CADTH

CADTH Drug Reimbursement Review

Pharmacoeconomic 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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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

BIA	budget impact analysis
DDAVP	desmopressin
FVIII	factor VIII
FVIII:C	factor VIII coagulant
QALY	quality-adjusted life-year
rFVIII	recombinant factor VIII
rVWF	recombinant von Willebrand factor
SAE	serious adverse event
VWD	von Willebrand disease
VWF	von Willebrand factor

Executive Summary

The executive summary comprises 2 tables (Table 1: Submitted for Review and Table 2: Summary of Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug	Recombinant von Willebrand factor (Vonvendi), 650 IU VWF:RCo and 1,300 IU VWF:RCo in a single-use vial, lyophilized powder for solution
Submitted price	• rVWF, 650 IU, intravenous injection: $1,002.89 per vial • rVWF, 1,300 IU, intravenous injection: $2,005.77 per vial
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)
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	January 10, 2019
Reimbursement request	• Adults diagnosed with severe VWD (aged ≥ 18) • Adults diagnosed with mild or moderate VWD who do not respond or are intolerant to DDAVP (aged ≥ 18)
Sponsor	Shire Pharma Canada ULC, now part of Takeda Canada Inc.
Submission history	Not previously reviewed

DDAVP = desmopressin; rVWF = recombinant von Willebrand factor; VWD = von Willebrand disease; VWF:RCo = von Willebrand factor ristocetin cofactor.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Decision-tree model
Target populations	Adult patients diagnosed with VWD (aged ≥ 18) Stratified analyses based on the following clinical scenarios: • management of on-demand bleeding episodes • perioperative management
Treatment	rVWF ± rFVIII (Advate)
Comparator	Antihemophilic factor/VWF complex (human) (Humate-P)
Perspective	Canadian publicly funded health care payer
Outcome	QALY
Time horizon	Each stratified analysis adopted a different time horizon: • 8 days for on-demand treatment of a bleeding episode • 16 days for perioperative management
Key data source	Study 071001 and Study 071101: single-arm studies on rVWF ± rFVIII A large retrospective observational study on antihemophilic factor/VWF complex
Submitted results for base case	Base-case results compared with antihemophilic factor/VWF complex: • on-demand treatment of a bleeding episode — rVWF ± rFVIII is dominant (costs less and is more effective) • perioperative management — ICER = $30,997 per QALY (incremental costs = $49, incremental QALYs = 0.0016) Key scenario analyses: • patient population to reflect reimbursement request (adults aged ≥ 18 diagnosed with severe VWD, or mild or moderate VWD who do not respond or are intolerant to DDAVP); results were the same as the base case since efficacy was assumed to be unchanged • on-demand treatment with dosing consistent with the product monograph; rVWF ± rFVIII remained dominant
Key limitations	• No head-to-head clinical trial to inform relative efficacy and safety or differences in resource utilization. Estimates from different sources were selected and naively compared in the model, with inputs selected that favoured rVWF ± rFVIII. Clinical experts consulted by CADTH suggested that they would not anticipate a difference between the products on these modelled inputs, including clinical effects and expected QALYs. • Human VWF and human coagulation factor VIII (Wilate) was not included as a comparator in the analysis. • The use of US costs to inform the price of antihemophilic factor/VWF complex and rFVIII is unlikely to reflect actual costs paid in Canada.
CADTH reanalysis results	• In light of the absence of comparative evidence to support a difference in efficacy, safety, or resource utilization between rVWF ± rFVIII and antihemophilic factor/VWF complex, CADTH set these model inputs to be identical in reanalyses. Analysis captured differences in the acquisition cost of the plasma protein products. • For on-demand bleeding episodes, rVWF ± rFVIII costs $4,514 more than antihemophilic factor/VWF complex. • For perioperative management, rVWF ± rFVIII costs $19,240 more than antihemophilic factor/VWF complex. • A price reduction of 40% was required for rVWF to have similar treatment acquisition cost as antihemophilic factor/VWF complex. The price reduction is sensitive to the price of plasma protein products (i.e., antihemophilic factor/VWF complex and rFVIII) and the proportion of patients on rVWF who are dosed concomitantly with rFVIII.

DDAVP = desmopressin; ICER = incremental cost-effectiveness ratio; QALY= quality-adjusted life-year; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; VWD = von Willebrand disease; VWF = von Willebrand factor.

Conclusions

CADTH found that the sponsor's base case included several assumptions that were favourable to recombinant von Willebrand factor (rVWF) but that were not supported by clinical evidence. There is currently no head-to-head clinical trial comparing rVWF with plasma-induced von Willebrand factor (VWF). CADTH undertook reanalyses to address this limitation by implementing identical settings for the efficacy, safety, and resource utilization of rVWF, with or without recombinant factor VIII (rFVIII), and antihemophilic factor/VWF complex. Where only blood product acquisition cost was considered, CADTH found that rVWF, with or without rFVIII, was $4,514 and $19,240 more costly than antihemophilic factor/VWF complex for on-demand bleeding episodes and for perioperative management, respectively. It was more expensive primarily due to the higher unit cost of rVWF ($1.54 per IU versus $0.92 per IU) and due to the additional cost of potential co-administration with rFVIII.

A price reduction of 40% is required for rVWF to have a treatment acquisition cost similar to that of antihemophilic factor/VWF complex. However, an even greater price reduction would be required if the actual cost of plasma-derived VWF were lower than the assumed price ($0.92 per IU), if the price of rFVIII were higher than the assumed price ($0.82 per IU), and/or if a greater proportion of patients required rFVIII dosed concomitantly with rVWF.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient group that participated in the CADTH review process.

Patient input was received from the Canadian Hemophilia Society. Respondents of the Canadian Hemophilia Society survey described von Willebrand disease (VWD) as being disabling, painful, and challenging to manage. Patients reported frequent bleeds and bruises that have a significant impact on quality of life and time lost at work and school. Most patients expressed concerns about the access to current treatment during a bleeding episode and the increased cost of travelling to hospital for treatment. Patients would like future treatments to have easier accessibility and administration, longer-lasting benefits, and fewer side effects.

No Canadian patients had experience with rVWF.

With respect to how the economic submission addresses the patient input received, the following are considerations:

- Since the health care payer perspective was adopted in this economic submission, patient-borne costs such as travelling were not considered. Given that both plasma protein products are intravenously administered, travelling costs would be expected to be similar for the treatment under review and the currently available comparators. The sponsor stated that rVWF has a longer half-life compared to plasma-derived VWF, and in the economic model, it was estimated to result in fewer infusions.
- Although rVWF is postulated to have potential benefits with respect to decreased risk of viral contamination, and the ability to avoid administration of additional rFVIII when it is not needed or contraindicated, there is limited evidence to support these claims and these were not captured in the economic model. rFVIII co-administration with rVWF is required in some circumstances, with attendant administration costs that have been incorporated into the economic model (assuming 11% of co-treatments).

The sponsor did not provide a scenario analysis addressing some of the non-health impacts of the condition (e.g., time lost at work and school), although it is not clear that a difference would be expected between treatments.

Economic Review

The current review is for rVWF (Vonvendi) for adult patients diagnosed with VWD (aged ≥ 18).

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis comparing rVWF (with or without rFVIII) with plasma-derived VWF (i.e., antihemophilic factor/VWF complex) for adult patients diagnosed with VWD.[1] Specifically, stratified analyses were conducted based on the following clinical scenarios: on-demand treatment of bleeding episodes and perioperative management of bleeding. These 2 subgroups within the stratified analyses are consistent with the Health Canada–indicated population. The sponsor's reimbursement request was based on severity of VWD, with reimbursement requested in adults who are diagnosed with severe VWD or those diagnosed with mild or moderate VWD who do not respond or are intolerant to desmopressin (DDAVP); this was examined in scenario analyses with the assumption that efficacy and dose would be the same as the base-case analyses.[1]

The recommended dosage regimen is personalized according to clinical judgment based on the patient's weight, disease type, severity of bleeding episodes or type of surgical intervention, and clinical and laboratory measures.[2] To manage a bleeding episode, the recommended first dose is 40 IU/kg to 80 IU/kg, with subsequent dose(s) of 40 IU/kg to 60 IU/kg every 8 hours to 24 hours as long as clinically necessary to maintain a hemostatic effect. Depending on a patient's baseline factor VIII coagulant (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; otherwise, a rFVIII product should be administered with the first infusion of rVWF to achieve a hemostatic plasma FVIII:C level.[2] For perioperative management, the dosage is customized to the patient's needs according to baseline and target levels of von Willebrand factor ristocetin cofactor and FVIII:C. The recommended minimum von Willebrand factor ristocetin cofactor peak target plasma levels prior to initiating surgery are 50 IU/dL for minor surgery and 100 IU/dL for major surgery. In case of major bleeding events or major surgeries requiring repeated, frequent infusions, monitoring of FVIII levels is recommended to decide if rFVIII is required for subsequent infusions and to avoid an excessive rise of FVIII.[2] As the sponsor's submitted price of rVWF is $1.54 per IU, the costs for each single-use vial are $1,002.89 (for 650 IU) and $2,005.77 (for 1,300 IU).[1] Assuming 11% of patients require co-administration of rFVIII and using a treatment acquisition cost obtained from the US Department of Veterans Affairs,[3] the total cost for a course of rVWF, with or without rFVIII, was estimated by the sponsor to be $5,902 per on-demand bleeding episode and $30,244 per episode of perioperative management, based on the dosing schedules observed in Study 071001 and Study 071101. For antihemophilic factor/VWF complex, the sponsor converted the price from a US source to Canadian cost.[3] Based on a price of $0.92 per IU and assuming dosing schedules from observational studies,[4,5] the sponsor's model estimated that the total cost for a course of antihemophilic factor/VWF complex would be $6,319 per on-demand bleeding episode, and $27,483 per episode of perioperative management. A detailed assumption on the total dosing used in the model can be found in Appendix 3 (Table 16 and Table 17).[1]

The analyses were conducted from the Canadian public payer perspective; the time horizon corresponded with the time to manage hemostasis and subsequent consequences for an episode of care (8 days for a bleeding episode and 16 days for a perioperative episode).[1] Discounting was not applied to costs and clinical outcomes due to the short time horizons.

Model Structure

The same decision-tree structure (Figure 1 in Appendix 3) was utilized to estimate the cost-utility of rVWF, with or without rFVIII, for an episode of care for both the on-demand bleeding and perioperative management scenario.[1] Patients entered the model at the start of a bleeding episode or when in a perioperative setting. Following initial treatment, patients may or may not achieve hemostasis.[1] In those achieving hemostasis, bleeding is resolved whereas in those for whom hemostasis is not achieved, patients were assumed to experience uncontrolled bleed requiring subsequent treatment to achieve hemostasis. Mortality was not considered in the model.

Model Inputs

In the base case, the patients' baseline characteristics reflected Study 071001 and 071101 for the on-demand and perioperative management settings, respectively.[1] For on-demand bleeding episodes, a mean weight of 76 kg was used in the model, with a distribution of 64.2%, 32.1%, and 3.7% for minor, moderate, and major bleeds, respectively.[1] For perioperative management, a mean weight of 78.6 kg was used, with a distribution of 6.7%, 26.7%, and 66.7% for oral, minor, and major surgeries, respectively.[1] The types of surgery were defined according to Study 071101. Oral surgeries included extractions of fewer than 3 non-molar teeth with no bony involvement. Minor surgical procedures included gastroscopy, placement of intravenous access devices, arthroscopy, colonoscopy, conization, and removal of small skin lesions; surgeries were considered major if they posed a significant risk of loss of large volumes of bleed or blood loss into a confined anatomical space (e.g., major orthopedic or cardiovascular surgery, extractions of impacted third molars).[1]

Model inputs unique to each subgroup are reported before common inputs applicable to both subgroups are reported.

On-Demand Bleeding Subgroup

The hemostatic efficacy of rVWF, with or without rFVIII, was obtained from a single-arm prospective phase III trial: Study 071001.[1] In this study, secondary efficacy outcomes included the number of treated bleeding episodes with a hemostatic efficacy rating of excellent or good (assessed by the treating physician by considering expected versus number of infusions to resolve bleeding), and the number of infusions and dose per bleeding episode.[6] When the outcome, hemostatic efficacy, was dichotomized (i.e., achieving hemostasis or not) to inform the probabilities within the decision tree, the hemostatic control of rVWF was reported to be 100%. Efficacy for antihemophilic factor/VWF complex was obtained from a retrospective study in the Canadian population.[7] This outcome was similarly dichotomized, resulting in 96.5% of patients achieving hemostasis based on a naive comparison. The definition of hemostatic efficacy of this retrospective study was similar but not identical to the scale used in Study 071001.[1]

The median doses of rVWF per bleeding episode were derived from Study 071001.[6] The median dose of antihemophilic factor/VWF complex per bleeding episode was estimated based on the daily dose of loading and maintenance therapy and the duration of treatment as reported in a prospective study by Gill et al. (2003).[5] The number of infusions for minor

and moderate bleeds was derived from Study 071001 for rVWF[6] and a retrospective study for antihemophilic factor/VWF complex.[7] The duration of hospitalization for antihemophilic factor/VWF complex in a major bleed was based on the same prospective study of plasma-derived VWF[5] and, as this was not measured in Study 071001, the sponsor assumed that this would be a day longer than the trial's observed last infusion (i.e., 2 infusion days + 1 day = 3 days).[1]

Perioperative Management Subgroup

The hemostatic efficacy of rVWF, with or without rFVIII, was obtained from Study 071101 based on the same outcome and ascertainment as noted earlier for bleeding episodes. Hemostatic control was achieved in 100% of patients.[1] Hemostatic efficacy of antihemophilic factor/VWF complex was similarly based on naive estimates from a retrospective study conducted in Canada,[7] in which hemostatic control was achieved in 98.6% of patients.

The median doses per surgery type for rVWF, with or without rFVIII, were based on Study 071101[8] while the median doses for antihemophilic factor/VWF complex were based on a published paper reporting on 2 prospective multi-centre studies in the US and in European countries.[4] The aforementioned literature further informed the respective number of hospitalization days by type of surgical intervention.

Inputs Common to Both On-Demand and Perioperative Management Settings

The same rates for treatment-related serious adverse events (SAEs) were applied in both settings.[1] Only SAEs deemed to be related to the treatment were included in the model, which were associated with costs and utility decrements. The rate of treatment-related SAEs for rVWF, with or without rFVIII ([redacted]%), was obtained from pooled analysis of Study 070701,[9] Study 071001,[6] and Study 071101[8] while the rate for antihemophilic factor/VWF complex (1.0%) was obtained from a pooled analysis of the publications by Gill et al. (2003) for on-demand bleeds[5] and Mannucci et al. (2013) for perioperative management.[4]

Identical utility weights were applied to common clinical inputs in both models.[1] The baseline utility for no events (0.736) was based on a study by Rae (2013)[10] on the Canadian population diagnosed with VWD using a national population-based survey. Additionally, 4 types of disutilities obtained from other published literature were applied in the model: 1) *disutility of infusion* (–0.230);[11] 2) *disutility of hospitalization* (–0.248);[12] 3) *disutility of uncontrolled bleed* (–0.413), which was an additive function of the disutility of hospitalization,[12] the disutility of bleed (–0.160),[13] and a weighted disutility reflecting the proportion of patients expected to have significant blood loss;[11] and 4) *disutility of treatment-related SAEs* (–0.105).[14-16]

The costs for rVWF were based on the sponsor's submitted price[1] whereas the price for antihemophilic factor/VWF complex and rFVIII were obtained from the US Department of Veterans Affairs.[3] rVWF was co-administered with rFVIII in 11% of injections as per Study 071001 for on-demand bleeding episodes and Study 071101 for perioperative management. Costs were based on published literature,[17] the Ontario Drug Benefit formulary,[18] and the Ontario Schedule of Benefits.[19] Administration was assumed to be either in a hemophilia clinic (i.e., minor and moderate bleed, and oral surgery) or in an inpatient setting (i.e., major bleed, minor, and major surgery). If hemostasis was not achieved after initial treatment, subsequent therapy assumed a 50% increase in the treatment's dose and additional hospitalization. Dose, duration, and the use of additional therapies (e.g., platelet transfusion, concomitant tranexamic acid) and diagnostic tests (e.g., factor VIII [FVIII] assay test) were assumed to be equal in both the treatment arm and the comparator arm. Additional

hospitalization of 3 days was assumed for on-demand bleeds and 7 days for perioperative management.[1]

Summary of Sponsor's Economic Evaluation Results

The sponsor's cost-effectiveness analysis was based on 5,000 probabilistic iterations, for which findings are presented as follows.

Base-Case Results

On-Demand Bleeding Subgroup

In the sponsor's base-case analysis for the on-demand setting, rVWF, with or without rFVIII, was dominant to antihemophilic factor/VWF complex (e.g., less costly and more effective).[1] Specifically, rVWF, with or without rFVIII, was associated with 0.0002 additional quality-adjusted life-years (QALYs) and $1,637 in lower costs compared to antihemophilic factor/VWF complex over the modelled time horizon of 8 days (Table 3; disaggregated results are presented in Table 18 and Table 19 in Appendix 3). The cost-effectiveness acceptability curves found that 91.7% of the results fell below $50,000 per QALY gain (Figure 2 in Appendix 3).[1] The results of the deterministic analysis were similar to the results of the probabilistic analysis.

The major cost driver in this subgroup was the lower costs to manage uncontrolled bleeding for rVWF, with or without rFVIII (a cost saving of $1,131), and the lower overall treatment acquisition costs associated with rVWF (a cost saving of $421) (Table 18). The major driver contributing to QALY gains for rVWF, with or without rFVIII, was the prevention of disutilities associated with uncontrolled bleed (0.0001) (Table 19).

Table 3: Summary of the Sponsor's Economic Evaluation Results — On-Demand Bleeding Episode

Drugs	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER ($ per QALY)
rVWF ± rFVIII	$6,135	–$1,637	0.0160	0.0002	Dominant
Antihemophilic factor/ VWF complex	$7,772	—	0.0158	—	—

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; VWF = von Willebrand factor.

Source: Sponsor's Pharmacoeconomic Submission.[1]

Perioperative Management Subgroup

In the sponsor's base-case analysis for the perioperative management setting, rVWF, with or without rFVIII, was associated with an additional 0.0016 QALYs and a $49 cost compared to antihemophilic factor/VWF complex over the modelled time horizon of 16 days (Table 4; disaggregated results are presented in Table 20 and Table 21 in Appendix 3).[1] This resulted in an incremental cost-effectiveness ratio for rVWF, with or without rFVIII, compared with antihemophilic factor/VWF complex of $30,997 per QALY gained (Table 4).[1] The results of the deterministic analysis were different from the results of the probabilistic analysis for the perioperative scenario. Specifically, the deterministic results suggested that rVWF, with or without rFVIII, would be dominant (with a cost of $404 less and 0.0016 additional QALYs).[1] The conflicting results between the deterministic and probabilistic results highlight the considerable decision uncertainty arising from parameter uncertainty within this analysis. The incremental cost-effectiveness plane (not presented here) found that the incremental

cost and effect pairs from the Monte Carlo simulation fell across all 4 quadrants of the plane. They ranged from rVWF, with or without rFVIII, being the dominant strategy (i.e., less expensive and more effective than antihemophilic factor/VWF complex) to being the dominated strategy (i.e., more expensive and less effective than antihemophilic factor/VWF complex). As such, the cost-effectiveness acceptability curves found that 50.1% of the results fell below $50,000 per QALY gain (Figure 3 in Appendix 3).[1] In other words, the sponsor's base case for the perioperative management subgroup was associated with a notable degree of decision uncertainty as rVWF, with or without rFVIII, had a 50.1% probability of being the optimal intervention at a willingness-to-pay threshold of $50,000 per QALY.

Treatment acquisition costs in this subgroup were expected to be greater ($2,754 more), although this was offset by lower administration-related costs from a shortened duration of infusion and hospitalization (a cost saving of $2,139) (Table 20 in Appendix 3). The major factor contributing to the QALY gains for rVWF, with or without rFVIII, was the prevention of disutilities related to infusions or hospitalization (0.0014) (Table 21 in Appendix 3).

Table 4: Summary of the Sponsor's Economic Evaluation Results — Perioperative Management Setting

Drugs	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER ($ per QALY)
Antihemophilic factor/ VWF complex	$36,025	—	0.0271	—	—
rVWF ± rFVIII	$36,081	$49	0.0286	0.0016	30,997

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor.

Source: Sponsor's Pharmacoeconomic Submission.[1]

Reimbursement-Requested Scenario

Under the sponsor's reimbursement request (for patients with severe VWD, or patients with mild or moderate VWD who do not respond or intolerant to DDAVP), results were reported to be the same as those of the base case (all VWD severities) as efficacy was assumed not to change.[1]

Sensitivity and Scenario Analysis Results

Uncertainty was addressed by probabilistic scenario analysis exploring dosing consistent with the approved product monograph in the on-demand bleeding subgroup. When doses were consistent with the product label, rVWF, with or without rFVIII, remained the dominant strategy in the on-demand bleeding setting. This scenario analysis was not reported for the perioperative setting because dosage in perioperative management is customized to the patient's needs, according to baseline and target levels of VWF and FVIII.[1]

A variety of 1-way deterministic sensitivity analyses were also undertaken. The deterministic sensitivity analyses suggested the on-demand bleeding model was robust whereas, for perioperative management, the results were very sensitive to the model inputs of hemostatic efficacy, dose, and number of days requiring treatment.[1]

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the economic analysis.

- **There was no head-to-head comparison to determine relative efficacy or safety and to inform differences in dose, number of infusions, or hospitalization days.** There is currently no head-to-head clinical trial that compares the 2 treatments directly. Comparative treatment efficacy within the economic model was instead obtained from prospective single-arm trials of rVWF, with or without rFVIII,[6,8] and a retrospective chart review study for antihemophilic factor/VWF complex.[7] The sponsor claimed that indirect treatment comparison was not feasible due to a lack of reported data on patient characteristics, bleed severity, or types of surgery in the Lillicrap study (2002).[1] As such, the submitted model's efficacy estimates were based on estimates from different sources selected and compared naively (i.e., non-randomized and non-adjusted).

  As noted in the CADTH Clinical Review Report, confounding factors may affect the results significantly. Given the subjectivity of the hemostatic rating scale, their different study designs, and unclear homogeneity in patient and bleeding severity, the relative hemostatic efficacy cannot be determined with certainty. Further, even the naive comparison led to very similar absolute values (100% versus 96.5% to 98.6%). The clinical experts consulted by CADTH expected that the 2 therapies would be similar in terms of clinical efficacy.

  As noted previously, a key cost driver in both subgroups was treatment acquisition costs. Differences were driven by different assumptions regarding the dosing and administration duration expected with each product. Naive comparisons informed these differences. In most circumstances, a higher dose and more frequent administration was assumed for antihemophilic factor/VWF complex than for rVWF, with or without rFVIII, in both scenarios. However, due to the inability to ensure homogeneity in patient characteristics, disease severity, and bleeding severity between the clinical studies informing these model parameters, it was not clear that observed differences reported in these studies would be realized if treating an identical patient. The clinical experts indicated that in the absence of direct evidence, differences in half-life between these products would not likely impact dosing frequency unless treatment was required over an extended duration. The majority of patients would expect similar weight-based dosing between the 2 products.

  Another key cost driver for the economic analysis was the duration of hospitalization. In the on-demand bleeding setting, differences in the duration of hospitalization was assumed between products to manage the initial bleeding episode and a longer duration of hospitalization was further assumed in cases of uncontrolled bleeding. The sponsor assumed 1 and 2 fewer hospitalization days to manage the initial on-demand moderate and major bleed, respectively, in patients receiving rVWF, with or without rFVIII, compared with antihemophilic factor/VWF complex based on a naive comparison of Study 071001[6] versus observational studies.[5,7] This implies that there are cost offsets related to hospitalization that one can expect with rVWF, with or without rFVIII. As this is based on a naive comparison between different types of studies, clinical experts consulted by CADTH did not consider this appropriate given that both plasma protein products are intravenously administered, and they would not expect a difference in hospital days between these products. Furthermore, the observational studies informing the model were published in the early 2000s; since then, expected hospital stay lengths have shortened. In the perioperative management setting, the duration of hospitalization was based on the type of surgery. CADTH could not validate the hospitalization days modelled (i.e., 5 days for minor surgery and 9 days for major surgery).[4] The referenced study instead reported on a pooled result for hospitalization based on both settings (i.e., 4 days for minor surgery and 7 days for major surgery) that more closely aligns with the duration assumed by the sponsor for rVWF, with or without rFVIII (i.e., 3 days for minor surgery and 6.5 days for major surgery).[8] No clear justification was provided on why the model selected the upper limits for hospitalization for the comparator product and this approach resulted in lower costs associated with the rVWF, with or without rFVIII, strategy. While there is purported to be a difference in half-life between the products, the clinical experts indicated that, in the absence of higher quality evidence indicating otherwise, a difference in hospitalization days between plasma-derived VWF and rVWF is

speculative only. Unless demonstrated from comparative evidence, a similar number of hospitalization days is expected.

Lastly, SAEs were also obtained from different studies,[4-6,8] composed of different patient groups and types of diseases. This made it difficult to confidently evaluate the relative safety of each product.

- In light of the clinical experts' feedback, CADTH set the relative efficacy, dose, number of infusions and hospitalization days, and adverse events to be identical. Specifically, the dosing reported for antihemophilic factor/VWF complex was applied to rVWF using total IU/kg per event listed in the sponsor's submission, assuming no wastage as suggested by the CADTH clinical experts.

- **Missing comparator:** The comparator in the submitted economic model was antihemophilic factor/VWF complex. However, in consultation with the clinical experts, it was noted that another plasma-derived VWF product is used in Canada: human VWF and human coagulation FVIII (Wilate). This comparator was not considered in the economic model.
  - CADTH conducted an exploratory analysis that included this comparator based on pricing available in the US, and converted the price to Canadian dollars, using a relative price approach. In this analysis, the price of human VWF and human coagulation FVIII was assumed to be $1.10 per IU (see Appendix 1).
- **The use of US pricing as a proxy for a Canadian price:** The unit price for antihemophilic factor/VWF complex was derived from US government contract pricing, which might not reflect the actual costs in Canada. CADTH conducted a review of published literature and was unable to identify alternative Canadian pricing.
  - As no Canadian pricing is available for the comparator, CADTH conducted 2-way price reduction analyses to highlight how the interpretation of the cost-effectiveness of rVWF, with or without rFVIII, may evolve when varying the price for antihemophilic factor/VWF complex.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (see Table 5).

Table 5: Key Assumptions of the Submitted Economic Evaluation — Not Noted as Limitations to the Submission

Sponsor's key assumption	CADTH comment
The relative efficacy of rVWF is expected to be similar across the spectrum of severity of bleeding.	Appropriate. The clinical experts consulted by CADTH agreed with this assumption.
The time horizon in the model was assumed to be 8 days and 16 days in the on-demand and perioperative management settings, respectively. The time horizons were derived from the median duration of the treatment of a major bleed with plasma-induced VWF.	Appropriate given episodic nature and that treatment of 1 episode is not likely to influence future episodes.
Antihemophilic factor (recombinant) (Advate) was the FVIII product assumed to be of use in alignment with the sponsor's clinical trial.	Inappropriate but unlikely to impact the model. Antihemophilic factor (recombinant) (Advate) is a treatment that was phased out in Canada in 2016.[20] However, clinical experts consulted by CADTH did not expect differences in treatment response across rFVIII products.
Minor and moderate on-demand bleeds were assumed to be treated in a hemophilia clinic. Major on-demand bleeds were assumed to require hospitalization.	Appropriate, and consistent with care in Canada.

Sponsor's key assumption	CADTH comment
Patients undergoing minor or major surgery were assumed to be hospitalized for the duration of therapy. Patients undergoing oral surgery were assumed to visit a hemophilia clinic for the infusion.	Appropriate. According to clinical experts consulted, depending on bleed frequency or the need for prophylaxis, there is a possibility that patients could be trained for home infusion.
Subsequent therapy when initial treatment did not result in hemostasis included up-dosing of 50% for both treatment arms and hospitalization for the whole duration of uncontrolled bleed. All patients requiring further treatment had to undergo a FVIII assay test, platelet transfusion, and concomitant tranexamic acid.	While uncertain, this may be a reasonable assumption as no difference was assumed between treatment regimens. However, uncontrolled bleeding may not always be due to suboptimal VWF and may be influenced by severity of bleed and other factors.
Disutility of uncontrolled bleed was a linear combination of disutility of hospitalization, disutility of a bleed, and disutility of significant blood loss.	Likely inappropriate. By using an additive function, the assumption is that these events are independent. It is not clear that all of these individual outcomes are independent: bleed is likely correlated with significant blood loss while significant blood loss is likely correlated with hospitalization.
One hospitalization day was used as a proxy for the costs of SAE treatment.	Uncertain. This assumption might slightly bias toward rVWF ± rFVIII with a higher AE rate ([redacted]% vs. 1%); however, given the low AE rates, this may have a minor impact on the results.

AE = adverse event; FVIII = factor VIII; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; SAE = serious adverse event; VWF = von Willebrand factor.

Base-Case Results

CADTH undertook a stepped analysis, incorporating each change proposed in Table 6 into the sponsor's base case to highlight the impact of each change in Table 7 and Table 8.

Table 6: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None		
Changes to derive the CADTH base case		
1. Relative efficacy of achieving initial hemostasis	The efficacy estimate was based on a naive comparison of individual studies.[d,f,h]	The same efficacy (100%) was assumed for both therapies.[a]
2. Median dose	The median dose was obtained from individual studies.[c,d,e,g,h,i]	The same median dose was assumed based on experts' opinions. Dosing reported for antihemophilic factor/VWF complex was applied to rVWF using total IU/kg per event listed in the sponsor's submission.[b] According to the experts, the total doses for perioperative management were on the higher end but still within the acceptable range. See Table 22 and Table 23 in Appendix 4 for details.
3. Number of infusions and hospitalization days	The number of infusions or hospitalization days were modelled and based on assumptions or individual studies.[d,e,f,g]	No difference was assumed.
4. Adverse events	The rates of treatment-related SAEs were obtained from individual studies.[c,d,e,g]	No difference in adverse events was assumed.

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
CADTH base case	1 + 2 + 3 + 4	

rVWF = recombinant von Willebrand factor; SAE = serious adverse event; VWF = von Willebrand factor.

[a] Given that bleeding was assumed to be controlled in all patients, no subsequent therapy would be modelled.

[b] Clinical experts consulted by CADTH indicated that weight-based dosing is performed without wasting vial contents, so that the actual dose is plus or minus 10% of the weight-based calculation. It was assumed that there would be no wastage and that, across a large number of patients, actual use would approximate weight-based dosing for both rVWF and plasma-induced VWF.

[c] {REF: 4: Manucci et al. 2013 Prophylactic efficacy and pharmacokinetically guided dosing}

[d] {REF: 5: Gill et al. 2003 Successful treatment of urgent bleeding in vWD with factor VIII/VWF}

[e] {REF: 6 CSR Report 071001. A phase III clinical study}

[f] {REF: 7 Lilicrap et al. 2002: Efficacy and safety of}

[g] {REF: 8 Manucci e tal 2013: Pharmacokinetics and safety of a novel}

[h] {REF: 21 Peyvandi et al. 2019 Phase III study of recombinant}

[i] {REF:22 Gill et al. 2015 Hemostatic efficacy}

The CADTH base case was only able to compare differences in the acquisition cost between rVWF, with or without rFVIII, and antihemophilic factor/VWF complex as there is currently no direct comparison available to inform differences in relative efficacy, dosage, duration of administration (and thus, the disutilities associated with infusions or hospitalization days), and frequency of adverse events.

The dosage used to calculate the treatment acquisition cost was based on the dosage for antihemophilic factor/VWF complex listed in the economic model,[4,5] and applied to both the treatment under review and its comparators according to the feedback provided by the clinical experts consulted by CADTH. The dosage differed by patient characteristics (average weight and distribution of bleeds, and surgery types). The clinical experts consulted by CADTH indicated that the usual administration of VWF products is based on weight, but typically the entire vial is used (i.e., dosed to be close to the target IU/kg but may be slightly above or below the weight-based calculation by 10%), so wastage is not a factor. Averaged over a large number of patients, it was assumed that even though the IU per vial may differ slightly, the delivered IU/kg would be the same for both products. The proportion of FVIII co-treatment (11%) and the FVIII dosage required were the same as in the sponsor's model. Detailed calculations of the costs of treatment acquisition can be found in Appendix 4.

Of note, the actual blood product acquisition costs of plasma-derived VWF are unknown (confidential) and it is plausible that the true costs could be lower than the US prices used.

On-Demand Bleeding Subgroup

CADTH applied each change listed in Table 6 to the sponsor's base case and the effect of each individual change can be found in Table 7. The CADTH reanalysis resulted in rVWF, with or without rFVIII, being more expensive by $4,514. No difference is expected in utilities and, as such, is not reported here.

Table 7: Summary of the Stepped Analysis of the CADTH Reanalysis Results — On-Demand Bleeding Episode

Stepped analysis	Drugs	Total costs ($)	Total QALYs	ICER ($/QALYs)
Sponsor's base case	rVWF ± rFVIII[a]	6,135	0.0160	Dominant
	Antihemophilic factor/VWF complex	7,772	0.0158	—
CADTH reanalysis 1	rVWF ± rFVIII	6,143	0.0160	Dominant
	Antihemophilic factor/VWF complex	6,647	0.0159	—
CADTH reanalysis 2	rVWF ± rFVIII	11,099	0.0160	17,541,118
	Antihemophilic factor/VWF complex	7,794	0.0158	—
CADTH reanalysis 3	rVWF ± rFVIII	6,232	0.0159	Dominant
	Antihemophilic factor/VWF complex	7,794	0.0158	—
CADTH reanalysis 4	rVWF ± rFVIII	6,131	0.0160	Dominant
	Antihemophilic factor/VWF complex	7,784	0.0158	—
CADTH base case	rVWF ± rFVIII	10,857	—	Cost difference: $4,514
	Antihemophilic factor/VWF complex	6,344	—	—

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; VWF = von Willebrand factor.

Perioperative Management Subgroup

CADTH applied each change listed in Table 6 to the sponsor's base case. The effect of each individual change can be found in Table 7. The CADTH reanalysis resulted in rVWF, with or without rFVIII, being more expensive by $19,240. No difference is expected in utilities and, as such, is not reported here.

Table 8: Summary of the Stepped Analysis of the CADTH Reanalysis Results — Perioperative Management Setting

Stepped analysis	Drugs	Total costs ($)	Total QALYs	ICER ($/QALYs)
Sponsor's base case	rVWF ± rFVIII[a]	36,081	0.0286	30,997
	Antihemophilic factor/VWF complex	36,025	0.0271	—
CADTH reanalysis 1	rVWF ± rFVIII	35,172	0.0287	456,102
	Antihemophilic factor/VWF complex	34,496	0.0273	—
CADTH reanalysis 2	rVWF ± rFVIII	51,770	0.0287	10,191,519
	Antihemophilic factor/VWF complex	35,575	0.0272	—
CADTH reanalysis 3	rVWF ± rFVIII	37,260	0.0273	15,625,369
	Antihemophilic factor/VWF complex	35,575	0.0272	—
CADTH reanalysis 4	rVWF ± rFVIII	35,160	0.0287	Dominant

Stepped analysis	Drugs	Total costs ($)	Total QALYs	ICER ($/QALYs)
	Antihemophilic factor/VWF complex	35,565	0.0272	—
CADTH base case	rVWF ± rFVIII	46,830	—	Cost difference: $19,240
	Antihemophilic factor/VWF complex	27,590	—	—

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; VWF = von Willebrand factor.

Scenario Analysis Results

A two-way price reduction analysis was undertaken to determine what price rVWF would have to be in order to achieve a treatment acquisition cost similar to that of antihemophilic factor/VWF complex. As the current Canadian price for antihemophilic factor/VWF complex is unknown (the converted US price used was CA$0.92 per IU), the price of antihemophilic factor/VWF complex was similarly varied. Results for the on-demand bleeding subgroup and the perioperative management subgroup are shown in Table 9 and Table 10, respectively. A price reduction of 40% is required for rVWF to have treatment acquisition cost similar to that of antihemophilic factor/VWF complex in on-demand bleeding episodes and perioperative management, assuming that the price of antihemophilic factor/VWF complex in Canada is $0.92 per IU.

Table 9: Cost and Cost Savings of rVWF, $[a] — CADTH Price Reduction Analyses, On-Demand Bleeding Episode

		Price of antihemophilic factor/VWF complex					
		No reduction ($0.92/IU)	**10% reduction ($0.83/IU)**	**30% reduction ($0.64/IU)**	**50% reduction ($0.46/IU)**	**70% reduction ($0.28/IU)**	**90% reduction ($0.09/IU)**
Price of rVWF[b]	**No price reduction ($1.54/IU)**	4,514	5,148	6,417	7,685	8,954	10,223
	10% reduction ($1.39/IU)	3,452	4,086	5,355	6,624	7,892	9,161
	30% reduction ($1.08/IU)	1,328	1,962	3,231	4,500	5,769	7,037
	50% reduction ($0.77/IU)	(796)	(161)	1,107	2,376	3,645	4,914
	70% reduction ($0.46/IU)	(2,919)	(2,285)	(1,016)	252	1,521	2,790
	90% reduction ($0.15/IU)	(5,043)	(4,409)	(3,140)	(1,871)	(603)	666

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

[a] Values in parentheses denote cost savings associated with rVWF.

[b] Analysis assumes 11% of patients require rFVIII. The price of rFVIII remained fixed at $0.82 per IU.

Table 10: Cost and Cost Savings of rVWF, $ — CADTH Price Reduction Analyses, Perioperative Management Setting

		Price of antihemophilic factor/VWF complex					
		No reduction ($0.92/IU)	10% reduction ($0.83/IU)	30% reduction ($0.64/IU)	50% reduction ($0.46/IU)	70% reduction ($0.28/IU)	90% reduction ($0.09/IU)
Price of rVWF[a]	No price reduction ($1.54/IU)	19,240	21,999	27,517	33,035	38,553	44,071
	10% reduction ($1.39/IU)	14,622	17,381	22,899	28,417	33,935	39,452
	30% reduction ($1.08/IU)	5,385	8,144	13,662	19,180	24,698	30,216
	50% reduction ($0.77/IU)	(3,851)	(1,092)	4,426	9,944	15,462	20,979
	70% reduction ($0.46/IU)	(13,088)	(10,329)	(4,811)	707	6,225	11,743
	90% reduction ($0.15/IU)	(22,324)	(19,565)	(14,047)	(8,529)	(3,011)	2,506

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

Note: Values in parentheses denote cost savings associated with rVWF.

[a] Analysis assumes 11% of patients require rFVIII. The price of rFVIII remained fixed at $0.82 per IU.

Given uncertainties in the proportion of patients by types of bleeds or surgeries, subgroup analyses were conducted to understand the cost difference within each subgroup (i.e., minor bleed, moderate bleed, severe bleed, oral surgery, minor surgery, and major surgery). Scenario analysis including the consideration of an alternative plasma-derived VWF comparator (i.e., human VWF and human coagulation FVIII), varying the proportion of rVWF patients requiring rFVIII, and price reduction scenarios in which the costs of rFVIII were varied can be found in Appendix 4. In all subgroups, rVWF plus rFVIII was found to be more costly compared to antihemophilic factor/VWF complex.

When the comparator was instead human VWF and human coagulation FVIII, the cost difference of rVWF plus rFVIII was $3,272 and $13,842 for on-demand bleeding episodes and perioperative management, respectively. The cost difference was smaller due to the higher unit price per IU of product for human VWF and human coagulation FVIII. If 100% co-treatment of rFVIII was assumed, the cost difference increased from $4,514 to $6,443 for on-demand bleeding episodes, and from $19,240 to $22,530 for perioperative management. If no co-treatment with rFVIII was required, the cost difference decreased to $4,275 and $18,593 for on-demand bleeding episodes and perioperative management, respectively. In addition, if the unit cost of rFVIII was reduced by 75% (i.e., $0.21 per IU), the cost difference decreased from $4,514 to $4,335 for on-demand bleeding episodes, and from $19,240 to $18,755 for perioperative management if assuming 11% for co-treatment of rFVIII.

Issues for Consideration

- rVWF is indicated for the treatment of all adult patients with VWD under Health Canada's indication, which is different from the sponsor's reimbursement request in patients with severe VWD, or patients with mild or moderate VWD who are intolerant or do not respond to DDAVP. The clinical experts consulted by CADTH noted that rVWF should be reserved for patients who would be given plasma-derived factor concentrates and expected that

patients receiving DDAVP would not be considered for VWF replacement therapy. As per the CADTH clinical review, DDAVP is more appropriate for the treatment of minor bleeding and perioperative management of minor surgery. 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 would be considered. A scenario analysis was undertaken by the sponsor to address the reimbursement population. By assuming the same efficacy in the reimbursement population, the same results from the sponsor's base case hold. This appears appropriate and, given no differences expected in efficacy, the CADTH reanalyses results would similarly apply to the reimbursement-requested population.

- VWF products (both rVWF and plasma-induced VWF) are administered in terms of number of vials within 10% of the calculated dose required according to the clinical experts consulted by CADTH. As such, the exact treatment acquisition cost might be slightly different from CADTH's calculations.
- Among perioperative patients, clinical experts consulted by CADTH noted that rVWF would be administered 12 hours to 24 hours as well as 1-hour pre-operation in a clinical setting. This would mean additional administration scheduled pre-operatively compared to plasma-derived VWF product. This was not accounted for in the sponsor's model nor in the CADTH reanalysis. This may incur additional administration costs that have not been accounted for in the analyses, making rVWF, with or without FVIII, even more costly.
- Anti-VWF binding antibodies were detected in 1 patient (6.7%) in Study 071101. Given the lack of data, it is unknown if anti-VWF binding antibodies could exhibit clinically important effect either during the episode, or in future episodes. If so, there may be an impact on both clinical effectiveness and costs as a larger dose may be needed.
- According to patients' input, patients would like to see easier accessibly and administration such as self-infusion for future VWF treatments. Both rVWF and plasma-derived VWF require IV infusions at outpatient clinics and hospitals.
- There may be a benefit from a recombinant product compared to plasma-derived products in the instance of a novel emerging pathogen for which current pathogen inactivation techniques are ineffective; however, the probability of this occurring is unknown.

Overall Conclusions

CADTH found that the sponsor's base case included several assumptions that were favourable to rVWF but that were not supported by any comparative clinical evidence. There is currently no head-to-head clinical trial comparing rVWF and plasma-derived VWF. All model inputs indicating a difference between rVWF, with or without rFVIII, and plasma-derived VWF products (i.e., relative efficacy, administration [number of infusions and hospitalization days], total median dose, and adverse events), were based on naive comparison between different types of studies without adjusting for any potential confounders such as patient characteristics or disease types. The clinical experts consulted by CADTH indicated that, in the absence of comparative evidence, they would expect relative efficacy, safety, dose, and duration of use to be the same between rVWF and plasma-derived VWF products.

As such, CADTH undertook reanalyses to address this limitation by setting the efficacy, safety, and resource utilization to be identical. In the CADTH base-case reanalysis, where only blood product acquisition cost was considered, rVWF, with or without FVIII, was found to be more costly by $4,514 for on-demand bleeding episodes and by $19,240 for perioperative management compared with antihemophilic factor/VWF complex. This was primarily due to the higher unit cost of rVWF ($1.54 versus $0.92, respectively) and the

potential co-treatment of rFVIII. A price reduction of 40% is required for rVWF to have a treatment acquisition cost that is similar to that of antihemophilic factor/VWF complex. CADTH further undertook a scenario analysis including 100% use of rFVIII and human VWF and human coagulation FVIII as a potential comparator. If 100% use of rFVIII was assumed, the cost difference increased. In another scenario analysis capturing an alternative comparator, human VWF and human coagulation FVIII, the cost difference for rVWF, with or without FVIII, decreased due to the higher unit price per IU assumed for human VWF and human coagulation FVIII. The CADTH appraisal is uncertain given the unknown Canadian price for plasma protein products. A greater price reduction would be required if the actual cost of plasma-derived VWF in Canada were lower than the assumed price ($0.92 per IU), if the price of rFVIII was higher than assumed ($0.82 per IU), and/or if a greater proportion of patients required rFVIII dosed concomitantly with rVWF.

Appendix 1: Cost Comparison Table

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts. Comparators may be recommended (appropriate) practice or actual practice. Existing product listing agreements are not reflected in the table and, as such, the table may not represent the actual costs to public drug plans.

Table 11: CADTH Cost Comparison Table for the Treatment of Bleeding in von Willebrand Disease — On Demand

Treatment	Dose form	Strength	Price (per IU)	Recommended dosage	Average daily treatment cost[d]
VWF, recombinant (Vonvendi)	**Lyophilized powder for solution in a single-use vial** **Intravenous injection**	**650 IU** **1,300 IU**	**$1.5429[a]** **$1.5429[a]**	***Minor*** **Initial dose 40 IU/kg to 50 IU/kg, then 40 IU/kg to 50 IU/kg every 8 hours to 24 hours if deemed clinically necessary** ***Major*** **Initial dose 50 IU/kg to 80 IU/kg, then 40 IU/kg to 60 IU/kg every 8 hours to 24 hours for 2 days to 3 days**	***Minor*[b]** **$5,014.43 to $17,049.05[c]** ***Major*[b]** **$6,017.31 to $22,063.47[c]**
Plasma-derived FVIII and VWF					
Antihemophilic factor/VWF complex (human) (Humate-P)	Reconstituted, intravenous injection in a single-use vial	250/600 IU 500/1,200 IU 1,000/2,400 IU	$0.92[d]	*Minor* 40 IU/kg to 50 IU/kg, every 8 hours to 24 hours *Major* 40 IU/kg to 80 IU/kg every 8 hours to 12 hours for 3 days, then 40 IU/kg to 60 IU/kg daily for up to 7 days of treatment	*Minor*[e] $2,760.00 to $9,936.00 *Major*[f] $5,520.00 to $15,546.00
Human VWF and human coagulation FVIII (Wilate)	Powder and solvent for solution for injection	500 and 500 IU 1,000 and 1,000 IU	$1.10[d]	*Minor* Initial dose 20 IU/kg to 40 IU/kg, then 20 IU/kg to 30 IU/kg every 12 hours to 24 hours *Major* Initial dose 40 IU/kg to 60 IU/kg, then 20 IU/kg to 40 IU/kg every 12 hours to 24 hours	*Minor*[h] $1,650.00 to $5,550.00 *Major*[h] $3,300.00 to $7,700.00

Treatment	Dose form	Strength	Price (per IU)	Recommended dosage	Average daily treatment cost[d]
Anti-hemorrhagic factor					
DDAVP	Solution, for IN administration	0.1 mg/mL	$52.0375	0.3 mcg/kg, max. dose of 20 mcg	$52.04 (max.: $104.08)
	Metered nasal spray	10 mcg			

Note: All calculations assume a standard patient weight of 70 kg.

DDAVP = desmopressin; FVIII = factor VIII; IN= intranasal; max. = maximum; VWF = von Willebrand factor.

[a] This is based on the sponsor's submitted price.[1]

[b] Day 1: Low dosage is based on initial low-dose range only; high dosage is based on initial high dose plus 1-time subsequent low dose (every 24 hours). Day 2 and beyond: Low dosage is based on a single low dose; high dosage is based on subsequent dosing (every 8 hours).

[c] Daily treatment costs for recombinant VWF do not include the additional costs of concomitant treatment with recombinant FVIII.

[d] CADTH calculated cost using the relative pricing of Wilate and Vonvendi as reported in Snyder et al. (2019).[23] Specifically, this was calculated according to the following formula: (cost of Humate-P [US$]/cost of Vonvendi [US$])*cost of Vonvendi (CA$) = 1.57/2.38*1.5429.

[e] Day 1: Low dosage is based on the minimum dose only; high dosage is based on the maximum dose only.

[f] Day 2 and beyond: [i]Low dosage consists of 40 IU/kg every 12 hours; high dosage consists of 80 IU/kg every 8 hours, for 3 days, as per the dosing regimen.

[g] FVIII/VWF activity corresponds to IU/vial; for example, 250/600 IU is 250 FVIII and 600 IU VWF per vial.

[h] Day 1: Low dosage is based on the initial low dose; high dosage is based on the initial high dose plus subsequent dosing (every 8 hours). Day 2 and beyond: Low dosage consists of 40 IU/kg every 12 hours; high dosage consists of 80 IU/kg every 8 hours, for 3 days, as per dosing regimen.

Table 12: CADTH Cost Comparison Table for the Perioperative Management of von Willebrand Disease

Treatment	Dose form	Strength	Price (per IU)	Recommended dosage (VWF:RCo target peak plasma level [IU/dL])[a, b,c]	Daily treatment cost
VWF, recombinant (Vonvendi)	**Lyophilized powder for solution in a single-use vial** **Intravenous injection**	**650 IU** **1,300 IU**	**$1.5429[d]** **$1.5429[d]**	***Minor*** **50 IU/dL to 60 IU/dL** ***Major*** **100 IU/dL** **Dose adjusted every 12 hours to 48 hours**	***Minor*** **$2,005.77 to $3,008.66[e]** ***Major*** **$5,014.43[e]**
Plasma-derived FVIII and VWF					
Antihemophilic factor/VWF (human) complex (Humate-P)	Reconstituted, intravenous injection in a single-use vial	250/600 IU 500/1,200 IU 1000/2,400 IU	$0.92[c]	*Minor* 50 IU/dL to 60 IU/dL *Major* 100 IU/dL Dose adjusted every 8 hours to 12 hours	*Minor* $1,104.00 to $1,656.00 *Major* $2,760.00
Human VWF and human coagulation FVIII (Wilate)	Powder and solvent for solution for injection	500 and 500 IU 1,000 and 1,000 IU	$1.10[f]	*Minor* 30 IU/dL to 60 IU/dL *Major* 80 IU/dL to 100 IU/dL Dose adjusted every 12 hours to 24 hours.[g]	*Minor* $1,650.00 *Major* $3,300.00

FVIII = factor VIII; IU = international units; VWF = von Willebrand factor; VWF:RCof = von Willebrand factor: ristocetin cofactor.

[a] The initial (loading) dose calculation uses the minimum target VWF:RCo level indicated in the range (IU/dL), baseline VWF:RCo level 20 IU.DL, IVR of 2.0 (IU/dL) ÷ (IU/kg), Δ of 80 IU/dL, and a body weight of 70 kg as per product monograph for both Vonvendi and Humate-P. Formula: Δ* VWF:RCo × BW (kg) ÷ IVR # = IU.

[b] This assumes that the initial maintenance dose for the prevention of excessive bleeding during and after surgery should be half the loading dose, irrespective of additional dosing required to meet FVIII:C targets, as per the Humate-P product monograph.[c] FVIII:C levels should be assessed within 3 hours prior to initiating the surgical procedure. If the levels are at the recommended minimum target levels, administer a dose of Vonvendi alone within 1 hour prior to the procedure to maintain adequate levels of VWF:RCo and FVIII:C (Table 2). If the FVIII:C levels are below the recommended minimum target levels, administer Vonvendi in addition to rFVIII to raise VWF:RCo and FVIII:C.

[d] Based on the sponsor's submitted price.[1]

[e] Daily rFVIII.

[f] CADTH treatment costs for von Willebrand factor, recombinant does not include the additional costs of concomitant treatment with calculated cost using relative pricing of Wilate and Vonvendi as reported in [23]

[g] EU product description was used in place of the Canadian Wilate product monograph.[24]

Table 13: List of Coagulation Factor VIII Products for On-Demand Bleeding, Available through Canadian Blood Services

Treatment	Dose form	Strength	Price [aa]	Recommended dosage, based on required FVIII activity level (% or IU/dL) *and/or* dose (IU/kg)[b]
Antihemophilic factor (recombinant, pegylated) (Adynovate)	Powder for IV injection	250 IU 500 IU 750 IU 1,000 IU 1,500 IU 2,000 IU 3,000 IU	NA	FVIII level 20% to 40% every 12 hours to 24 hours until bleeding episode is resolved
Antihemophilic factor (recombinant BDD, Fc-fusion protein) (Eloctate)	Powder for injection	250 IU 500 IU 750 IU 1,000 IU 1,500 IU 2,000 IU 3,000 IU	NA	*Minor and moderate:* FVIII level 40% to 60%; or 20 IU/kg to 40 IU/kg every 24 hours to 48 hours until bleeding is resolved *Major:* FVIII level 80% to 100%; or 40 IU/kg to 50 IU/kg every 12 hours to 24 hours until bleeding is resolved
Antihemophilic factor (recombinant, BDD, pegylated) (Jivi)	Vial	250 IU 500 IU 1,000 IU 2,000 IU 3,000 IU	NA	*Minor:* FVIII level 20% to 40%; or 10 IU/kg to 20 IU/kg every 24 hours to 48 hours until bleeding is resolved *Moderate:* FVIII level 30% to 60%; or 15 IU/kg to 30 IU/kg every 24 hours to 48 hours until bleeding is resolved *Major:* FVIII level 60% to 100%; or 30 IU/kg to 50 IU/kg every 8 hours to 24 hours until bleeding is resolved
Antihemophilic factor (recombinant) (Kovaltry)	Vial	250 IU 500 IU 1,000 IU 2,000 IU 3,000 IU	NA	*Minor:* FVIII level 20% to 40% (or single dose of 10 IU/kg to 30 IU/kg) every 12 hours to 24 hours, at least 1 day, until bleeding episode is resolved *Moderate to major:* FVIII level 30% to 60%; or 10 IU/kg to 30 IU/kg every 12 hours to 24 hours, 3 days to 4 days or more as required, until bleeding episode is resolved
Antihemophilic factor (recombinant, BDD) (Nuwiq)	Powder and solvent for IV injection	250 IU 500 IU 1,000 IU 2,000 IU 2,500 IU 3,000 IU 4,000 IU	NA	*Minor:* FVIII level 20% to 40% every 12 hours to 24 hours until bleeding episode is resolved *Moderate to major:* FVIII level 30% to 60% every 12 hours to 24 hours for 3 days to 4 days or more, until pain and disability are resolved
Antihemophilic factor (recombinant, BDDrFVIII) (Xyntha)	Powder in vial	250 IU 500 IU 1,000 IU 2,000 IU	NA	*Minor:* FVIII level 20% to 40% every 12 hours to 24 hours as necessary, or at least 1 day, until resolved *Moderate:* FVIII level 30% to 60% every 12 hours to 24 hours for 3 days to 4 days, until adequate hemostasis is achieved *Major:* FVIII level 60% to 100% every 8 hours to 24 hours, until bleeding is resolved or until hemostasis is achieved

BDD = B-domain deleted; BDDrFVIII = B-domain deleted recombinant factor VIII; FVIII = factor VIII; NA = not available.

[a] Prices are not presented given that the Canadian list price is not available for these products.

[b] Recommended dosage is based on required FVIII activity level (% or IU/dL) and/or dose (IU/kg), as indicated in the respective product monograph.

Note: Advate is not available in Canada and is excluded from this table.

Table 14: List of Coagulation FVIII Products for Perioperative Management

Treatment	Dose form	Strength	Price[a]	Recommended dosage (based on required FVIII activity level (% or IU/dL) *and/or* dose (IU/kg)[b]
Antihemophilic factor (recombinant, pegylated) (Adynovate)	Lyophilized powder for solution	250 IU 500 IU 1,000 IU 2,000 IU	NA	*Minor surgery:* FVIII level 60% to 100%, or 30 IU/kg to 50 IU/kg. Single dose within 1 hour before surgery; thereafter, 8 hours to 24 hours for maintenance of FVIII levels at 30% to 60% or longer as deemed clinically necessary *Major surgery:* FVIII level 80% to 120% (pre- and post-operative), or 40 IU/kg to 60 IU/kg. Single dose within 1 hour before surgery; thereafter, every 8 hours to 24 hours to maintain FVIII levels at ≥ 80%, day 1 to day 3, then ≥ 50% for day 4 to day 7, and ≥ 30% until bleeding stops and healing is achieved
Antihemophilic factor (recombinant, single chain) (Afstyla)	Lyophilized powder with diluent for reconstitution	200 IU 500 IU 1,000 IU 1,500 IU 2,000 IU 2,500 IU 3,000 IU	NA	*Minor surgery:* FVIII level 30% to 60%, or 15 IU/kg to 30 IU/kg every 24 hours for at least 1 day, until healing is achieved *Major surgery:* FVIII level 80% to 100% (pre- and post-operative), or 40 IU/kg to 50 IU/kg every 8 hours to 24 hours until adequate wound healing, and at least another 7 days to maintain FVIII activity of 30% to 60%
Antihemophilic factor (recombinant BDD, Fc-fusion protein) (Eloctate)	Lyophilized powder for solution	250 IU 500 IU 750 IU 1,000 IU 1,500 IU 2,000 IU 3,000 IU	NA	*Minor surgery:* FVIII level 50% to 80%, or 25 IU/kg to 40 IU/kg. Single infusion followed by repeat dose every 24 hours as needed to control bleeding *Major surgery:* FVIII level 80% to 120%, or initial dose of 40 IU/kg to 60 IU/kg (pre-operative), followed by 40 IU/kg to 50 IU/kg (repeat dose) after 8 hours to 24 hours, every 24 hours for maintenance, as required
Antihemophilic factor (recombinant, BDD, pegylated) (Jivi)	IV injection	250 IU 500 IU 1,000 IU 2,000 IU 3,000 IU	NA	*Minor surgery:* FVIII level 30% to 60% (pre- and post-operative), or 15 IU/kg to 30 IU/kg for at least 1 day, until healing is achieved *Moderate surgery:* FVIII level 80% to 100% (pre- and post-operative), or 40 IU/kg to 40 IU/kg until wound healing is adequate, followed by another 7 days to maintain FVIII level 30% to 60%
Antihemophilic factor (recombinant) (Kovaltry)	IV injection	250 IU 500 IU 1,000 IU 2,000 IU 3,000 IU	NA	*Minor surgery:* FVIII level 30% to 60% every 24 hours for at least 1 day, until hemostasis is achieved *Major surgery:* FVIII level 80% to 100% (pre- and post-operative) every 8 hours to 24 hours for at least 7 days, until wound healing is adequate
Antihemophilic factor (recombinant, BDD) (Nuwiq)	Powder and solvent for solution for IV injection	250 IU 500 IU 1,000 IU 2,000 IU	NA	*Minor surgery:* FVIII level 30% to 60% every 24 hours for at least 1 day, until healing is achieved

Treatment	Dose form	Strength	Price[a]	Recommended dosage (based on required FVIII activity level (% or IU/dL) *and/or* dose (IU/kg)[b]
		2,500 IU 3,000 IU 4,000 IU		*Major surgery:* FVIII level 80% to 100% every 8 hours to 24 hours for at least 7 days, until wound healing is adequate
Antihemophilic factor (recombinant, BDDrFVIII) (Xyntha)	Lyophilized powder for reconstitution in a single-use vial	250 IU 500 IU 1,000 IU 2,000 IU	NA	*Minor surgery:* FVIII level 20% to 40% every 12 hours to 24 hours as necessary, or at least 1 day, until resolved *Moderate surgery:* FVIII level 30% to 60% every 12 hours to 34 hours for 3 days to 4 days until adequate hemostasis is achieved *Major surgery:* FVIII level 60% to 100% every 8 hours to 24 hours until bleeding is resolved or until hemostasis is achieved
Antihemophilic factor (recombinant) (Zonovate)	Lyophilized powder for reconstitution in a single-use vial	250 IU 500 IU 1,000 IU 1,500 IU 2,000 IU 3,000 IU	NA	*Minor surgery:* FVIII level 30% to 60% every 24 hours or at least 1 day, until healing is achieved *Major surgery:* FVIII level 80% to 100% every 8 hours to 24 hours until wound healing is adequate, and at least another 7 days thereafter

BDD = B-domain deleted; BDDrFVIII = B-domain deleted recombinant factor VIII; FVIII = factor VIII; NA = not available.

[a] Prices are not presented given that the Canadian list price is not available for these products.

[b] Recommended dosage is based on required FVIII activity level (% or IU/dL) and/or dose (IU/kg), as indicated in the respective product monograph.

Note: Advate is not available in Canada and is excluded from this table.

Appendix 2: Submission Quality

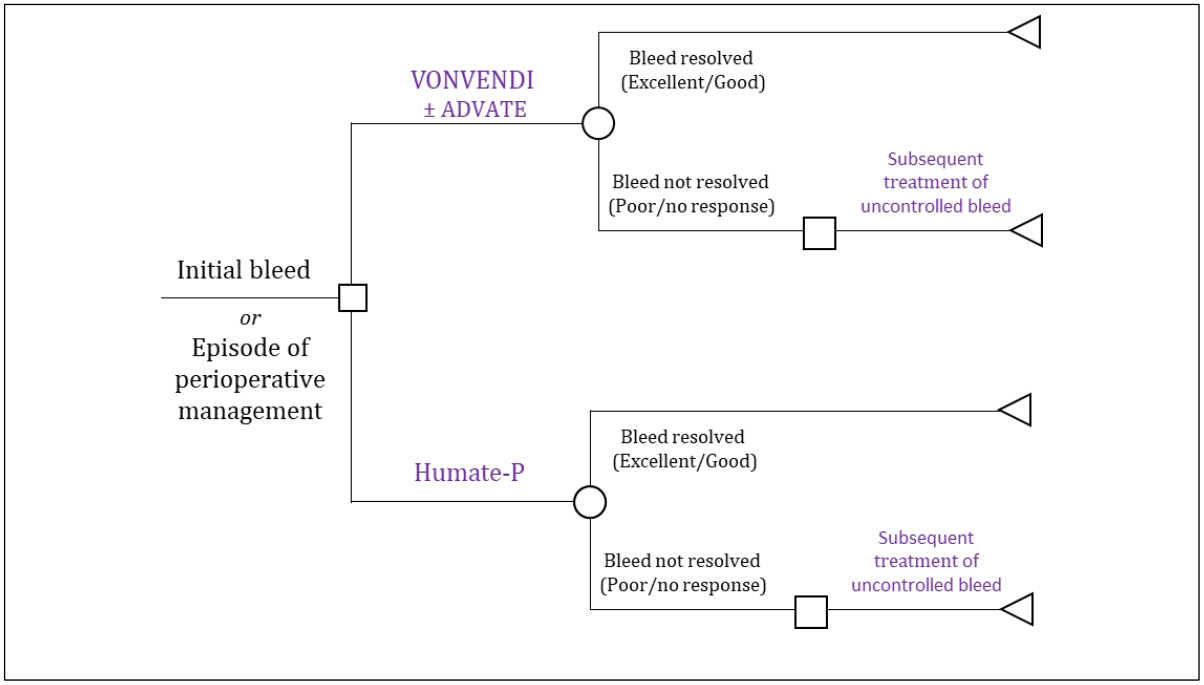
Table 15: Submission Quality

Description	Yes	No	Comments
Population is relevant, with no critical intervention missing and no relevant outcome missing	☐	☒	The sponsor used antihemophilic factor/VWF complex Humate-P as the plasma-derived VWF comparator in the model. However, human VWF and human coagulation FVIII (Wilate) is also commonly used in Canada.
Model has been adequately programmed and has sufficient face validity	☒	☐	
Model structure is adequate for decision problem	☒	☐	
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	☒	☐	
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	☐	☒	Most sensitivity analyses undertaken in the submission were deterministic.
Submission was well organized and complete, and information was easy to locate (clear and transparent reporting, technical documentation available in enough details)	☒	☐	The report was generally well organized. However, further details are required on how the 11% of FVIII co-administration was derived as it is quite different from the data presented in the CADTH Clinical Review Report.

FVIII = factor VIII; VWF = von Willebrand factor.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Figure 1: Model Structure



Source: Sponsor's Pharmacoeconomic Submission.[1]

Detailed Total Therapy Costs of the Sponsor's Base Case

Table 16: Total Therapy Costs of rVWF Versus Antihemophilic Factor/VWF Complex (On-Demand Bleeding Episode Subgroup)

Drugs	Distribution (%)[a]	Total IU/kg (VWF)[a, b]	Total IU/kg (FVIII)[a]	Total cost ($)[c]
Minor bleed				
rVWF + rFVIII	0.642	43.3	33.5	5,295
Plasma-derived VWF		57.4	NA	3,999
Moderate bleed				
rVWF	0.321	52.7	36.9	6,419
Plasma-derived VWF		134.7	NA	9,385
Major bleed				
rVWF + rFVIII	0.037	100.0	39.0	11,975
Plasma-derived VWF		[redacted]	NA	20,032

FVIII = factor VIII; NA = not available; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; VWF = von Willebrand factor.

[a] Obtained from sponsor's model, based on Study 071001.[6]

[b] Obtained from sponsor's model, based on Gill et al. (2003).[5]

[c] Table 26 in Sponsor's Pharmacoeconomic Submission.

Table 17: Total Therapy Costs of rVWF Versus Antihemophilic Factor/VWF Complex — Perioperative Management Subgroup

Drugs	Distribution (%)[a]	Total IU/kg (VWF)[a, b]	Total IU/kg (FVIII)[a]	Total cost ($)[c]
Oral surgery				
rVWF + rFVIII	0.067	108.4	[redacted]	13,569
Plasma-derived VWF		64.0	NA	4,615
Minor surgery				
rVWF	0.267	119.9	[redacted]	15,147
Plasma-derived VWF		292.5	NA	21,055
Major surgery				
rVWF + rFVIII	0.667	307.6	[redacted]	37,951
Plasma-derived VWF		448.5	NA	32,340

FVIII = factor VIII; NA = not applicable; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; VWF = von Willebrand factor.

[a] Obtained from sponsor's model, based on Study 071101.

[b] Obtained from sponsor's model, based on Mannucci et al. (2013);[4] see Table 29 in Sponsor's Pharmacoeconomic Submission.

[c] Table 30 in Sponsor's Pharmacoeconomic Submission.

Detailed Results of the Sponsor's Base Case

Table 18: Disaggregated Model Results in On-Demand Bleeding Episode — Costs, CA$

	rVWF ± rFVIII	Antihemophilic factor/ VWF complex	Incremental costs
Acquisition costs	5,885	6,306	(421)
Administration costs	228	316	(88)
Treatment of uncontrolled bleed costs	11	1,141	(1,131)
SAE costs	12	9	2
Total costs	6,135	7,772	(1,637)

rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; SAE = serious adverse event; VWF = von Willebrand factor.

Source: Sponsor's Pharmacoeconomic Submission.[1]

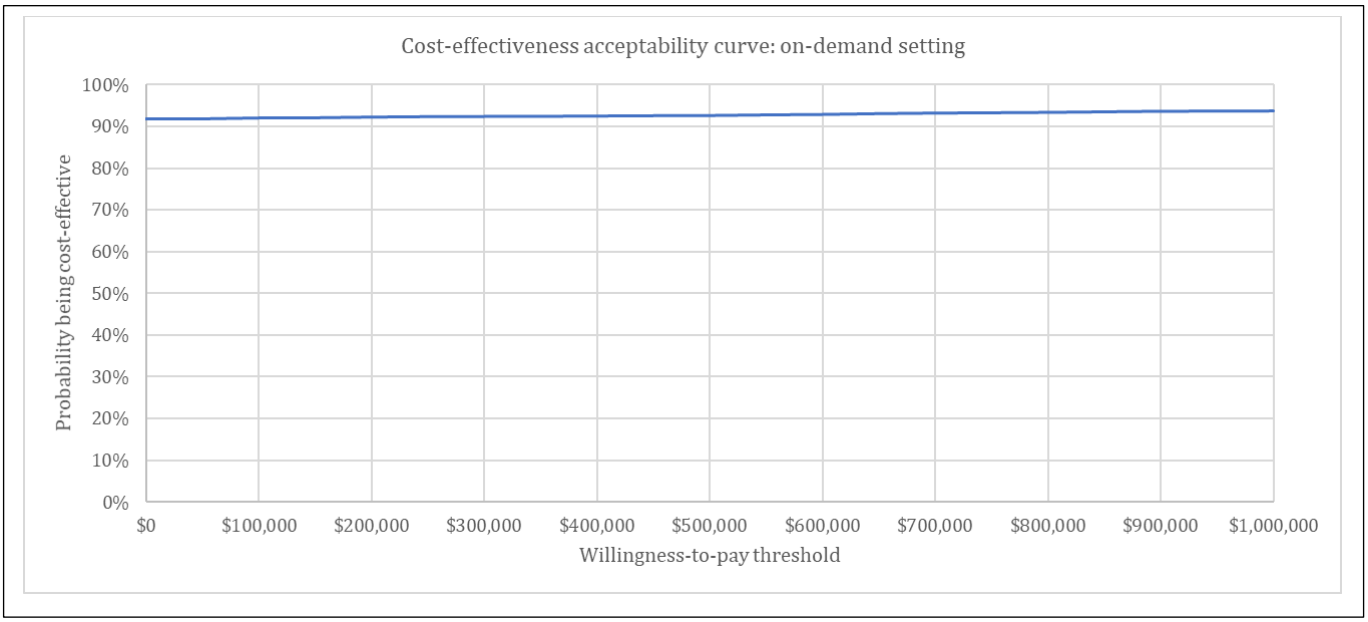
Table 19: Disaggregated Model Results in On-Demand Bleeding Episode — QALYs

	rVWF ± rFVIII	Antihemophilic factor/ VWF complex	Incremental QALY
Baseline utility	0.0161050	0.0161050	0.0000000
Disutility of administration	–0.0001339	–0.0002030	0.0000691
Disutility of uncontrolled bleed	–0.0000007	–0.0001183	0.0001176
Disutility of SAE	–0.0000036	–0.0000028	–0.0000008
Total QALYs	**0.0159668**	**0.0157809**	**0.0001859**

QALY = quality-adjusted life-year; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; SAE = serious adverse event; VWF = von Willebrand factor.

Source: Sponsor's Pharmacoeconomic Submission.[1]

Figure 2: Cost-Effectiveness Acceptability Curve — On-Demand Bleeding Episode



Source: Sponsor's Pharmacoeconomic Submission.[1]

Table 20: Disaggregated Model Results in Perioperative Management Setting — Costs, CA$

	rVWF ± rFVIII	Antihemophilic factor/ VWF complex	Incremental costs
Acquisition costs	30,522	27,768	2,754
Administration costs	5,027	7,166	(2,139)
Treatment of uncontrolled bleed costs	520	1,081	(561)
SAE costs	12	9	2
Total costs	36,081	36,025	49

rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; SAE = serious adverse event; VWF = von Willebrand factor.

Source: Sponsor's Pharmacoeconomic Submission.[1]

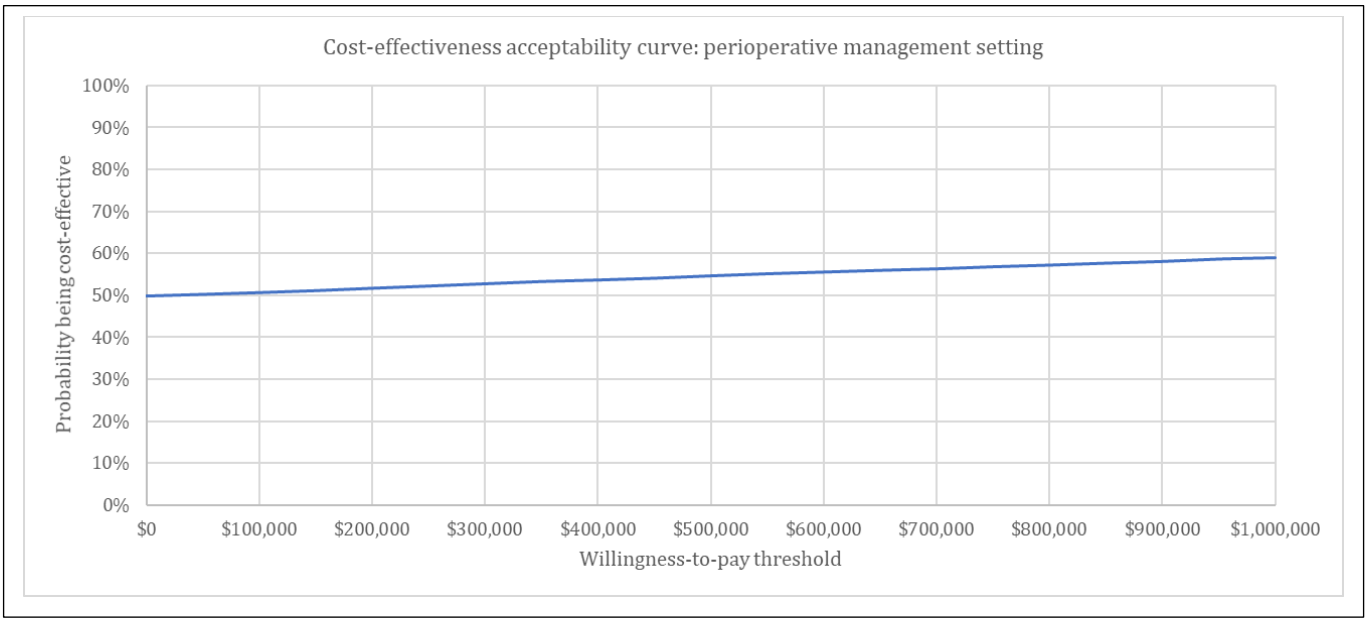
Table 21: Disaggregated Model Results in Perioperative Management Setting — QALYs

	rVWF ± rFVIII	Antihemophilic factor/VWF complex	Incremental QALY
Baseline utility	0.0322100	0.0322100	0.0000000
Disutility of administration	–0.0035402	–0.0050394	0.0014992
Disutility of uncontrolled bleed	–0.0000322	–0.0001089	0.0000767
Disutility of SAE	–0.0000036	–0.0000028	–0.0000008
Total QALYs	**0.028634**	**0.027059**	**0.001575**

QALY = quality-adjusted life-year; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; SAE = serious adverse event; VWF = von Willebrand factor.

Source: Sponsor's Pharmacoeconomic Submission.[1]

Figure 3: Cost-Effectiveness Acceptability Curve in Perioperative Management Setting



Source: Sponsor's Pharmacoeconomic Submission.[1]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Detailed Calculation of the CADTH Base Case

Table 22: Acquisition Costs of rVWF Versus Antihemophilic Factor/VWF Complex — On-Demand Bleeding Episode Subgroup

Drugs	Distribution (%)[a]	Total IU/kg (VWF)[b]	Total IU/kg (FVIII)[a]	Total dose of VWF product, IU[c]	Total dose of rFVIII[c]	Total cost ($)[d]
Minor bleed						
rVWF + rFVIII	0.642	57.4	33.5	4,362	2,546	6,948
Plasma-derived VWF			NA		NA	4,013
Moderate bleed						
rVWF	0.321	134.7	36.9	10,237	2,804	16,018
Plasma-derived VWF			NA		NA	9,418
Major bleed						
rVWF + rFVIII	0.037	[redacted]	39	21,850	2,964	33,916
Plasma-derived VWF			NA		NA	20,102

FVIII = factor VIII; NA = not applicable; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; VWF = von Willebrand factor.

[a] Obtained from sponsor's model, based on Study 071001.[6]

[b] Obtained from sponsor's model, based on Gill et al. (2003).[5]

[c] Assumes patient weight of 76 kg and an equal number of infusions per bleeding event.

[d] Total cost calculated is based on cost per IU; no wastage was considered. Clinical experts consulted by CADTH indicated that weight-based dosing is performed without wasting vial contents, so that actual dose is plus or minus 10% of the weight-based calculation. It was assumed that there would be no wastage and that, across a large number of patients, actual use would approximate weight-based dosing for both rVWF and plasma-induced VWF.

Weighted total cost of rVWF, with or without rFVIII = 0.642*$6,948 + 0.321*$16,018 + 0.037*$33,916 = $10,857

Weighted total cost of antihemophilic factor/VWF complex = 0.642*$4,013 + 0.321*$9,418 + 0.037*$20,102 = $6,344

Cost difference = $10,857 – $6,344 = **$4,514**

Table 23: Acquisition Costs of rVWF Versus Antihemophilic Factor/VWF Complex — Perioperative Management Subgroup

Drugs	Distribution (%)[a]	Total IU/kg (VWF)[b]	Total IU/kg (FVIII)[a]	Total dose of VWF product, IU[c]	Total dose of rFVIII[c]	Total cost ($)[d]
Oral surgery						
rVWF + rFVIII	0.067	64	[redacted]	5,030	4,873	8,186
Plasma-derived VWF			NA		NA	4,628
Minor surgery						
rVWF + rFVIII	0.267	292.5	[redacted]	22,991	6,995	36,036
Plasma-derived VWF			NA		NA	21,151
Major surgery						
rVWF + rFVIII	0.667	448.5	[redacted]	35,252	7,467	54,962
Plasma-derived VWF			NA		NA	32,432

FVIII = factor VIII; NA = not applicable; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; VWF = von Willebrand factor.

[a] Obtained from sponsor's model, based on Study 071101.

[b] Obtained from sponsor's model, based on Mannucci et al. (2013);[4] see Table 29 in Sponsor's Pharmacoeconomic Submission.

[c] Assumes patient weight of 78.6 kg and an equal number of infusions.

Weighted total cost of rVWF, with or without rFVIII = 0.067*$8,186 + 0.267*$36,036 + 0.667*$54,962 = $46,830

Weighted total cost of antihemophilic factor/VWF complex = 0.067*$4,628 + 0.267*$21,151 + 0.667*$32,432 = $27,590

Cost difference = $46,830 – $27,590 = **$19,240**

Additional Subgroup Analyses

CADTH also undertook several subgroup analyses by different severity of bleeds and types of surgeries (Table 24 and Table 25). The FVIII doses were also tested according to the clinical experts' opinion assuming all patients are given rFVIII. Specifically, in the perioperative population, no FVIII co-treatment was assumed for oral surgeries, and half FVIII dose was assumed for minor surgeries. Furthermore, the comparator human VWF and human coagulation FVIII (Wilate) is another plasma-derived VWF product available in Canada and its acquisition cost was also compared to those of rVWF, with or without rFVIII, using the same dose as the CADTH base case.

Table 24: Additional Analyses — On-Demand Bleeding Episode Subgroup

	ICERs for rVWF vs. antihemophilic factor/VWF complex	
	Sponsor base case (ICER, $ per QALY)	**CADTH reanalysis (cost difference of acquisition cost, $)**
Base case	Dominant	4,514
Minor bleed subgroup	1,237,341	2,934
Moderate bleed subgroup	Dominant	6,600
Major bleed subgroup	Dominant	13,814
Scenario analysis: 100% rFVIII	1,522,752	6,443
Scenario analysis: 0% rFVIII	Dominant	4,275
Scenario analysis: rVWF vs. Wilate ($1.10/IU)	—	3,272

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; vs. = versus; VWF = von Willebrand factor.

Table 25: Additional Analyses — Perioperative Management Subgroup

	ICERs for rVWF vs. antihemophilic factor/VWF complex	
Subgroups	**Sponsor base case (ICER)**	**CADTH reanalysis (cost difference of acquisition cost)**
Base case	30,997	19,240 (19,126 with adjusted rFVIII)[a]
Oral surgery subgroup	Dominated	3,558 (3,119 without rFVIII)
Minor surgery subgroup	Dominant	14,885 (14,570 with half rFVIII)
Major surgery subgroup	1,189,452	22,530
Scenario analysis: 100% rFVIII	Dominant	24,476
Scenario analysis: 0% rFVIII	Dominant	18,593
Scenario analysis: rVWF vs. Wilate ($1.10/IU)	—	13,842

FVIII = factor VIII; ICER = incremental cost-effectiveness ratio; rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; vs. = versus; VWF = von Willebrand factor.

[a] This is the dosage suggested by clinical experts who CADTH consulted; specifically, there is no FVIII for oral surgery and 1 infusion of FVIII for minor surgery.

Furthermore, since the actual cost of rFVIII in Canada was not available, 3 price scenarios (with 25%, 50%, and 75% price reductions) were undertaken to vary the cost of rFVIII used in the sponsor's submission. The results are reported in Table 26 and Table 27 for the on-demand bleeding subgroup and the perioperative subgroup, respectively.

Table 26: Price Reduction of rFVIII — On-Demand Bleeding Episode

	Total cost of rFVIII	Total cost of rVWF (assuming 11% rFVIII)	Cost difference (rVWF – antihemophilic factor/VWF complex)
No price reduction ($0.82/IU)	2,168	10,857	4,514
25% reduction ($0.62/IU)	1,626	10,798	4,454
50% reduction ($0.41/IU)	1,084	10,738	4,394
75% reduction ($0.21/IU)	542	10,678	4,335

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

Table 27: Price Reduction of rFVIII — Perioperative Management Setting

	Total cost of FVIII	Total cost of rVWF (assuming 11% rFVIII)	Cost difference (rVWF – antihemophilic factor/VWF complex)
No price reduction ($0.82/IU)	5,883	46,830	19,240
25% reduction ($0.62/IU)	4,412	46,668	19,078
50% reduction ($0.41/IU)	2,942	46,506	18,917
75% reduction ($0.21/IU)	1,471	46,344	18,755

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

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Key take-aways of the budget impact analysis

- CADTH identified the following key limitations with the sponsor's analysis:
  - There is uncertainty in the eligible population size and the expected use of VWF replacement products.
  - The analysis assumed a lower dose of rVWF based on non-comparative evidence.
  - Some inputs were not aligned with those used in the submitted pharmacoeconomic analysis.
  - Oral surgery was incorrectly combined with minor surgery, with treatment acquisition costs based on minor surgery.
  - The analysis inappropriately excluded treatment with human VWF and human coagulation FVIII (Wilate).
- The CADTH reanalyses included aligning the dose of rVWF to that of antihemophilic factor/VWF complex, changing the expected use of rFVIII among patients in the on-demand and perioperative management settings and patients' weight to align with the economic submission, and incorporating costs of oral surgery separately.
- Based on the CADTH reanalyses, the anticipated budget impact from the introduction of rVWF is expected to be $1,570,865 in year 1, $2,392,778 in year 2, and $4,049,755 in year 3, with a 3-year budget impact of $8,013,398. CADTH was unable to address uncertainties in the derivation of the target population size, which is a key driver of results. If the size of the population is smaller, the financial impact of introducing rVWF would be expected to be smaller.

Summary of Sponsor's Budget Impact Analysis

In the submitted budget impact analysis (BIA), the sponsor assessed the introduction of rVWF, with or without rFVIII, for adults (aged ≥ 18 years) with or without recombinant antihemophilic factor in patients with VWD compared with antihemophilic factor/VWF complex. The patient population was aligned with the economic evaluation. The BIA was undertaken from the public payer perspective for the Canadian setting over a 3-year time horizon using an epidemiological approach (Figure 4). The sponsor included the acquisition costs associated with plasma protein products but excluded markups and dispensing fees (Table 29). Data for the model were obtained from various sources, including the sponsor's pivotal trials, published literature, and the sponsor's market research (Table 28).

The sponsor made the following assumptions:

- patients receiving Humate-P therapy will not require additional rFVIII
- no patient would require VWF replacement therapy for both on-demand and perioperative management settings; rather, the expected use of VWF replacement therapy was mutually exclusive between these settings.

Figure 4: Sponsor's Estimation of the Size of the Eligible Population

Figure 4 contained confidential information and was removed at the request of the sponsor.

Note: An average growth rate was calculated for each jurisdiction based on its respective population within the last 5 years.

Source: Sponsor's submitted budget impact analysis.[25]

Table 28: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1/year 2/year 3, if appropriate)
Target population (see Figure 4)	

Proportion of patients with VWD by type of bleed
• On-demand therapy
  ○ Major
  ○ Minor
• Perioperative management
  ○ Major
  ○ Minor
	
	36%
	64%
	
	67%
	33%

Market uptake (3 years)	
Uptake (reference scenario) Antihemophilic factor/VWF complex	[redacted]%/[redacted]%/[redacted]%
Uptake (new treatment scenario) Antihemophilic factor/VWF complex rVWF/rFVIII	[redacted]%/[redacted]%/[redacted]% [redacted]%/[redacted]%/[redacted]%

rFVIII = recombinant factor VIII; rVWF = recombinant von Willebrand factor; VWD = von Willebrand disease; VWF = von Willebrand factor.

Source: Sponsor's submitted budget impact analysis.[25]

Table 29: Sponsor's Costs per Treatment Within the Budget Impact Analysis

Drugs	Setting/subgroup	Unit price (per IU)	Annual number of bleeds	Total dose to resolve all bleeds (IU)	Weight distribution	Weighted annual cost, per patient
rVWF	On demand: Minor	$1.5429	[redacted]	43.3	[redacted]%	$13,567
	On demand: Major		[redacted]	100.0	[redacted]%	
	Perioperative management: Minor		[redacted]	119.9	[redacted]%	
	Perioperative management: Major		[redacted]	307.6	[redacted]%	
rFVIII	On demand: Minor	$0.8201	[redacted]	33.50	[redacted]%	$3,288
	On demand: Major		[redacted]	39.00	[redacted]%	
	Perioperative management: Minor		[redacted]	[redacted]	[redacted]%	
	Perioperative management: Major		[redacted]	[redacted]	[redacted]%	
Anti-hemophilic factor/ VWF (human) complex	On demand: Minor	$0.9174	[redacted]	57.40	[redacted]%	$17,362
	On demand: Major		[redacted]	[redacted]	[redacted]%	
	Perioperative management: Minor		[redacted]	292.00	[redacted]%	
	Perioperative management: Major		[redacted]	448.50	[redacted]%	

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

Source: Sponsor's submitted budget impact analysis.[25]

Summary of the Sponsor's Budget Impact Analysis Results

Results of the sponsor's base case suggested cost savings of $369,010 in year 1, $562,084 in year 2, and $951,323 in year 3, for a total cost savings of $1,882,417 over the 3-year time horizon, with the reimbursement of rVWF in the treatment of adult patients with VWD.

CADTH Appraisal of the Sponsor's Budget Impact Analysis

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the results of the BIA.

- **Estimation of target population and expected use of VWF replacement products are uncertain:** The estimated target population was derived using epidemiological studies of VWD and market research conducted by the sponsor. However, there is uncertainty in the epidemiological data as the sponsor's market research lacked transparency and could not be validated by CADTH. The sponsor further assumed that patients would receive therapy in only the on-demand setting or the perioperative management setting. However, CADTH's clinical experts noted that a small but unknown proportion of patients with VWD may require VWF replacement in both clinical settings. CADTH's clinical experts were also unable to validate the estimated annual number of bleeds assumed in the submitted BIA, which informed cost calculations.
    - CADTH was unable to address uncertainties related to the epidemiological data for VWD.
- **Differences in dose between products:** The sponsor assumed that patients would require fewer doses of rVWF based on naive comparisons between the sponsor's pivotal trials and an observational study for antihemophilic factor/VWF complex.[4,7] See the section CADTH Appraisal of the Sponsor's Economic Evaluation for further details. Although the longer half-life associated with rVWF could impact patients requiring multiple doses over an extended duration, the clinical experts did not expect differences in half-life to impact dosing frequency.
    - As part of CADTH's base-case reanalysis, the dosing reported for the antihemophilic factor/VWF complex was applied to rVWF.
- **Some inputs are not aligned with the pharmacoeconomic analysis:** The submitted BIA assumed that 20% of patients would require concomitant medication with rFVIII in addition to rVWF and a patient weight of 70 kg.[25] These inputs differed from the economic model, which assumed that 11% of patients would require concomitant medication with rFVIII and different patient weights in each setting.[1] The clinical experts consulted by CADTH indicated that the values in the economic model were reasonable.
    - In CADTH's base-case reanalysis, these inputs were changed to align with those in the economic evaluation.
- **Aggregation of costs relevant to oral surgery patients:**. In the sponsor's pharmacoeconomic submission, total therapy costs in the perioperative management subgroup were calculated by considering dosing of oral surgery separately from other surgery types. In the submitted BIA, the proportion of patients expected to receive treatment for oral surgery was combined into those receiving treatment for minor surgery with the dosing for minor surgery applied. As such, treatment costs expected in VWD patients requiring VWF replacement for oral surgery were not captured. This likely overestimated the budget impact in both the treatment and comparators groups.
    - As part of CADTH's base-case reanalysis, minor surgery was further stratified to consider oral surgery separately. The treatment costs associated with the dosing of rVWF, with or without FVIII, and antihemophilic factor/VWF complex for oral surgery, based on the CADTH reanalysis of the sponsor's economic evaluation, was further incorporated into the analysis.

- **Missing comparators:** As noted in CADTH's appraisal of the sponsor's economic evaluation, the sponsor excluded human VWF and human coagulation FVIII from the analysis. The evaluation inappropriately assumed that rVWF would take market shares only from the antihemophilic factor/VWF complex. See the section CADTH Appraisal of the Sponsor's Economic Evaluation for further details. This adds uncertainty to the budget impact estimates since a proportion of patients that was expected to switch to rVWF may not have been adequately accounted for in the model.
  - Due to structural limitations, CADTH was unable to address the exclusion of human VWF and human coagulation FVIII. The expected costs associated with a treatment course for each of these products can be found in Appendix 1.

CADTH Reanalyses of the Budget Impact Analysis

The values and assumptions used by the sponsor in comparison with those used by CADTH in its reanalyses are noted in Table 30.

Table 30: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None		
Changes to derive the CADTH base case		
1. Dose of rVWF	On-demand minor bleed: 43.3 IU/kg On-demand major bleed: 100.0 IU/kg Perioperative management minor surgery: 119.9 IU/kg Perioperative management major surgery: 307.6 IU/kg	On-demand minor bleed: 57.4 IU/kg On-demand major bleed: [redacted] IU/kg Perioperative management minor surgery: 292.5 IU/kg Perioperative management major surgery: 448.5 IU/kg See Table 22 and Table 23 in Appendix 4.
2. Patient weight	70 kg	77.3 kg[a]
3. Proportion of patients requiring concomitant rFVIII	20%	11%
4. Oral surgery costs	Excluded	Included (dose: 64 IU/kg)
CADTH base case	—	Reanalyses 1 + 2 + 3 + 4

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

[a] A pooled patient weight, based on the on-demand and perioperative management settings was used to inform the weight of patients. No wastage was assumed, similar to the approach taken in the pharmacoeconomic evaluation. Clinical experts consulted by CADTH had indicated that weight-based dosing is performed without wasting vial contents, so that actual dose is plus or minus 10% of the weight-based calculation.

The results of the CADTH stepwise reanalysis are presented in summary format in Table 31 and a more detailed breakdown is presented in Table 32.

With the revised analyses, the expected budget impact of introducing rVWF for adults with VWD is expected to be $1,570,865 in year 1, $2,392,778 in year 2, and $4,049,755 in year 3 with a total 3-year budget impact of $8,013,398. CADTH conducted key scenario analyses with results presented in Table 33. CADTH was unable to address uncertainties in the derivation of the target population size, which is a key driver of results. If the size of the population is smaller or the expected use is lowered, the financial impact of introducing rVWF would be expected to be smaller.

Table 31: Summary of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	3-year total ($)
Submitted base case	–$1,882,417
CADTH reanalysis 1	$7,497,512
CADTH reanalysis 2	–$2,078,726
CADTH reanalysis 3	–$2,059,956
CADTH reanalysis 4	–$1,787,479
CADTH base case	$8,013,398

Table 32: Detailed Breakdown of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	Scenario	Year 1 ($)	Year 2 ($)	Year 3 ($)	3-year total ($)
Submitted base case	Reference	–2,041,954	–3,110,353	–5,264,242	–10,416,549
	New treatment	1,672,944	2,548,268	4,312,920	8,534,132
	Budget impact	**–369,010**	**–562,084**	**–951,323**	**–1,882,417**
CADTH base case	Reference	–2,219,700	–3,381,099	–5,722,479	–11,323,278
	New treatment	3,790,565	5,773,878	9,772,234	19,336,676
	Budget impact	**1,570,865**	**2,392,778**	**4,049,755**	**8,013,398**

Table 33: CADTH Estimated Budget Impact in Key Scenario Analyses

Scenario analysis	Year 1 ($)	Year 2 ($)	Year 3 ($)	3-year total ($)
100% concomitant rFVIII	1,947,748	2,966,856	5,021,375	9,935,979
Price of rVWF reduced by 40%	73,271	111,609	188,896	373,776
Oral surgery subgroup (no rFVIII co-treatment)	10,852	16,530	27,977	55,358
Minor surgery subgroup (50% dose reduction of rFVIII)	81,174	123,647	209,271	414,092
Major surgery subgroup	314,575	479,169	810,989	1,604,733
Minor or moderate bleed on-demand subgroup	185,811	283,032	479,028	947,871
Major bleed on-demand subgroup	976,095	1,486,810	2,516,412	4,979,317
50% price reduction for rFVIII (i.e., $0.41 per IU)	1,547,574	2,357,302	3,989,711	7,894,587
Vial wastage assumed	1,570,865	2,392,778	4,049,755	8,013,398

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

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