [redacted] patients of type 3 VWD treated with rVWF plus rFVIII or with rVWF alone. Hemostatic efficacy was "excellent" or "good" for all treated bleeding episodes.

Subgroup analyses based on the severity of bleeding was also performed. There were 7 major bleeding episodes, [redacted]moderate bleeding episodes, and 122 minor bleeding episodes. Hemostatic efficacy was "excellent" or "good" for all treated bleeding episodes.

Details of hemostatic efficacy of the study drug for bleeding episodes in the subgroups are provided in Table 13.

Table 13: Hemostatic Efficacy in Subgroups — Treatment and Control of BEs, Full Analysis Set

	Rating of hemostatic efficacy			
VWD type, n of BEs (%)	**Excellent**	**Good**	**Moderate**	**None**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bleeding severity, n of BEs (%)	**Excellent**	**Good**	**Moderate**	**None**
Minor N = 122	[redacted]	[redacted]	[redacted]	[redacted]
Moderate N = 61	[redacted]	[redacted]	[redacted]	[redacted]
Major N = 7	[redacted]	[redacted]	[redacted]	[redacted]
Unknown n = 2	[redacted]	[redacted]	[redacted]	[redacted]
All n = 192	186 (96.9)	6 (3.1)	0	0

BE = bleeding episode; VWD = von Willebrand disease.

Source: Clinical Study Report for Study 071001.[14]

Perioperative Management

In Study 071101, overall hemostatic efficacy was rated as “excellent” or “good” for all 15 treated patients (Clopper-Pearson exact 90% CI, 81.9% to 100%), including 10 with major surgery, 4 with minor surgery, and 1 with oral surgery. Similar results were reported for subgroups by surgery classification and VWD subtypes.

Details of overall hemostatic efficacy of the study drug for perioperative management are shown in Table 14.

Table 14: Overall Hemostatic Efficacy — Perioperative Management, Full Analysis Set

Rating	Patients undergoing elective surgery N = 15
Excellent, n (%)	11 (73.3)
Good, n (%)	4 (26.7)
Moderate, n (%)	0 (0)
None, n (%)	0 (0)
Group rating, n (%, 90% CI[a])	
Excellent/good	15 (100, 90% CI 81.9 to 100)
Moderate/none	0 (0, 90% CI NA)

CI = confidence interval; NA = not applicable.

[a] CIs at the 90% level for the proportion of patients with "excellent/good" grouped rating were based on an exact Clopper-Pearson test and are presented as percentages.

Source: Clinical Study Report for Study 071101.[15]

Subgroup analyses of overall hemostatic efficacy based on surgical classifications were performed. Hemostatic efficacy was "excellent" or "good" for all patients regardless of their type of surgery (Table 8).

Subgroup analyses of overall hemostatic efficacy based on VWD subtype were also performed. Hemostatic efficacy was "excellent" or "good" for all patients regardless of their VWD types (Table 8).

Table 15: Overall Hemostatic Efficacy in Subgroups — Perioperative Management, Full Analysis Set

Rating	Patients undergoing elective surgery N = 15
Surgical classification, n (%)	
Minor surgery (n = 4)	
Excellent	4 (100)
Good	0
Moderate	0
None	0
Major surgery (n = 10)	
Excellent	7 (70)
Good	3 (30)
Moderate	0
None	0
Oral surgery (n = 1)	
Excellent	0
Good	1 (100)
Moderate	0
None	0
VWD type, n (%)	
Type 1 (n = 3)	

Rating	Patients undergoing elective surgery N = 15
Excellent	2 (66.7)
Good	1 (33.3)
Moderate	0
None	0
Type 2A (n = 2)	
Excellent	1 (50)
Good	1 (50)
Moderate	0
None	0
Type 2B (n = 1)	
Excellent	1 (100)
Good	0
Moderate	0
None	0
Type 2M (n = 1)	
Excellent	0
Good	1 (100)
Moderate	0
None	0
Type 3 (n = 8)	
Excellent	7 (87.5)
Good	1 (12.5)
Moderate	0
None	0

VWD = von Willebrand disease.

Source: Clinical Study Report for Study 071101.[15]

The mean ratings for actual intraoperative blood loss relative to predicted blood loss and intraoperative hemostatic efficacy at completion of surgery were rated as “excellent” or “good” for intraoperative actual versus predicted blood loss (100%; Clopper-Pearson exact 90% CI, 81.9 to 100) and for intraoperative hemostatic efficacy (100%; Clopper-Pearson exact 90% CI, 81.9 to 100) (Table 16).

Subgroup analyses of intraoperative hemostatic efficacy based on surgical classifications and VWD subtype were performed. Intraoperative hemostatic efficacy was “excellent” or “good” for all patients regardless of their type of surgery or VWD type (data not shown).

Table 16: Intraoperative Hemostatic Efficacy — Perioperative Management, Full Analysis Set

Rating, n (%)	Patients undergoing elective surgery N = 15
Intraoperative actual vs. predicted blood loss rating, n (%, 90% CI)	
Excellent	13 (86.7, 90% CI NA)
Good	2 (13.3, 90% CI NA)
Moderate	0 (0, 90% CI NA)
None	0 (0, 90% CI NA)
Intraoperative actual vs. predicted blood loss grouped rating, n (%, 90% CI)	
Excellent/good	15 (100; 90% CI 81.9 to 100)
Moderate/none	0 (0, 90% CI NA)
Intraoperative hemostatic efficacy rating, n (%, 90% CI)	
Excellent	13 (86.7, 90% CI NA)
Good	2 (13.3, 90% CI NA)
Moderate	0 (0, 90% CI)
None	0 (0, 90% CI)
Intraoperative hemostatic efficacy rating, n (%, 90% CI)	
Excellent/good	15 (100; 90% CI, 81.9 to 100)
Moderate/none	0 (0, 90% CI)

CI = confidence interval; NA = not applicable; vs. = versus.

Note: CIs at the 90% level for the proportion of patients with "excellent/good" grouped rating were based on an exact Clopper-Pearson test and were presented as percentages.

Source: Clinical Study Report for Study 071101.[15]

During surgery, the mean actual blood loss assessed by the operating surgeon was 94.3 mL and mean predicted blood loss was 106.1 mL. Subgroup results in patients who underwent major surgeries or patients with type 3 VWD were consistent with those in the overall population (Table 17).

Table 17: Intraoperative Blood Loss — Perioperative Management, Full Analysis Set

	Patients undergoing elective surgery N = 15
Actual blood loss, mL, mean (SD)	94.3 (177.88)
Actual blood loss, mL, median (range)	50.0 (0 to 700)
Predicted blood loss, mL, mean (SD)	106.1 (161.82)
Predicted blood loss, mL, median (range)	50.0 (0 to 600)
Actual blood loss relative to predicted blood loss, %, mean (SD)	69.6 (44.77)
Actual blood loss relative to predicted blood loss, %, median (range)	50.0 ([redacted])
Subgroup of surgical classification	
Minor, n = 4	
Actual blood loss, mL, mean (SD)	0
Predicted blood loss, mL, mean (SD)	2.5 (5)
Actual blood loss relative to predicted blood loss, %, mean (SD)	NA
Major, n = 10	

	Patients undergoing elective surgery N = 15
Actual blood loss, mL, mean (SD)	127.0 (209.27)
Predicted blood loss, mL, mean (SD)	152.8 (186.33)
Actual blood loss relative to predicted blood loss, %, mean (SD)	68.9 (34.48)
Subgroup of VWD subtype	
Type 1, n = 3	
Actual blood loss, mL, mean (SD)	115.0 (103.32)
Predicted blood loss, mL, mean (SD)	100 (100)
Actual blood loss relative to predicted blood loss, %, mean (SD)	[redacted]
Type 2A, n = 2	
Actual blood loss, mL, mean (SD)	42.5 (53.03)
Predicted blood loss, mL, mean (SD)	10 (NA)
Actual blood loss relative to predicted blood loss, %, mean (SD)	[redacted]
Type 2B, n = 1	
Actual blood loss, mL, mean (SD)	50 (NA)
Predicted blood loss, mL, mean (SD)	50 (NA)
Actual blood loss relative to predicted blood loss, %, mean (SD)	[redacted]
Type 2M, n = 1	
Actual blood loss, mL, mean (SD)	50 (NA)
Predicted blood loss, mL, mean (SD)	50 (NA)
Actual blood loss relative to predicted blood loss, %, mean (SD)	[redacted]
Type 3, n = 8	
Actual blood loss, mL, mean (SD)	110.6 (240.87)
Predicted blood loss, mL, mean (SD)	134.4 (206.46)
Actual blood loss relative to predicted blood loss, %, mean (SD)	[redacted]

NA = not available; SD = standard deviation; VWD = von Willebrand disease.

Source: Clinical Study Report for Study 071101.[15]

Dose of Infused Study Drug

Treatment and Control of Bleeding Episodes

Outcomes included in this section are the dose of the infused study drug and number of infusions required to treat a bleeding episode.

In Study 071001 as per the protocol, rVWF plus rFVIII was used for the initial infusion to treat a bleeding episode. Of 192 bleeding episodes, 182 (94.8%) were treated with an initial dose of rVWF plus rFVIII, and 10 (5.2%) were treated with an initial dose of rVWF alone. For subsequent infusions, the protocol required the additional use of rFVIII only on an as-needed based on FVIII levels. rVWF alone was used more frequently than rVWF plus rFVIII: 60.0% of second infusions (21 out of 35), 80.0% of third infusions (8 out of 10), and 100.0% of fourth infusions (1 out of 1) were with rVWF alone.

The mean total dose of rVWF plus rFVIII or rVWF alone was 57.4 IU/kg per bleeding episode (SD = 30.27). The mean actual dose for co-infusion of rVWF plus rFVIII was 48.6 IU/kg rVWF per bleeding episode (SD = [redacted]) and [redacted] IU/kg rFVIII per bleeding episode (SD = [redacted]), and 64.1 IU/kg rVWF for rVWF infused alone per bleeding episode (SD = [redacted]) (Table 18).

Table 18: Dose of Infused Study Drug Required for Treatment of BE, Full Analysis Set

	Mean (SD) total dose per BE (IU/kg) N = 22
Total dose per BE for rVWF + rFVIII or rVWF alone	
Number of BEs	174
rVWF	57.4 (30.27)
Total dose per BE for rVWF + rFVIII	
Number of BEs	166
rVWF	48.6 ([redacted])
rFVIII	[redacted]
Total dose per BE for rVWF alone	
Number of BEs	30
rVWF	64.1 ([redacted])

BE = bleeding episode; FVIII = factor VIII; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; SD = standard deviation.

Source: Clinical Study Report for Study 071001.[14]

In the subgroup analyses based on the severity of bleeding episodes, the mean total dose of rVWF plus rFVIII or rVWF alone was 103.5 IU/kg per major bleeding episode (SD = 28.46), 66.8 IU/kg per moderate bleeding episode (SD = 39.40), and 49.4 IU/kg per minor bleeding episode (SD = 18.08) (Table 19).

In the subgroup analyses based on VWD subtype, the mean total dose of rVWF plus rFVIII or rVWF alone was [redacted] IU/kg per bleeding episode in patients with type 2A VWD, [redacted] IU/kg per bleeding episode in patients with type 2N VWD, and [redacted] IU/kg per bleeding episode in patients with type 3 VWD (Table 19).

Table 19: Dose of Infused Study Drug — rVWF Plus rFVIII or rVWF Alone — Required for Treatment of BE in Subgroups, Full Analysis Set

	Mean (SD) total dose of rVWF ± rFVIII (IU/kg) N = 22
Subgroup of severity of bleeds	
Major/severe[a] (7 BEs)	103.5 (28.46)
Moderate[a] (61 BEs)	66.8 (39.40)
Minor[a] (122 BEs)	49.4 (18.08)
Unknown[a] (2 BEs)	33.4 (0.46)
Subgroup of VWD type	
2A[b] ([redacted] BEs)	[redacted]
2N[b] ([redacted] BEs)	[redacted]
3[b] ([redacted] BEs)	[redacted]

BE = bleeding episode; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; SD = standard deviation; VWD = von Willebrand disease.

[a] Subgroup based on severity of bleeding.

[b] Subgroup based on VWD subtype.

Source: Clinical Study Report for Study 071001.[14]

The median total number of infusions administered per patient (for PK assessments, treatment of bleeding episodes, and home treatment qualification) was 5.0 (range = 1 to 44). In 192 bleeding episodes, the mean number of infusions was 1.2 infusions for treatment of a bleeding episode (SD = 0.56), and the median number of infusions was 1.0 infusion (range = 1 to 6). More than 80% of the bleeding episodes were controlled by 1 infusion of rVWF plus rFVIII or rVWF alone during the study. Of these, 94.8% of the bleeding episodes were controlled with 1 infusion of rVWF plus rFVIII. (Table 20).

Table 20: Number of Infusions Required per BE, Full Analysis Set

Number of infusions required	% of BEs treated with rVWF + rFVIII or rVWF alone	% of rVWF + rFVIII	% of rVWF alone
1	157/192 (81.8%)	182/192 (94.8%)	10/192 (5.2%)
2	25/192 (13%)	14/35 (40%)	21/35 (60%)
3	9/192 (4.7%)	2/10 (20%)	8/10 (80%)
4	1/192	0	1/1 (100%)

BE = bleeding episode; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor.

Source: Clinical Study Report for Study 071001.[14]

In the bleeding severity subgroup, 1 infusion of rVWF plus rFVIII or rVWF alone was required for [redacted] of minor bleeding episodes compared to [redacted] for moderate bleeding episodes and [redacted] for major bleeding episodes. [redacted] infusions of rVWF plus rFVIII or rVWF alone were required for [redacted] minor bleeding episodes, [redacted] moderate bleeding episodes, and [redacted] major bleeding episodes, and [redacted] infusions of rVWF plus rFVIII or rVWF alone were required for [redacted] minor bleeding episodes, [redacted] moderate bleeding episodes, and [redacted] major bleeding episodes (Table 21).

In the VWD subtype subgroup, [redacted] infusion of rVWF plus rFVIII or rVWF alone was required for [redacted] of type 2A VWD compared to [redacted] for type 2N VWD and [redacted] for type 3 VWD. [redacted] infusions of rVWF plus rFVIII or rVWF alone were required for [redacted] type 2A VWD and [redacted] type 3 VWD. [redacted] and [redacted] infusions of rVWF plus rFVIII or rVWF alone were required for type 3 VWD only.

Table 21: Number of Infusions Required — rVWF Plus rFVIII or rVWF Alone — per BE in Subgroups, Full Analysis Set

Number of infusions required			
Subgroup of bleeding severity, n of BEs (%)			
	Minor	Moderate	Major
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
Subgroup of VWD type, n of BEs (%)			
	2A	2N	3
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]

Number of infusions required			
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]

BE = bleeding episode; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; VWD = von Willebrand disease.

Source: Clinical Study Report for Study 071001.[14]

Perioperative Management

Fifteen patients received 121 infusions of rVWF, with or without rFVIII. Among them, a total of [redacted] infusions of rVWF plus rFVIII were administered in 5 patients.

In study 071101, the median total dose (IU/kg) administered per patient (including doses for PK assessments, used during surgery, treatment of bleeds, and maintenance of hemostasis) was 306.4 IU/kg rVWF (range = 63.8 to 701.6) for all patients treated with rVWF, with or without rFVIII. Details are provided in Table 22.

Table 22: Total Dose of rVWF, With or Without rFVIII, for All Patients, Safety Analysis Set

Reason for treatment	n	Median (IU/kg)	Minimum (IU/kg)	Maximum (U/kg)
Pharmacokinetic dose		[redacted]	[redacted]	[redacted]
Pre-operative priming infusion	15	55.0	36.1	59.9
Pre-operative initial loading dose	15	35.8	8.0	82.7
Intraoperative dose	1	NA	18.1	18.1
Post-operative dose (day 0 to day 14)	13	189.8	36.1	533.3
Total surgical dose	15	220.4	63.8	648.4
Bleeding episode	[redacted]	[redacted]	[redacted]	[redacted]
To maintain hemostasis	[redacted]	[redacted]	[redacted]	[redacted]
Total dose	15	306.4	63.8	701.6

rVWF = recombinant von Willebrand factor; rFVIII = recombinant factor VIII.

Source: Clinical Study Report for Study 071101.[15]

Survival

This outcome was not assessed as an efficacy outcome in the clinical trials included in this review; no formal hypotheses were stated or formally tested. Information pertaining to this outcome was reported as deaths in the safety evaluation of Study 071001 and Study 071101. No patients died during either study.

Health-Related Quality of Life

Treatment and Control of Bleeding Episodes

In Study 071001, the [redacted] was used to measure the effect of the study drug on the patient's HRQoL. [redacted] (Table 23).

[redacted] (Table 23).

Table 23: HRQoL — Treatment and Control of BEs, Full Analysis Set

	FAS N = 22
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Perioperative Management

In Study 071101, [redacted]

[redacted]

Table 24: HRQoL — Perioperative Management, Safety Analysis Set

	SAS N = 15
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Number of Transfusions Needed

Treatment and Control of Bleeding Episodes

This outcome was not assessed in Study 071001.

Perioperative Management

The number of transfusions needed was not formally assessed in Study 071101; however, intraoperative transfusion of packed red blood cells was required by 1 patient with type 3 VWD who underwent major surgery. The reason for the transfusion was specified as "standards of surgical management." Transfusion was not needed for the other 14 patients.

Use of Rescue Therapy for Uncontrolled Bleeding

This outcome was not assessed in either study.

Hospitalization Due to Uncontrolled Bleeding

This outcome was not assessed in either study.

Productivity (e.g., Return to School and/or Work, Return to Normal Functioning)

This outcome was not assessed in either study.

Pharmacokinetic Parameters

Treatment and Control of Bleeding Episodes

In Study 071001, a total of 16 patients in Arm 1 and Arm 2 were included in the crossover PK analysis (50 IU/kg VWF:RCo rVWF + 38.5 IU/kg rFVIII, or 50 IU/kg VWF:RCo rVWF +

placebo). Fifteen patients in Arm 3 were included in a repeated PK analysis: PK of rVWF alone was evaluated at a dose of 80 IU/kg VWF:RCo at the start of the study and repeated PK assessment was performed using the same dose after 6 months of treatment of bleeding episodes.

Results of the crossover PK assessments showed that after a single infusion of rVWF at a dose of 50 IU/kg VWF:RCo, the mean $T_{1/2}$ was 21.9 hours for rVWF and 19.6 hours for rVWF plus rFVIII.

The rVWF PK profile was comparable at 50 IU/kg VWF:RCo and 80 IU/kg VWF:RCo. The repeated PK assessments at 80 IU/kg VWF:RCo showed consistency between pre-treatment and end-of-study PK results.

In addition, all PK parameters for VWF:Ag were consistent with those for VWF:RCo, suggesting that the addition of rFVIII to rVWF did not change rVWF PK parameters.

Details of PK analyses are provided in Table 27, Appendix 2.

Perioperative Management

Eleven patients were included in the PK analyses. Results of the assessments showed that after a single infusion of rVWF at a dose of 50 IU/kg VWF:RCo, the mean $T_{1/2}$ was 17.83 hours for VWF:RCo and [redacted] hours for VWF:Ag.

Details of PK assessment results are presented in Table 28, Appendix 2.

Harms

Only those harms identified in the review protocol are reported as follows.

Adverse Events

Treatment and Control of Bleeding Episodes

In Study 071001, [redacted] patients ([redacted]%) reported at least 1 AE during or after infusion with study drug. All AEs were of mild to moderate severity. Commonly reported AEs included iron deficiency anemia ([redacted]%), vomiting ([redacted]%), upper respiratory tract infection ([redacted]%), arthralgia ([redacted]%), and headache ([redacted]%).

Perioperative Management

In Study 071101, a total of 12 AEs were reported by 6 patients ([redacted]%) during or after infusion with the study drug. Most of the AEs were mild to moderate in severity: acne, dry skin, iron deficiency anemia, peripheral swelling, nasopharyngitis, joint swelling, dizziness, headache, pelvic pain, and DVT.

Serious Adverse Events

Treatment and Control of Bleeding Episodes

In Study 071001, [redacted] patients reported SAEs, including osteomyelitis, constipation, uterine polyp, spontaneous abortion, GI hemorrhage, mesenteric hematoma, hemorrhoids, chest discomfort, and increased heart rate. None of these SAEs occurred in any more than 1 patient.

Perioperative Management

In Study 071101, 2 patients experienced SAEs: 1 moderate DVT and 1 severe diverticulitis.

Withdrawals Due to Adverse Events

Treatment and Control of Bleeding Episodes

In Study 071001, [redacted] stopped treatment due to AEs (chest discomfort and increased heart rate).

Perioperative Management

No patients discontinued due to AEs in Study 071101.

Mortality

Treatment and Control of Bleeding Episodes

No deaths occurred during Study 071001.

Perioperative Management

No deaths occurred during Study 071101.

Notable Harms

Treatment and Control of Bleeding Episodes

In Study 071001, 1 patient (2.7%) reported a hypersensitivity reaction to the study drug and 1 patient (2.7%) reported an infusion-related reaction of tachycardia. There were no reports of thrombotic events or development of anti-drug antibodies. There was no report on blood-borne infections.

Perioperative Management

In Study 071101, 1 patient reported thrombotic events and 1 patient developed binding antibodies to VWF on post-operative day 7 through study completion. No other anti-drug antibodies were reported in the study population. No other notable harms identified in the CADTH review protocol were reported.

Details of harms outcomes of the 2 studies are presented in Table 25 and Table 26.

Table 25: Summary of Harms — Treatment and Control of BEs, Safety Analysis Set

	SAS N = 37
Patients with ≥ 1 AE	
n (%)	[redacted]
Common events (> 5%), n (%)	
Iron deficiency anemia	[redacted]
Anemia	[redacted]
Vertigo	[redacted]
Vomiting	[redacted]
Nausea	[redacted]
Infusion site paresthesia	[redacted]
Upper respiratory tract infection	[redacted]
Contusion	[redacted]
Laceration	[redacted]

	SAS N = 37
Arthralgia	[redacted]
Back pain	[redacted]
Headache	[redacted]
Patients with ≥ 1 SAE	
n (%)	[redacted]
Patients with ≥ 1 WDAE	
n (%)	[redacted]
Deaths	
n (%)	[redacted]
Notable harms, n (%)	
Thrombotic events	[redacted]
Hypersensitivity reaction	[redacted]
Injection site reaction	[redacted]
Infusion-related reaction	[redacted]
Anti-drug antibodies	[redacted] [a]

AE = adverse event; BE = bleeding episode; FVIII = factor VIII; SAE = serious adverse event; SAS = safety analysis set; VWF = von Willebrand factor; WDAE = withdrawal due to adverse event.

[a] No patients developed anti-VWF neutralizing or binding antibodies; no patients developed anti-FVIII neutralizing antibodies.

Source: Clinical Study Report for Study 071001.[14]

Table 26: Summary of Harms — Perioperative Management, Safety Analysis Set

	SAS N = 15
Patients with ≥ 1 AE	
n (%)	6 (40)
Patients with ≥ 1 SAE	
n (%)	2 (13.3)
Patients with ≥ 1 WDAE	
n (%)	0
Deaths	
n (%)	0
Notable harms, n (%)	
Thrombotic events	1 (6.7)
Hypersensitivity reaction	0
Injection site reaction	0
Infusion-related reaction	0
Anti-drug antibodies	1 (6.7) [a]

AE = adverse event; SAE = serious adverse event; SAS = safety analysis set; VWD = von Willebrand disease; VWF = von Willebrand factor; WDAE = withdrawal due to adverse event.

[a] One patient with type 3 VWD developed anti-VWF binding antibodies.

Source: Clinical Study Report for Study 071101.[15]

Critical Appraisal

Internal Validity

One of the key limitations of the included trials are their non-randomized, non-controlled study design. In a non-randomized, non-controlled trial, confounding factors may affect the results. In Study 071001, patients were allocated to treatment arms based on the investigator's discretion after having a conversation with each patient. There was no information on how the investigator determined which patient would be assigned to each group. It is possible that this method of treatment allocation introduced bias into the results. In Study 071101, non-randomization may have also resulted in bias as a bleeding event may be attributed to the surgical procedure or VWD per se, rather than insufficient treatment effect of a particular intervention. Further, in both studies, efficacy outcomes and harms outcomes were not examined between rVWF and any control group, whether placebo or other active treatments. While it may not have been feasible to conduct a placebo-controlled study, other plasma-derived VWF concentrates are available and could have been used in the study. The clinical experts consulted for this review indicated that they did not anticipate the efficacy of rVWF to differ from available plasma-derived VWF therapy.

In both studies, the patients and attending physicians were not blinded to the treatment. Therefore, when a subjective rating scale was used to measure the treatment effect, results of the assessment could be biased. The clinical experts for this review also questioned the accuracy of using unvalidated instruments in the 2 trials.

In Study 071001, 37 patients were included in the safety analysis set while only 22 patients were included in the FAS, which was primarily used for efficacy analyses. The FAS consisted of all patients with at least 1 hemostatic assessment; therefore, this was not a true intention-to-treat population. The small number of study participants makes data interpretation difficult when the observed treatment effect could be due to chance. Alternatively, a true effect may not be detected due to insufficient power of the trial. However, the findings of the sensitivity analyses were supportive of the primary analysis; therefore, it is unlikely that the lack of intention-to-treat population would have had a significant impact on the study results. In Study 071101, 15 patients were enrolled. All 15 patients were included in the FAS and the PP analysis set. [redacted]out of 15 participants discontinued the treatment prematurely. It's unlikely that the study results would be significantly affected by [redacted]. In this study, missing data were not imputed. Patients with partial data were evaluated on a case-by-case basis to determine if sufficient data were available for meaningful analysis.

Several efficacy outcomes in both trials were descriptively reported without performing formal statistical testing — specifically, the dose of infused study drug required for treatment of bleeding episodes, the number of infusions required per bleeding episode in Study 071001, the actual intraoperative blood loss, the dose of the study drug in Study 071101, and HRQoL results and all subgroup analyses in the 2 trials. In the absence of formal statistical testing, no inferences can be made regarding the results of the aforementioned outcomes.

The clinical experts consulted by CADTH for this review indicated that even though the outcomes used in clinical practice, such as control of the acute bleeding assessed by the clinical observation of no overt blood loss, are aligned with the outcomes used in Study 071001 and Study 071101, the primary efficacy outcomes in these 2 trials were evaluated

using an unvalidated, physician-completed hemostatic efficacy rating scale. There are concerns around the reliability of using this type of subjective tool to measure patient outcomes. For example, 1 component of the scale used in Study 071001 was the estimated number of infusions required to treat a bleeding episode. However, the estimation can vary depending on the physician's experience or the differences in practice guidelines in different areas. The clinical experts consulted for this review also question the accuracy of using this type of rating scale, and suggested that additional laboratory measurements would be needed to provide more objective evaluation on the treatment effect of the study drug. Other measures such as the total dose and number of infusions are objective.

[redacted].

Subgroup analyses of interest to this review were by severity of bleeding and VWD type. They were conducted in Study 071001 and Study 071101. It is unclear whether the subgroup analyses were pre-specified. One of the limitations of these subgroup analyses is the small number of study participants in each subgroup. For example, in Study 071001, there were fewer than 5 patients in the subgroup of type 2 VWD. Therefore, the treatment effect of the study drug in these subgroups cannot be fully explored. In addition, since only descriptive results were reported in subgroup analyses, it is not possible to conclude whether the treatment effect differs for bleeds of different severities, in patients with different VWD types, or when used as perioperative management during different types of surgical procedures.

In the two trials, although co-administration of rFVIII was guided by a patient's baseline FVIII:C, if most of the bleeding episodes were successfully managed by rVWF plus rFVIII, it is not clear whether the treatment effect of rVWF alone is different from the combination of rVWF plus rFVIII, as rFVIII may have contributed to increased efficacy that may not have been seen with rVWF alone. This was the case in Study 071001, where 81.8% of patients who required 1 injection for bleeding control received rVWF plus rFVIII (see Table 20).

External Validity

Patients with significant comorbid conditions or poor performance status were excluded from the trials, resulting in a highly selected patient population. It was acknowledged that some patients with such comorbid conditions would likely receive rVWF in clinical practice. However, based on the study population, the treatment effect of rVWF may not be generalized to patients with comorbid conditions who may be eligible to receive treatment with a VWF replacement therapy.

The indication for rVWF approved by Health Canada does not restrict use to any specific VWD subtype or severity. The majority of patients enrolled in study 071001 had type 3 VWD, while approximately 5% had type 1 VWD. According to the experts consulted for this review, the study populations in these 2 trials are reflective of typical Canadian patients diagnosed with severe VWD, according to the baseline patient characteristics. The inclusion criteria and patients' baseline characteristics in Study 071001 and Study 071101 suggested that the study participants had severe VWD, which is consistent with the

anticipated place in therapy for rVWF, according to the clinical experts consulted for this review.

Further, the approved indication for perioperative management does not restrict the use of rVWF to severity of the surgical procedure. In Study 071101, only patients undergoing planned surgical procedures were included in the study, which allowed for pre-operative loading doses to be carefully managed. It is uncertain whether the results of this study would be generalizable to patients with VWD undergoing emergency surgery. In addition, most patients enrolled in Study 071101 were undergoing major surgery, with only 1 having planned oral surgery (6.7%). It is uncertain whether the study findings can be generalized to patients with VWD who will undergo oral surgery.

The mean dosing in the 2 studies was consistent with dosing recommendations for the treatment of bleeding episodes and perioperative management described in the product monograph of the study drug.

Indirect Evidence

No indirect evidence was submitted by the sponsor for this review. CADTH conducted a literature search to identify potentially relevant indirect treatment comparisons in patients with VWD. No relevant indirect comparisons were identified in the literature search.

Other Relevant Evidence

No sponsor-submitted long-term extension studies or additional relevant studies were considered to address important gaps in the evidence; therefore, no additional evidence was included in this review.

The sponsor submitted 3 studies to inform inputs of their pharmacoeconomic analyses. The CADTH review team examined the validity of relevant clinical results of these studies. A summary of critical appraisal of these studies is provided in Appendix 4.

Discussion

Summary of Available Evidence

Two phase III trials submitted by the sponsor (Study 071001, N = 37; Study 071101, N = 15) are included in this systematic review. The trials included adult patients with severe VWD (aged ≥ 18 years).

Study 071001 was a phase III, parallel-group, open-label, non-controlled, multi-centre trial that assessed the efficacy, safety, and PK of rVWF, with or without rFVIII, in the treatment of bleeding episodes in adult patients diagnosed with severe type 3 VWD and severe non–type 3 VWD. Eligible study participants were assigned to 1 of 4 treatment groups at the discretion of the investigator: Arm 1 — PK50 plus treatment for bleeding episodes; Arm 2 — PK50 only; Arm 3 — PK80 plus treatment for bleeding episodes; and Arm 4 — treatment for bleeding episodes only. In total, the on-demand treatment period was 12 months. The primary end point of this study was the number of patients with treatment success for treated bleeding episodes at the end of the study. Treatment success was defined as a mean efficacy rating score of less than 2.5, taking into account all bleeding episodes, and was measured using a physician-completed hemostatic efficacy rating scale. The mean efficacy score was based on a 4-point rating scale defined using the prospectively estimated number of infusions needed to treat the bleeding episodes as assessed by the investigator versus the actual number of infusions administered. Secondary efficacy end points included the number of study drug–treated bleeding episodes with an efficacy rating of “excellent” or “good,” and the number of infusions and number of units of rVWF plus rFVIII and/or rVWF alone per bleeding episode. In this study, the mean age of patients was 37 years and most were White ([redacted]%). The majority of the study participants (78%) had type 3 VWD and were receiving on-demand treatment exclusively in the 24 months prior to and at study enrolment ([redacted]% and [redacted]%, respectively).

Study 071101 was an open-label, non-randomized, non-controlled, phase III trial conducted to evaluate the efficacy and safety of rVWF, with or without rFVIII, as a prophylactic treatment for major or minor elective surgeries in adult patients with severe VWD. All patients received doses of either rVWF alone or rVWF plus rFVIII, depending on the respective VWF and FVIII levels. Treatment duration was expected to last [redacted] from screening to the study completion visit. The primary efficacy outcome measure was the percentage of patients in each overall investigator-assessed hemostatic efficacy category (i.e., “excellent,” “good,” “moderate,” “none”) 24 hours after the last perioperative infusion or at completion of the study, whichever occurred earlier. Secondary efficacy end points included intraoperative and post-operative blood loss, and the dose of rVWF required for perioperative management in the study population. The PK profile of rVWF was also examined. In this study, the mean age of patients was 39 years. More than half of the study participants (53%) had type 3 VWD. Ten out of 15 patients underwent major surgeries.

The major limitations of the included trials were the non-randomized, non-controlled, open-label study design and a lack of comparative evidence between study drug and other active treatments (e.g., plasma-derived VWF concentrate replacement therapy). In addition, given the small number of study participants and the limitations associated with the subgroup analyses in these small trials, the results should be interpreted with caution, and no meaningful conclusions can be drawn from the subgroup analyses. Some of the important clinical outcomes for patients with VWD were not measured in the included studies, such as hospitalization due to uncontrolled bleeding or productivity. For some of the efficacy

outcomes, only descriptive statistics were available to summarize the treatment effect of the study drug.

Interpretation of Results

Efficacy

Treatment and Control of Bleeding Episodes

In Study 071001, all patients achieved treatment success (primary efficacy end point, defined as a mean efficacy rating score of less than 2.5, taking into account all bleeding episodes) when they were treated with rVWF, with or without rFVIII, during the 12 months of the study period. The results of sensitivity analyses were aligned with the primary analysis. The rate of patients with treatment success was 100% for bleeding episodes, including or excluding GI bleeds. The results also showed that hemostatic efficacy of the study drug was rated as "excellent" or "good" (secondary efficacy outcome) for all treated bleeding episodes. The clinical experts consulted for this review indicated that the primary efficacy outcome of this study was based on a subjective, physician-completed rating scale, and the accuracy of this scale is unclear, as compared to the other more objective measurements, such as the actual number of infusions given. Although the study drug demonstrated a potential hemostatic effect for acute bleeding episodes in patients with VWD, the results should be interpreted with caution due to limitations associated with the non-randomized, non-controlled nature of the study design and the small number of participants in each group.

The total dose of rVWF plus rFVIII or rVWF alone was 57.4 IU/kg per bleeding episode (SD = 30.27). The mean actual dose for co-infusion of rVWF plus rFVIII was 48.6 IU/kg rVWF per bleeding episode (SD = 15.3) and 35.9 IU/kg rFVIII per bleeding episode (SD = 13.90), and 64.1 IU/kg rVWF for rVWF infused alone per bleeding episode (SD = 31.24).

In the 192 bleeding episodes that occurred in Study 071001, the mean number of study drug infusions was 1.2 (SD = 0.56) for treatment of a bleeding episode. In addition, 94.8% of the bleeding episodes were treated with 1 infusion of rVWF plus rFVIII. More than 80% of the bleeding episodes were controlled by 1 infusion of rVWF plus rFVIII or rVWF alone during the study.

Both the dose of infused study drug required for treatment of bleeding episodes and the number of infusions required per bleeding episode were descriptively reported in Study 071001 without performing formal statistical testing. Therefore, no inferences can be made regarding the results of the aforementioned outcomes.

In this study,

[redacted].

Subgroup analyses by VWD subtypes (type 2A, type 2N, and type 3) or severity of bleeding (minor, moderate, and major) were reported in this study. Results of the subgroup analyses suggested that hemostatic efficacy was "excellent" or "good" for all treated bleeding episodes, regardless of VWD subtypes or severity of bleeding. However, given the small

sample size in each subgroup and that no formal statistical comparisons were conducted, no conclusions can be made pertaining to hemostatic efficacy for the subgroup analyses.

Perioperative Management

In Study 071101, overall hemostatic efficacy (primary efficacy outcome) was rated as "excellent" or "good" for all 15 patients, including 10 with major surgery, 4 with minor surgery, and 1 with oral surgery. The intraoperative hemostatic efficacy was also rated as "excellent" or "good" in all 15 patients. The mean ratings for actual intraoperative blood loss relative to predicted blood loss and intraoperative hemostatic efficacy at completion of surgery (secondary efficacy outcome) were rated as "excellent" or "good" for every outcome for all 15 treated patients.

Subgroup analyses of overall hemostatic efficacy based on surgical classifications (major, minor, and oral surgery) or VWD type (type 1, type 2A, type 2B, type 2M, and type 3) were performed. Hemostatic efficacy was "excellent" or "good" for all patients, regardless of their type of surgery or VWD type. However, no conclusions can be made pertaining to these results as no formal statistical comparisons were conducted.

Limitations associated with the primary efficacy outcome of this study are similar to those previously noted for Study 071001: the efficacy rating scale used in Study 071101 was based on a subjective, physician-completed rating scale and the accuracy of this scale is unclear, as compared to the other more objective measurements. Although the study drug demonstrated a potential hemostatic effect for acute bleeding episodes in patients with VWD, the results should be interpreted with caution — in particular, for the results in subgroup analyses, given the small sample size of Study 071101.

During surgery, the mean actual blood loss assessed by the operating surgeon (secondary efficacy outcome) was numerically less than predicted blood loss in the study population (actual blood loss was 94.3 mL versus predicted blood loss of 106.1 mL). The experts do not consider this difference clinically important, given the challenges of accurately measuring intraoperative blood loss and the small sample size of this study.

Fifteen patients received 121 infusions of rVWF, with or without rFVIII. Among them, a total of 11 infusions of rVWF plus rFVIII were administered in 5 patients. The median total dose (IU/kg) administered per patient (including the doses for PK assessments, during the surgery, treatment of bleeds, and maintenance of hemostasis) was 306.4 IU/kg rVWF (range = 63.8 to 701.6) for all patients treated with rVWF, with or without rFVIII. The doses of the study drug in this study were consistent with the dosing recommendation described in the product monograph of rVWF.

The outcomes of intraoperative blood loss, dose of study drug, HRQoL results, and all subgroup analyses in Study 071101 were descriptively reported in Study 071001 without performing formal statistical testing. In the absence of formal statistical testing, no inferences can be made regarding the results of the aforementioned outcomes.

[redacted].

Harms

Treatment and Control of Bleeding Episodes

During the overall study period of 12 months, approximately [redacted] of patients experienced at least 1 AE, the majority of which were of [redacted]. None of the patients stopped treatment of the study drug due to AEs, and no deaths were reported throughout the duration of the study. For the notable harms identified in the CADTH review protocol, 1 patient reported a hypersensitivity reaction and 1 patient reported an infusion-related reaction of tachycardia.

Perioperative Management

In Study 071101, [redacted] of patients experienced at least 1 AE. The AEs reported in the study population were acne, dry skin, iron deficiency anemia, peripheral swelling, nasopharyngitis, joint swelling, dizziness, headache, pelvic pain, and DVT. These AEs were mild to moderate in severity. Two patients reported SAEs: 1 moderate DVT and 1 severe diverticulitis. No patient withdrew from the study due to AEs. For notable harms identified in the CADTH review protocol, 1 patient reported thrombotic events and another patient developed anti-VWF binding antibodies.

Other Considerations

Both trials included in this CADTH review included patients with severe VWD. In practice, it is also important to determine the severity of the disease, when dosage and frequency may be personalized according to the type and severity of the bleeding episodes and surgical intervention; laboratory monitoring may be personalized as well. As noted by the clinical experts consulted by CADTH, factor concentrates are reserved for major bleeding episodes regardless of VWD type, minor bleeding episodes in non–type 1 or non–type 2A or type 1 DDAVP–non-responders, or prolonged bleeding episodes in DDAVP-responders.

According to the experts consulted by CADTH, there is no generally accepted definition of mild, moderate, or severe VWD in practice. The severity of the disease is generally parallel to the plasma VWF levels, where a lower level of measured units correlates to more severe disease — for example, with severe disease having less than 5% activity and mild disease having 5% to 30% activity, according to the experts. In addition, type 3 VWD is considered severe disease while in patients with type 2 VWD, severity of disease may be classified by bleeding symptoms and associated complications. In patients with severe VWD, a major or severe bleeding event can occur, such as severe or refractory epistaxis, menorrhagia, GI bleeding, central nervous system trauma, hemarthrosis, or traumatic hemorrhage.[13]

In Study 071001, patients were considered to have severe disease if they had type 1 VWD (VWF:RCo < 20 IU/dL), type 2A VWD (VWF:RCo < 20 IU/dL), type 2B (diagnosed by genotype), type 2N (FVIII:C < 10% and historically documented genetics), type 2M VWD, type 3 (VWF:Ag ≤ 3 IU/dL), or severe VWD with a history of requiring substitution therapy with VWF concentrate to control bleeding. In Study 071101, similar criteria were used to define severe VWD: VWD with a history of requiring substitution therapy with VWF concentrate to control bleeding. This includes type 1 (VWF:RCo < 20 IU/dL), type 2A (as

verified by multimer pattern), type 2B (diagnosed by genotype), type 2N (FVIII:C < 10% and historically documented genetics), type 2M, or type 3 (VWF:Ag ≤ 3 IU/dL). The clinical experts consulted for this review agree that these criteria are reasonable to identify patients with severe VWD.

The clinical experts also indicated that patients with historic inadequate response to DDAVP or who are intolerant or at risk of adverse effects of DDAVP would be those in whom a VWF-factor replacement would most likely be used. They specified that the use of DDAVP is made on a situational basis for a given patient; it depends on the target VWF and FVIII required for the clinical situation and the level that the patient has previously achieved with DDAVP test challenge.

One important distinction is that rVWF is not co-formulated with FVIII, as are the currently available plasma-derived VWF concentrates available in Canada. The clinical experts consulted by CADTH noted that in most cases when rVWF is given, co-administration with a FVIII concentrate would be needed. However, in circumstances when FVIII levels are increasing with repeated VWF administration and are subsequently associated with higher risk of thromboembolic events, it would be desirable to have product without FVIII.

The only VWF concentrates that are currently available in Canada are derived from human plasma and may carry the risk of transmitting blood-borne infections. This information is included in the Warnings and Precautions section of the Health Canada product monograph.[11] The risk of transmitting blood-borne infection was not assessed in either Study 071001 or Study 071101, but rVWF does not contain any exogenous human or animal plasma-derived components.[13]

Conclusions

Two phase III, non-randomized, non-controlled, open-label clinical trials were included in this review to provide evidence on the efficacy and safety of rVWF in adult patients with VWD (aged ≥ 18 years) for 1) the treatment and control of acute bleeding episodes (Study 071001) and 2) perioperative management (Study 071101). rVWF administered according to the Health Canada–approved dose was associated with high treatment success rates in terms of hemostatic efficacy in both studies. The hemostatic effect of rVWF in on-demand and surgical bleed management was rated as “excellent” or “good” in all study participants. [redacted]. The majority of the reported AEs were mild to moderate in intensity. Isolated cases of thrombotic event, hypersensitivity reaction, infusion-related reactions, and development of anti-VWF binding antibodies were reported in the study population. There were no deaths during either study. The main limitations of the included trials were the small sample size, non-randomized design, the lack of a control group, the use of subjective rating scale in measuring hemostatic efficacy of the study drug, lack of statistical testing, and lack of comparative evidence. Overall, there is uncertainty associated with the potential benefit of rVWF compared to treatments already available in Canada, due to the low quality of the evidence supporting the efficacy and safety of rVWF to control bleeding episodes and for perioperative management.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) Cochrane Central Register of Controlled Trials (CCTR) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 29 2020
Alerts:	Monthly search updates until project completion
Study Types:	No studies specified
Limits:	Publication date limit: No date limits Humans Language limit: English- and French-language Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase); keyword (CDSR and DARE)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
.jw	Journal word title
freq=#	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

MULTI-DATABASE STRATEGY	
1	((Willebrand* adj2 factor adj4 (rco or recombin*)) or rVWF or ((rco or recombin*) adj3 vwf) or vonvendi* or GTPL6755 or vonicog* or veyvondi* or Bax 111 or Bax111).ti,ab,hw,rn,ot,kf,nm.
2	1 use medall
3	((Willebrand* adj2 factor adj4 (rco or recombin*)) or rVWF or ((rco or recombin*) adj3 vwf) or vonvendi* or GTPL6755 or vonicog* or veyvondi* or Bax 111 or Bax111).ti,ab,dq,kw.
4	*recombinant von Willebrand factor/
5	3 or 4
6	5 use oemezd
7	conference abstract.pt.
8	conference review.pt.
9	7 or 8
10	6 not 9
11	2 or 10
12	exp animals/
13	exp animal experimentation/ or exp animal experiment/
14	exp models animal/
15	nonhuman/
16	exp vertebrate/ or exp vertebrates/
17	or/12-16
18	exp humans/
19	exp human experimentation/ or exp human experiment/
20	or/18-19
21	17 not 20
22	11 not 21
23	remove duplicates from 22

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period. Search – Von Willebrand disease	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period. Search – Von Willebrand disease	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Cochrane Central Register of Controlled Trials	Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Wiley platform.	

Grey Literature

Search dates:	May 22 2020
Keywords:	Von Willebrand/ Vonvendi
Limits:	Publication years: No date limits
Updated:	Search updated prior to the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)

Appendix 2: Detailed Outcome Measures

Table 27: PK Assessments — Treatment and Control of BEs, Full PK Analysis Set

	Full PK analysis set
PK50 for VWF:RCo — treatment = rVWF + rFVIII, crossover (N = 16)	
$AUC_{0\text{-}96h}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	33.3 (27.0% to 39.6%)
$AUC_{0\text{-}inf}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	36.1 (27.5% to 44.7%)
$T_{1/2}$, hours, mean (95% CI)	19.6 (14.1% to 25.1%)
C_{max}, U/dL, mean (95% CI)	92.5 (77.2% to 107.8%)
IR at C_{max} ([U/dL]/[U VWF:RCo/kg]), mean (95% CI)	1.8 (1.5% to 2.1%)
PK50 for VWF:RCo — treatment = rVWF, crossover (N = 14)	
$AUC_{0\text{-}96h}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	34.5 (29.7% to 39.3%)
$AUC_{0\text{-}inf}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	37.5 (31.3% to 43.7%)
$T_{1/2}$, hours, mean (95% CI)	21.9 (17.1% to 26.8%)
C_{max}, U/dL, mean (95% CI)	90.7 (78.3% to 103.1%)
IR at C_{max} ([U/dL]/[U VWF:RCo/kg]), mean (95% CI)	1.8 (1.6% to 2.1%)
PK50 for VWF:Ag — treatment = rVWF +rFVIII, crossover (N = 16)	
$AUC_{0\text{-}96h}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	62.9 (53.4% to 72.4%)
$AUC_{0\text{-}inf}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	67.6 (57.2% to 78.0%)
$T_{1/2}$, hours, mean (95% CI)	22.7 (19.9% to 25.4%)
C_{max}, U/dL, mean (95% CI)	110.3 (97.8% to 122.8%)
IR at C_{max} ([U/dL]/[U VWF:RCo/kg]), mean (95% CI)	2.2 (1.9% to 2.4%)
PK50 for VWF:Ag — treatment = rVWF, crossover (N = 14)	
$AUC_{0\text{-}96h}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	64.4 (57.7% to 71.2%)
$AUC_{0\text{-}inf}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	69.5 (61.0% to 77.9%)
$T_{1/2}$, hours, mean (95% CI)	25.1 (22.1% to 28.0%)
C_{max}, U/dL, mean (95% CI)	107.2 (96.6% to 117.8%)
IR at C_{max} ([U/dL]/[U VWF:RCo/kg]), mean (95% CI)	2.1 (1.9% to 2.4%)
PK80 for VWF:RCo — visit = PK1, repeated (N = 15)	
$AUC_{0\text{-}96h}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	34.9 (30.3% to 39.4%)
$AUC_{0\text{-}inf}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	36.2 (31.3% to 41.1%)
$T_{1/2}$, hours, mean (95% CI)	19.1 (16.4% to 21.9%)
C_{max}, U/dL, mean (95% CI)	155.1 (137.9% to 172.4%)
IR at C_{max} ([U/dL]/[U VWF:RCo/kg]), mean (95% CI)	1.9 (1.7% to 2.2%)
PK80 for VWF:RCo — visit = PK2, repeated (N = 13)	
$AUC_{0\text{-}96h}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	34.9 (29.0% to 40.7%)
$AUC_{0\text{-}inf}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	36.7 (30.2% to 43.2%)
$T_{1/2}$, hours, mean (95% CI)	21.2 (16.3% to 26.2%)
C_{max}, U/dL, mean (95% CI)	149.0 (127.5% to 170.5%)
IR at C_{max} ([U/dL]/[U VWF:RCo/kg]), mean (95% CI)	1.9 (1.6% to 2.1%)
PK80 for VWF:Ag — visit = PK1, repeated (N = 15)	
$AUC_{0\text{-}96h}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	63.6 (54.2% to 73.1%)

	Full PK analysis set
$AUC_{0\text{-}inf}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	70.4 (59.1% to 81.8%)
$T_{1/2}$, hours, mean (95% CI)	27.8 (23.8% to 31.8%)
C_{max}, U/dL, mean (95% CI)	182.1 (159.6% to 204.6%)
IR at C_{max} ([U/dL]/[U VWF:RCo/kg]), mean (95% CI)	2.3 (2.0% to 2.6%)
PK80 for VWF:Ag — visit = PK2, repeated (N = 13)	
$AUC_{0\text{-}96h}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	72.8 (61.5% to 84.1%)
$AUC_{0\text{-}inf}$/dose ([h*U/dL]/[U VWF:RCo/kg]), mean (95% CI)	80.4 (66.8% to 94.1%)
$T_{1/2}$, hours, mean (95% CI)	27.2 (22.8% to 31.6%)
C_{max}, U/dL, mean (95% CI)	192.2 (165.0% to 219.4%)
IR at C_{max} ([U/dL]/[U VWF:RCo/kg]), mean (95% CI)	2.4 (2.1% to 2.7%)

$AUC_{0\text{-}96h}$ = area under the curve from time 0 to 96 hours; $AUC_{0\text{-}inf}$ = area under the curve from time 0 to infinity; BE = bleeding episode; CI = confidence interval; C_{max} = maximum plasma concentration; h = hour; IR = incremental recovery; PK = pharmacokinetics; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; $T_{1/2}$ = half-life; VWF:Ag = von Willebrand factor antigen; VWF:RCo. = von Willebrand factor ristocetin cofactor.

Source: Clinical Study Report for Study 071001.[14]

Table 28: PK Assessments — Perioperative Management, PK Analysis Set

	PK analysis set N = 11
VWF:RCo, IU/dL	
$AUC_{0\text{-}96h}$/dose ([h*IU/dL]/[IU VWF:RCo/kg]), mean (95% CI)	37.5 (25.31% to 49.69%)
$AUC_{0\text{-}inf}$/dose ([h*IU/dL]/[IU VWF:RCo/kg]), mean (95% CI)	34.08 (24.27% to 43.88%)
$T_{1/2}$, hours, mean (95% CI)	17.83 (12.90% to 22.76%)
C_{max}, IU/dL, mean (95% CI)	96.27 (81.49% to 111.1%)
IR at C_{max} ([IU/dL]/[IU VWF:RCo/kg]), mean (SD)	1.96 (0.45)
VWF:Ag, IU/dL	
$AUC_{0\text{-}96h}$/dose ([h*IU/dL]/[IU VWF:RCo/kg]), mean (95% CI)	71.67 (58.34% to 85.01%)
$AUC_{0\text{-}inf}$/dose ([h*IU/dL]/[IU VWF:RCo/kg]), mean (95% CI)	58.68 (49.29% to 68.07%)
$T_{1/2}$, hours, mean (95% CI)	27.65 (23.42% to 31.87%)
C_{max}, IU/dL, mean (95% CI)	97.64 (85.30% to 110.0%)
IR at C_{max} ([IU/dL]/[IU VWF:RCo/kg]), mean (SD)	1.99 (0.38)

$AUC_{0\text{-}96h}$ = area under the curve from time 0 to 96 hours; $AUC_{0\text{-}inf}$ = area under the curve from time 0 to infinity; CI = confidence interval; C_{max} = maximum plasma concentration; h = hour; IR = incremental recovery; PK = pharmacokinetics; $T_{1/2}$ = half-life; VWF:Ag = von Willebrand factor antigen; VWF:RCo. = von Willebrand factor ristocetin cofactor.

Source: Clinical Study Report for Study 071101.[15]

Appendix 3: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- Hemostatic efficacy rating scale
- [redacted]
- [redacted]

Findings

Table 29: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
Hemostatic efficacy rating scale	A 4-point Likert scale of "excellent," "good," "moderate," or "none" to evaluate the hemostatic efficacy of treatment for a bleeding event	No literature was identified that tested the hemostatic efficacy rating scale for reliability, validity, or responsiveness in patients with VWD.	No MID information was reported in populations with VWD.
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

HRQoL = health-related quality of life; MID = minimal important difference; [redacted]; VWD = von Willebrand disease; [redacted]

Hemostatic Efficacy Rating Scale

Hemostatic efficacy was evaluated using a 4-point rating scale of "excellent," "good," "moderate," or "none." In Study 071001, the hemostatic efficacy rating was based on the actual number of infusions administered to control the bleed versus the treating physician's estimate of the number of infusions required (Figure 9).[14] In Study 071101, the assessment was based on hemostasis relative to a hemostatically normal patient without VWD (Figure 10).[15] The overall hemostatic efficacy was assessed by the study investigator while the intraoperative rating was provided by the surgeon.

Clinical trials evaluating the treatment of bleeding episodes often use a multi-point Likert scale to evaluate hemostatic efficacy. Kessler et al. pointed out the subjectivity of this assessment since it can be at the discretion of the physician, trial investigator, patient, or caretaker during home treatment.[23] Hemostatic efficacy trials can also use a 3-point Likert scale with outcomes of "excellent/good" "fair/poor" or "none" which can make comparisons with studies using a different scale challenging. Furthermore, the categories of these scoring systems are inconsistently defined among studies and the descriptions often do not appear to be sensitive to small differences in treatment outcomes.

No literature was identified that reported on the reliability, validity, or responsiveness of this rating scale in patients with VWD. There was also no MID information reported in populations with VWD.

Figure 9: Efficacy Rating Criterion Used in Study 071001

In-Text Table 1
Efficacy Rating Scale

Rating	Efficacy Rating Criterion	
	Minor and Moderate Bleeding Events	Major Bleeding Events
Excellent (=1)	• Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode • No additional VWF containing coagulation factor containing product required	• Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode • No additional VWF containing coagulation factor containing product required
Good (=2)	• 1-2 infusions greater than estimated required to control that bleeding episode • No additional VWF containing coagulation factor containing product required	• <1.5x infusions greater than estimated required to control that bleeding episode • No additional VWF containing coagulation factor containing product required
Moderate (=3)	• 3 or more infusions greater than estimated used to control that bleeding event • No additional VWF containing coagulation factor containing product required	• ≥1.5x more infusions greater than estimated used to control that bleeding event • No additional VWF containing coagulation factor containing product required
None (=4)	• Severe uncontrolled bleeding or intensity of bleeding not changed • Additional VWF containing coagulation factor containing product required	• Severe uncontrolled bleeding or intensity of bleeding not changed • Additional VWF containing coagulation factor containing product required

VWF = von Willebrand factor.

Note: The estimated number of infusions required for treatment of different types of bleeds at various anatomical locations was determined and individualized by the investigator, using general guidance provided in the study protocol of Study 071001.

Source: Clinical Study Report for Study 071001.[14]

Figure 10: Efficacy Rating Criterion Used in Study 071101

Table 11.1-1 PRIMARY EFFICACY ASSESSMENT	
RATING	**Overall assessment of hemostatic efficacy 24 hours after last perioperative IP infusion or at day 14 completion visit (whatever occurs earlier)**
Excellent (1)	Intra-, and postoperative hemostasis achieved with rVWF with or withoutADVATE was as good or better than that expected for the type of surgical procedure performed in a hemostatically normal subject
Good (2)	Intra-, and postoperative hemostasis achieved with rVWF with or without ADVATE was probably as good as that expected for the type of surgical procedure performed in a hemostatically normal subject
Moderate (3)	Intra-, and postoperative hemostasis with rVWF with or without ADVATE was clearly less than optimal for the type of procedure performed but was maintained without the need to change the rVWF concentrate
None (4)	Subject experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of rVWF concentrate

rVWF = recombinant von Willebrand factor.

Source: Clinical Study Report for Study 071101.[15]

[redacted]

[redacted]

Appendix 4: Summary and Critical Appraisal of Studies Supporting the Economic Analysis

Aim

To examine the validity of relevant clinical results of the 3 studies used to inform inputs of the pharmacoeconomic analyses submitted by the sponsor[24-26]

Findings

Gill et al. (2003)

Objective

The objective of the study[24] was to evaluate the efficacy and safety of Humate-P for the treatment of emergency bleeding episodes in patients with VWD. Specifically, the daily dosing, including loading and maintenance doses, and the duration of treatment for major bleeds reported from this study were used to inform the on-demand subgroup within the sponsor's submitted pharmacoeconomic model. Furthermore, results from treatment-related SAEs from this study were pooled with another study (Mannucci et al.[2013]) to provide an estimate on the rates of SAEs for both the on-demand and perioperative management analysis.

Description of the Study

This was a prospective, multi-centre (N = 19 centres in the US), open-label, single-arm study conducted between November 1998 and August 1999. Thirty-three patients with congenital VWD for whom DDAVP was inadequate were enrolled. Although dosing recommendations were specified as part of the study protocol, dosing was ultimately at the discretion of the investigator. The recommended loading dose was 60 IU VWF:RCo/kg to 80 IU VWF:RCo/kg body weight while a maintenance dose was suggested at 40 IU VWF:RCo/kg to 60 IU VWF:RCo/kg every 8 hours to 12 hours for 3 days. After that time, if further treatment was necessary, the same maintenance dose would continue on a daily schedule. Hemostatic efficacy was measured by the investigator's daily rating of "excellent/good," "fair/poor," or "none" during treatment and an overall rating following bleeding event resolution. All statistical analyses were descriptive and 2-sided CIs using the Clopper-Pearson method were calculated for patients with "excellent/good" hemostatic efficacy.

Of the 33 patients enrolled, 9 (27%) had multiple bleeding events (range = 2 events to 8 events). Thirty-one patients (94%) were Caucasian, 1 (3%) was African American, and 1 (3%) was Native Alaskan. The study group was composed of 18 females (55%) and 26 patients (79%) were over the age of 16. Nine patients had type 1 VWD, 8 had type 2 VWD, 12 had type 3 VWD, and 4 were unspecified. A total of 53 serious bleeding events were treated, with 48 complete follow-ups and 5 discontinuations due to withdrawn consent, doctor's decision, scheduling conflict, and those lost to follow-up (2).

The median loading dose was 67.0 IU VWF:RCo/kg (range = 25.7 to 143.2), the median maintenance dose was 74.0 IU VWF:RCo/kg (range = 16.4 to 182.9), the median number of infusions was 2 (range = 1 to 36), and the median treatment duration was 3 days (range = 1

to 67). For overall hemostatic efficacy, 52 events were rated “excellent/good” (95% CI, 88.1% to 100%). One of the 52 events exhibited “temporary ineffectiveness” described as 3 consecutive days of “fair/poor” or “none.” Twenty-four AEs were reported for 12 bleeding events in 10 patients (23%); they included mild allergic reaction, menorrhagia, anemia, hemorrhage, nausea, GI hemorrhage, vomiting, and insomnia, though none resulted in discontinuation of study medication. SAEs were reported for 2 treatment episodes of 2 patients. These were menorrhagia and anemia in 1 event and hemorrhage in the other.

Patients who were treated for longer than 7 days tended to receive a higher medication dose, but less frequently. There was no association between VWD type and treatment dose or duration. Despite the wide range of doses and number of infusions given, in general, the severity of the event had the greatest influence on the loading and maintenance doses, number of infusions, and treatment duration.

Critical Appraisal

The study included only 33 patients, but both males and females and each of the 3 types of VWD were represented in the study population.

The median loading dose of 67.0 IU VWF:RCo/kg in the study was higher than that recommended in the Humate-P product monograph, which suggests a loading dose of 40 IU VWF:RCo/kg to 50 IU VWF:RCo/kg for treatment of a major or minor bleeding event in patients with type 1 mild or moderate/severe VWD, respectively, and 40 IU VWF:RCo/kg to 60 IU VWF:RCo/kg for treatment of a major bleed in patients with moderate or severe VWD.[10] The recommended loading dose is also 40 IU VWF:RCo/kg to 50 IU VWF:RCo/kg for those with a minor bleed and type 2 VWD or type 3 VWD, whereas 40 IU VWF:RCo/kg to 80 IU VWF:RCo/kg is suggested for a major bleed in the same patient group. The median maintenance dose used in the study was 74 IU VWF:RCo; the Humate-P product monograph suggests the initial maintenance dose should be half the loading dose with subsequent doses adjusted to achieve target plasma levels for VWF:RCo and FVIII:C, based on type of surgery and number of days after surgery. According to the clinical experts consulted by CADTH, the methods used in Canadian clinical practice align with those in the Humate-P product monograph for loading doses in that patient factor levels are similarly monitored and maintenance doses are adjusted to achieve target levels. The study’s recommended loading dose was on the higher end of the product monograph’s range while the study’s recommended maintenance dose was suggested based on body weight rather than on measured plasma protein levels. The median loading dose was within the study recommendations while the median maintenance dose was higher than that of the study recommendations. Although dosing recommendations were provided, the decision was ultimately up to each investigator’s clinical judgment, which may better reflect clinical practice.

FVIII:C levels were measured during the study and patients who required FVIII:C supplementation received an increased dose of study drug. The study did not report the doses or frequency of rFVIII for those who required it. The daily and overall efficacy ratings of bleeding events were based on a description of the adequacy of hemostasis. Thus, there was still a degree of subjectivity and variability that could occur among clinicians at different treatment centres.

Lillicrap (2002)

Objective

The objective of the study by Lillicrap study[24] was to evaluate the safety and efficacy of Humate-P dosed in VWF:RCo in the treatment of patients with VWD in Canada. The results of overall hemostatic efficacy (Humate-P in on-demand treatment of bleeding episodes and perioperative management) and duration of treatment (for minor and moderate on-demand bleeds) were used to inform the sponsor's pharmacoeconomic model.

Description of the Study

This was a retrospective single-arm observational study. Data were collected by reviewing the medical records of patients with VWD treated for on-demand control of bleeding episodes, perioperative management, and long-term prophylaxis under the Canadian Emergency Drug Release Program from November 22, 1991, to April 30, 1996. The key inclusion criteria were documented diagnosis of VWD, including the standard criteria of an objective clinical bleeding history, laboratory test data (VWF:Ag, VWF:RCo, FVIII:C, and sometimes VWF multimers), and sometimes a family history of a bleeding disorder. No exclusion criteria was reported. Humate-P dose was based on the German package insert. In the study analysis, the FVIII:C units were converted to VWF:RCo units (i.e., average ratio of 2.6 IU VWF:RCo per IU FVIII:C). The efficacy was rated by the treating physician as follows: excellent = hemostasis achieved (i.e., complete bleeding stop); good = slight oozing (adequate control of bleeding, no need for additional unplanned treatment); poor = moderate control of bleeding (i.e., need additional unplanned treatment); none = severe uncontrolled bleeding. Study variables were summarized by descriptive statistics (e.g., mean, range, SD). Various subgroup analyses (e.g., demographics, VWD type, indication for use) were conducted.

A total of 97 patients with VWD (infants, children, adolescents, and adults) were included. The median age was 20.4 years (range = 0.4 years to 81.1 years). Of the 97 patients, 32 patients were classified as type 1 VWD, 23 as type 2 VWD, 28 as type 3 VWD, and 14 as type 2N or type 2M, or acquired VWD.

Twenty-five different lots of Humate-P were used to treat 437 different events. Among the 437 events, 344 events were hemorrhagic events, 73 were surgical interventions, and 20 were prophylactic infusion cycles. The category of patients with prophylactic infusion is beyond the scope of the indication under review; therefore, data for this population were not reported in the current summary.

Overall, the median dose per infusion used to treat surgical events was 69.1 IU VWF:RCo/kg (range = 12 to 223); and the median dose for bleeding events was 55.3 IU VWF:RCo/kg (range = 17 to 228). The majority of events required treatment for 10 days or less (91%). Twenty-three bleeding events were treated for 10 days or more. Efficacy was assessed by the physician based on dosing in VWF:RCo activity. The information on the number of infusions was not reported in the study.

An overall clinical result of "excellent" or "good" was reported in 97% of treatment events (424 out of 437). An "excellent/good" outcome was reported in 99% of surgical cases (72 out of 73) and 97% of bleeding events (332 out of 344).

The author indicated that the findings in this study confirm the safety and efficacy of Humate-P using VWF:RCo dosing in pediatric and adult patients with various types of VWD.

Critical Appraisal

The data in the study were collected from Canadian patients; therefore, it is unlikely that generalizability of the patient population represents an issue. Hemostatic efficacy was assessed using a rating scale similar to that used in the rVWF trials. No literature was identified that reported on the reliability, validity, or responsiveness of this rating scale in patients with VWD. For treatment of bleeding events, the median dose of 55.3 IU VWF:RCo/kg was aligned with Health Canada's recommended dose in the Humate-P product monograph[10] (i.e., 40 IU/kg to 80 IU/kg). The median dose of 69.1 IU VWF:RCo/kg used to treat surgical events was also aligned with Health Canada's recommended dose[10] (i.e., 40 IU/kg to 100 IU/kg). The key limitations of this study were the nature of the retrospective study design and no control group; therefore, the potential effect of confounding factors is unknown.

Mannucci (2013)

Objective

The objective of the study[26] was to assess the prophylactic perioperative efficacy of Humate-P (Haemate P in the EU) in adults and children with VWD undergoing elective surgery. The results pertaining to the median dose and number of hospitalization days were used to inform the perioperative subgroup within the sponsor's submitted pharmacoeconomic model. As noted earlier, the results from treatment-related SAEs from this study were pooled with that reported by Gill et al. (2003)[24] to provide an estimate on the rates of SAEs for both the on-demand and perioperative management analysis.

Description of the Study

The report by Mannucci (2013) was a pooled analysis of 2 prospective, multi-centre, open-label, single-arm studies (N = 62). One study (total N = 35; 3 for oral surgery, 4 for minor surgery, and 28 for major surgery) was conducted primarily in the US[27,28] and the other (total N = 27; none for oral surgery, 11 for minor surgery, and 16 for major surgery) was conducted in the European Union (EU).[29] The key inclusion criteria in the 2 studies were adults and children (any age in the US study; > 5 years of age in the EU study) with a confirmed diagnosis of VWD (clinical and laboratory) who were inadequately responsive to DDAVP for management of surgery and scheduled to undergo elective surgery. The surgical procedures were categorized as follows: oral surgery (simple tooth extraction), minor surgery (simple procedures not involving a risk to life could be performed in an outpatient clinic, with or without sedation), and major surgery (procedures involving considerable risk to life or limb, frequently involving general anesthesia). The 2 studies [27-29] evaluated the prophylactic effect of perioperative use of Humate-P/Haemate P. The doses of Humate-P/Haemate P (loading doses and maintenance doses) were calculated using a patient's recovery values, although VWF:RCo and FVIII: C target levels differed between the protocols of the 2 studies. The plasma sample test was conducted in a central laboratory in the US study; In the EU study, the laboratory test was done at local laboratories using standard methods, as well as at a central coagulation laboratory (Ulrich Budde, Hamburg, Germany). The authors indicated that a limited pooled analysis of the data from the 2 studies (e.g., for overall hemostatic efficacy) was feasible because of their similar designs.

The overall hemostatic efficacy was achieved in 95% of the pooled population of 62 adults and children when assessed 24 hours after the last infusion in the US study[27,28] or taken as the worst rating between surgery and day 14 in the EU study.[29] Fifty-one patients (81%) reported at least 1 AE in the pooled analysis (US study, 86%; EU study, 75%). Nineteen patients (30%) experienced 35 bleeding events.

The median total dose per oral surgery in the US study was 64.0 IU/kg (range = 63 IU/kg to 202 IU/kg). The median total dose per oral surgery was not reported in the EU study. The median total dose per minor surgery was 292.0 IU/kg in the US study (range = 226 IU/kg to 859 IU/kg) and 238.5 IU/kg in the EU study (range = 143.6 IU/kg to 849.3 IU/kg). The median total dose per major surgery was 241.0 IU/kg in the US study (range = 79 IU/kg to 1,699 IU/kg) and 448.5 IU/kg in the EU study (range = 167.1 IU/kg to 1,297.4 IU/kg) .

The number of hospitalization days in the US study and the EU study was not clearly reported in the Mannucci study. However, it was reported that, for the pooled sample, the median duration of post-surgery treatment was 1 day for oral surgery (range = 1 day to 2 days), 4 days for minor surgery (range = 1 day to 17 days), and 7 days for major surgery (range = 1 day to 26 days).

No SAEs were reported in the US study. One SAE was reported in the EU study (a pulmonary embolism).

The author indicated that this pooled analysis confirmed the feasibility of pharmacokinetically guided dosing of Humate-P/Haemate P and showed its efficacy and safety in the prevention of excessive perioperative bleeding.

Critical Appraisal

The key limitations of this study were that both original studies were single-arm studies and did not employ any control group. The definitions of the hemostatic efficacy score were not comparable with the scale used in the pivotal study (Study 071101). The number of hospitalization days in the US study and EU study that the Pharmaceutical Review Report used was not clearly reported in the study by Mannucci et al.. In addition, the overall hemostatic efficacy was pooled from studies conducted in the US and Europe; whether the treatment practice differs in the US and EU compared to Canada is unknown. For example, the number of days in hospital may be impacted by the clinical practice variation in different countries.

Therefore, the validity of the findings of the pooled analysis remains uncertain.

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