

CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology Clinical Review

Office of Blood Review & Research

STN 125577/0

Sponsor: Baxter Healthcare corporation

Product: von Willebrand factor (Recombinant)

Indication: Prevention and treatment of bleeding episodes in adults (age 18 years and older) diagnosed with von Willebrand disease.

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INTRODUCTION

von Willebrand disease (VWD) is the most common of the hereditary coagulation factor deficiencies, caused by qualitative and/or quantitative deficiencies of von Willebrand factor (VWF), which is a large multimeric plasma glycoprotein that mediates platelet adhesion and aggregation at sites of vascular injury. VWF also serves to stabilize coagulation factor VIII (FVIII), where FVIII is an essential cofactor of secondary hemostasis. The aim of VWD

treatment is to adjust the dual defect of hemostasis; i.e., abnormal coagulation characterized by low levels of FVIII and abnormal platelet adhesion demonstrated by a prolonged skin bleeding time.

Baxter has developed a human recombinant VWF (rVWF) intended for the treatment of VWD. rVWF synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line expressing the VWF gene. No exogenously added raw materials of human or animal origin are employed in the cell culture, purification, or formulation of the final container product. The only proteins present in the final container product other than rVWF are trace quantities of murine immunoglobulin (IgG, from the immune-affinity purification), host cell (CHO) protein, rFurin (used to further process rVWF), and recombinant factor VIII (rFVIII).

rVWF is formulated as a sterile, non-pyrogenic, white to off-white powder for intravenous injection. rVWF in a single-use vial contains nominally 650 or 1300 International Units (IU) VWF Ristocetin Cofactor (VWF:RCo). The product contains the following stabilizers and excipients: tri-sodium citrate-dihydrate, glycine, mannitol, trehalose-dihydrate, and polysorbate 80.

Each vial containing rVWF is labeled with the number of units of VWF:RCo expressed either as a percentage (relative to normal human plasma) or in international units relative to the international standards for VWF:RCo activity in plasma. After reconstitution of the lyophilized powder, all dosage strengths yield a clear, colorless solution.

CLINICAL PHARMACOLOGY LABELING COMMENTS

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

~~VONVENDI is recombinant von Willebrand factor (rVWF) expressed by CHO cells and, unlike plasma VWF, is not exposed to proteolysis by ADAMTS13 during the manufacturing process. VONVENDI contains all sizes of multimers including ultra large non proteolysed multimers found in the physiological storage sites, for example the Weibel Palade bodies. The ultra large multimers are the most active VWF multimers, which are also observed in the endogenous VWF immediately after secretion from the storage sites. VONVENDI has unique functional *in vitro* properties that is only detectable under blood flow conditions and is the closest to the endogenous physiological VWF.~~

VONVENDI allows for the correction of the hemostatic abnormalities experienced by VWD patients by 1) acting as an adhesive molecule, mediating both parts of primary hemostasis, platelet adhesion to damaged vascular sub-endothelial tissues like collagen and platelet aggregation, and 2) functioning as a carrier protein for factor VIII also protecting it from rapid proteolysis.

~~*In vitro* studies with direct visualization have demonstrated that the presence of ULM in high-shear flow conditions leads to rapid platelet VWF conglomerate formation as well as platelet adhesion to and platelet aggregation on collagen, which is found in vascular sub-endothelium. Under high flow conditions, the presence of ADAMTS13 has been shown to limit platelet VWF conglomerate formation as well as aggregate formation on collagen to less than 10 minutes. In clinical studies exposure of VONVENDI to ADAMTS13 in circulation showed that the proteolysis of ULMs of VONVENDI begins immediately and that proteolytic products can be found for 6-12 hours, making the multimeric composition of VONVENDI similar to that of plasma derived VWF concentrates. That also indicates that mode of operation and control of VWF function under high shear flow may not be fully reflected in degradation bands but may require different approaches to measure it.~~

VONVENDI has also been shown to stabilize endogenous factor VIII². The factor VIII binding capacity and affinity of to rVWF is comparable to that of VWF present in plasma and platelets, allowing for VONVENDI to reduce factor VIII clearance by acting as a carrier protein³.

12.2 Pharmacodynamics

~~VONVENDI contains high levels of ULM when compared to plasma derived VWF. An *in vitro* pharmacodynamic study with VONVENDI investigated the primary hemostatic efficacy of~~

ULMs in human VWF deficient blood matrices. Eight adult subjects with VWD and 3 normal healthy volunteers provided blood samples for the assessment of VWF mediated platelet adhesion and aggregation to collagen under shear stress. All adult subjects had VWF:Ag <40% and among these patients, 5 had VWF:Ag <10% and/or VWF:RCo <10%. VWF activity under high shear flow conditions of 30,000s⁻¹ was tested before and after addition of 3 different types of VWF to the donor blood samples. These high shear rates were chosen to examine the functional capabilities of VONVENDI and in particular the specific role of its ultra large multimers under flow conditions that appear very challenging for platelet deposition and thus subsequent wound closure: very high shear force acting on the flowing cells (platelets) as well as the bonds. All blood samples were spiked with either VONVENDI, rVWF fraction lacking ULMs, or a VWF/FVIII concentrate. Results demonstrate that VONVENDI was effective in the formation of rVWF platelet conglomerates under such high shear forces. As shown in several *in vitro* and *in vivo* studies, ADAMTS13 is effectively and specifically cleaving ULMs, thereby acting as an effective regulatory counterpart.^{1,4}

12.3 Pharmacokinetics

The pharmacokinetic profile of VONVENDI was determined in two clinical trials by assessment of VWF:RCo, VWF: Ag, VWF:CB, and factor VIII activity. Subjects were evaluated in the non-bleeding state. A single infusion of VONVENDI will lead to an increase in FVIII:C after at least 6 hours. The table below summarizes the pharmacokinetics of VONVENDI after infusions of 50 IU/kg (please provide duration of infusion) in terms of VWF:RCo (PK₅₀) or 80 IU/kg VWF:RCo (PK₈₀) VONVENDI.

Please provide PK data in Table 4 as arithmetic mean and standard deviation with range.

Please include AUC values without dose normalization.

Please mention the impact of multiple dosing on the PK of VWF:RCo.

Please provide the source of data (study #) in Table 4. This information is only needed for FDA evaluation and need not to be included in the package insert.

Table 4 Pharmacokinetic Assessment of VWF:RCo^{a,b}

Parameter [unit]	Phase 1 PK ₅₀ VONVENDI with ADVATE Median (90% CI)	Phase 3 PK ₅₀ VONVENDI Median (95% CI)	Phase 3 PK ₈₀ VONVENDI Median (95% CI)
T _{1/2} [hours]	16.0 (11.9 to 17.7)	19.4 (15.5 to 31.3)	18.4 (16.4 to 22.1)
CL [dL/kg/hours]	0.034 (0.027 to 0.040)	0.031 (0.021 to 0.035)	0.027 (0.024 to 0.034)
IR at C _{max} [(U/dL)/ (U VWF:RCo/kg)]	1.45 (1.3 to 1.95)	1.8 (1.5 to 2.2)	1.8 (1.7 to 2.2)
AUC _{0-inf} /Dose [(h*U/dL)/	29.8 (25.10 to 37.30)	32.7 (29.0 to 47.8)	36.9 (29.2 to 41.7)

(U VWF:RCo/kg)			
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^a Full analysis set

^b During the clinical trials two different VWF RCo assays with different sensitivity and working ranges were used. **Please describe the two different assay methods and sensitivity range in the footnote.**

RECOMMENDATION

The study design and results of the PK studies are acceptable from clinical pharmacology perspective. The sponsor should update the clinical pharmacology labeling section based on the suggestions of the FDA.

STUDY #1

Study Title: Recombinant von Willebrand Factor/Recombinant Factor VIII Complex (rVWF:rFVIII): A Phase 1 study evaluating the pharmacokinetics, safety, and tolerability in severe von Willebrand disease (Study 070701)..

The objectives of this study were as follows:

- To evaluate the tolerability and safety after single doses of rVWF:rFVIII at 2, 7.5, 20 and 50 IU/kg von Willebrand factor : Ristocetin cofactor activity (VWF:RCo).
- To assess the immunogenicity and thrombogenicity of rVWF:rFVIII.
- To evaluate the pharmacokinetics (PK) after single doses of rVWF:rFVIII at 2, 7.5, 20 and 50 IU/kg VWF:RCo.
- To compare the area under the VWF:RCo plasma concentration vs. time curves (AUC) for rVWF:rFVIII and plasma-derived VWF/FVIII (pdVWF/FVIII) following single infusions of each product.

This was a multicenter, controlled, randomized, single-blind prospective Phase 1 dose escalation study. The study consisted of 4 sequentially enrolled cohorts who received a single IV infusion of rVWF:rFVIII as follows:

Cohort	Dose and IP	Subject diagnosis
Cohort 1	rVWF:rFVIII with 2 IU/kg VWF:RCo	Type 3 VWD
Cohort 2	rVWF:rFVIII with 7.5 IU/kg VWF:RCo	Type 3 VWD
Cohort 3	rVWF:rFVIII with 20 IU/kg VWF:RCo	Type 3 VWD
Cohort 4A	rVWF:rFVIII and pdVWF/FVIII with 50 IU/kg VWF:RCo, in random order	Type 3 VWD
Cohort 4B	rVWF:rFVIII and pdVWF/FVIII with 50 IU/kg VWF:RCo, in random order	Severe type 1VWD

The subjects were between 18 to 60 years of age and had hereditary type 3 VWD (<3 IU/dL VWF:Ag) or severe type 1 or type 2A VWD (VWF:RCo <10% and FVIII:C<20%). The product was Baxter's rVWF combined with rFVIII (ADVATE) at a fixed ratio (1.3±0.2:1 VWF:RCo/FVIII:C). Plasma-Derived pdVWF/FVIII (Humate-P/Haemate P) was used for cohort 4 only. Cohort 4 included a two-period randomized-controlled crossover with a marketed pdVWF/FVIII concentrate. The median duration of infusion ranged between 2 min (cohort 1 with 2 IU/kg VWF:RCo) up to 21 min (cohort 4B with 50 IU/kg VWF:RCo and FVIII). The demographics of the subjects are shown in Table 1.

Blood samples for PK study were taken at 15, 30, and 60 minutes after drug infusion, and at 3, 6, 9, 12, 24, 28, 32, 48, 72, and 96 hours. Pharmacokinetic parameters of Von Willebrand factor:Ristocetin cofactor activity (VWF:RCo), Von Willebrand factor:antigen (VWF:Ag), Von

Willebrand factor:collagen binding (VWF:CB), and rFVII:C were estimated by non-compartmental analysis. The PK parameters of these moieties are summarized in Tables 2-5. The PK of 2 IU/kg rVWF:rFVIII could not be estimated because the VWF levels were below the detection limit for the majority of PK time points. The following analytical methods were used in measuring the concentrations of different moieties of (rVWF:rFVIII):

VWF Ristocetin Cofactor Activity (VWF:RCo) provides a measure of the ability of VWF to bind platelet glycoprotein Ib (GPIb), a key step in primary hemostasis. Stabilized platelets are agglutinated in the presence of VWF and the antibiotic Ristocetin.

VWF Collagen Binding (VWF:CB) provides a measure of the ability of VWF to bind to sub-endothelial collagen, another key step in primary hemostasis. VWF:CB is measured using a (b) (4) for detection.

VWF antigen (VWF:Ag) is a measure of total VWF protein and was assessed using a (b) (4)

FVIII:C was measured by (b) (4).

Table 1
Demographic and Baseline Characteristics - Categorical Data
(Study 070701: Safety Analysis Set)

Parameter	Category	Cohort ^a					Total N = 32 n (%)
		1 N = 3 n (%)	2 N = 5 n (%)	3 N = 5 n (%)	4A N = 22 n (%)	4B N = 3 n (%)	
Gender	Male	2 (66.7%)	3 (60.0%)	5 (100.0%)	11 (50.0%)	1 (33.3%)	17 (53.1%)
	Female	1 (33.3%)	2 (40.0%)	0 (0.0%)	11 (50.0%)	2 (66.7%)	15 (46.9%)
Race	White	3 (100.0%)	5 (100.0%)	4 (80.0%)	22 (100.0%)	3 (100.0%)	31 (96.9%)
	Black or African American	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	0 (0.0%)	0 (0.0%)	1 (20.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
	American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Native Hawaiian or other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Hispanic or Latino	0 (0.0%)	2 (40.0%)	1 (20.0%)	3 (13.6%)	0 (0.0%)	4 (12.5%)
	Non-Hispanic or Latino	3 (100.0%)	3 (60.0%)	4 (80.0%)	19 (86.4%)	3 (100.0%)	28 (87.5%)

^a Each subject can occur in cohort 1, 2 or 3 and in cohort 4A.

VWF ristocetin cofactor activity (VWF:RCo):

The median initial recoveries (IR) [U/dL per IU/kg infused] following the 50 IU/kg dose were 1.45 for recombinant and 1.52 for the plasma-derived concentrates. The highest median IR was observed in the 7.5 IU/kg dose group (2.4), likely due to the small sample size in that cohort

(N=5). The median VWF:RCo half-life of rVWF at the 50 IU/kg dose was 16 hours. T_{1/2} with pdVWF:FVIII at the same dose level was 12.6 hours, The median half-lives of VWF:RCo were shorter with the lower investigated doses: 7.1 hours and 13.2 hours with the 7.5 IU/kg and 20 IU/kg doses, respectively. Clearance (mL/hour/kg) was shorter with recombinant than with plasma-derived VWF at 50 IU/kg dose level: 3.4 with rVWF vs. 4.7 mL/hour/kg with pdVWF.

VWF Antigen (VWF:Ag):

Following 50 IU/kg dose, half-lives of rVWF:rFVIII and pdVWF in terms of VWF:Ag were 25.3 and 18.2 hours, respectively. Clearance of rVWF:rFVIII for VWF:Ag following 50 IU/kg was 2.8 mL/hour/kg and for pdVWF was 2.7 mL/hour/kg.

VWF Collagen Binding Activity (VWF:CB):

Following 50 IU/kg dose, half-lives of rVWF:rFVIII and pdVWF in terms of VWF:CB were 24.4 and 16.4 hours, respectively. Clearance of rVWF:rFVIII for VWF:CB following 50 IU/kg was 2.1 mL/hour/kg and for pdVWF was 2.6 mL/hour/kg.

Factor VIII:C (FVIII:C):

Following 50 IU/kg dose, half-lives of rVWF:rFVIII and pdVWF in terms of FVIII:C were 24.3 and 19.1 hours, respectively. Clearance of rVWF:rFVIII for FVIII:C following 50 IU/kg was 1.6 mL/hour/kg and for pdVWF was 1.9 mL/hour/kg.

Table 2: Pharmacokinetic parameters following 7.5 IU/kg rVWF/FVIII dose

Parameters	VWF:RCo	VWF:AG	VWF:CB	FVIII:C
AUC (U*hr/dL)	254 ± 82	429 ± 104	443 ± 165	1950 ± 965
CL (mL/hr/kg)	3.3 ± 1.1	1.9 ± 0.4	2.0 ± 0.9	0.5 ± 0.2
Half-lfe (hrs)	7.5 ± 1.2	28.2 ± 5.8	23.1 ± 7.7	21.9 ± 2.5
MRT (hrs)	14.3 ± 6.3	39.5 ± 7.8	28.8 ± 6.7	36.2 ± 6.1
V _{ss} (mL/kg)	42.6 ± 7.8	73 ± 23.3	52.2 ± 9.9	16.6 ± 6.9
IR (U/dL)/U/kg)	2.2 ± 0.3	2 ± 0.3	2,1 ± 0.6	6.9 ± 3.9

CL = clearance, MRT = mean residence time, V_{ss} = volume of distribution at steady state, IR = in-vivo recovery, VWF:RCo Von Willebrand factor:Ristocetin cofactor activity, VWF:Ag Von Willebrand factor:antigen, VWF:CB Von Willebrand factor:collagen binding,

Table 3: Pharmacokinetic parameters following 20 IU/kg rVWF/FVIII dose

Parameters	VWF:RCo	VWF:AG	VWF:CB	FVIII:C
AUC (U*hr/dL)	591 ± 181	838 ± 341	922 ± 293	2959 ± 740
CL (mL/hr/kg)	3.7 ± 1.4	2.8 ± 1.2	2.4 ± 0.8	0.7 ± 0.2
Half-lfe (hrs)	23.6 ± 24.7	26.1 ± 8.3	15.7 ± 5.4	20.4 ± 5.2
MRT (hrs)	23.4 ± 12.1	30.2 ± 7.2	24.1 ± 4.9	36.1 ± 8.2
V _{ss} (mL/kg)	77.2 ± 18.7	77.8 ± 18.5	55.9 ± 17.1	25.2 ± 5.8
IR (U/dL)/U/kg)	1.5 ± 0.3	1.6 ± 0.5	2.1 ± 0.7	2.8 ± 0.6

Table 4: Pharmacokinetic parameters following 50 IU/kg rVWF/FVIII dose

Parameters	VWF:RCo	VWF:AG	VWF:CB	FVIII:C
AUC (U*hr/dL)	1541 ± 554	2245 ± 683	2998 ± 965	5376 ± 2380
CL (mL/hr/kg)	3.8 ± 2.8	2.8 ± 2.9	2.1 ± 2.0	1.6 ± 2.7
Half-lfe (hrs)	19.3 ± 11.0	25.3 ± 6.3	24.4 ± 14.6	24.3 ± 6.5
MRT (hrs)	36.8 ± 13.6	33.5 ± 10.7	31.7 ± 20.5	38.9 ± 12.4
Vss (mL/kg)	79.9 ± 25.2	72.3 ± 22.0	49.4 ± 21.0	37.1 ± 11.6
IR (U/dL)/U/kg)	1.7 ± 0.6	1.7 ± 0.5	2.7 ± 0.8	2.1 ± 0.8

Table 5: Pharmacokinetic parameters following 50 IU/kg pdVWF/FVIII dose

Parameters	VWF:RCo	VWF:AG	VWF:CB	FVIII:C
AUC (U*hr/dL)	1180 ± 500	2254 ± 1012	2360 ± 1169	3361 ± 1350
CL (mL/hr/kg)	5.1 ± 1.5	2.7 ± 0.8	2.6 ± 0.7	1.9 ± 0.7
Half-lfe (hrs)	14.6 ± 6.4	18.2 ± 3.3	16.4 ± 3.9	19.1 ± 5.1
MRT (hrs)	18.7 ± 5.5	22.3 ± 5.2	18.8 ± 4.1	36.7 ± 7.5
Vss (mL/kg)	92.2 ± 32.4	58.4 ± 15.4	47.7 ± 12.8	58.2 ± 17.1
IR (U/dL)/U/kg)	1.6 ± 0.6	2.3 ± 0.7	3.0 ± 1.0	1.3 ± 0.3

To assess the PK equivalence of rVWF:rFVIII and pdVWF/FVIII, the 90% confidence interval for the difference of the mean logarithms of AUC_{0-∞} between the 2 study groups was calculated. The 90% confidence interval was outside the accepted limit of 0.8 to 1.25 for all VWF moieties indicating that rVWF:rFVIII and pdVWF/FVIII were not PK bioequivalent (Table 6).

Table 6
PK Equivalence: Ratio of Geometric Means of the Area Under the Curve
(Study 070701)

PK Parameter	Cohort	Parameter	Dataset	N	Ratio of Geometric Means	90% CI for Ratio of Geometric Means
VWF:RCo	Cohort 4A/B	AUC _{0-inf}	FADS	20	1.26	1.02; 1.56
			PADS	9	1.49	1.34; 1.65
VWF:Ag	Cohort 4A	AUC _{0-inf}	FADS	17	0.93	0.69; 1.26
			PADS	7	0.98	0.78; 1.23
VWF:CB	Cohort 4A	AUC _{0-inf}	FADS	17	1.18	0.87; 1.59
			PADS	7	1.36	1.18; 1.56
FVIII:C	Cohort 4A	AUC _{0-inf}	FADS	17	1.36	0.93; 1.99
			PADS	7	1.76	1.39; 2.22

^a pdVWF/FVIII = 100 percentage

FADS = Full Pharmacokinetic Analysis Data Set; PADS = Per Protocol Analysis Data Set

Conclusions: The PK of rVWF:rFVIII in terms of its moieties differ from each other. The PK of rVWF/FVIII for VWF:RCo was linear between 20 and 50 IU/kg dose. The half-life of rVWF:rFVIII is longer than pdVWF and the clearance of rVWF:rFVIII is slower than pdVWF. rVWF:rFVIII and pdVWF are not pharmacokinetically equivalent.

Figure 1: Concentration vs time plot of VWF:RCO after administration of rVWF (50 IU/kg)

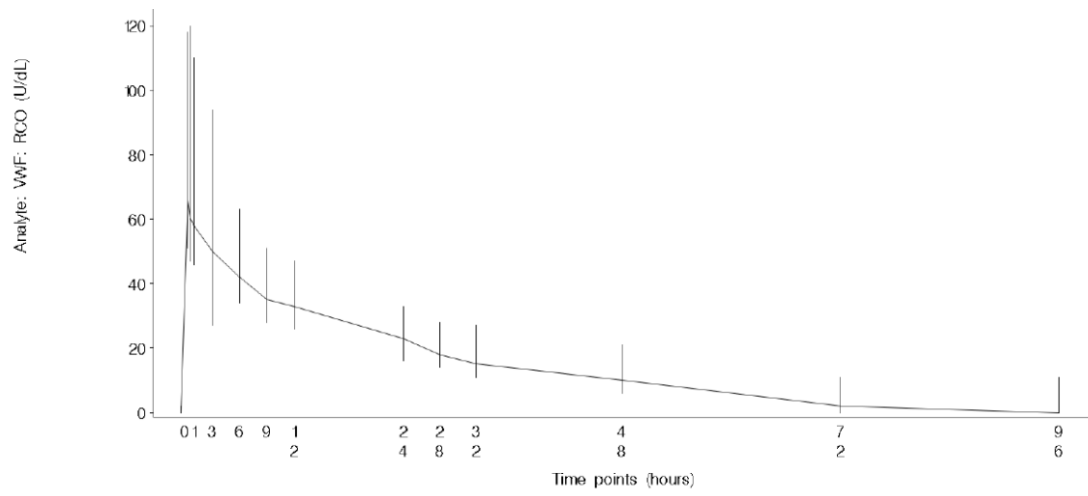


Figure 2: Concentration vs time plot of VWF:Ag after administration of rVWF (50 IU/kg)

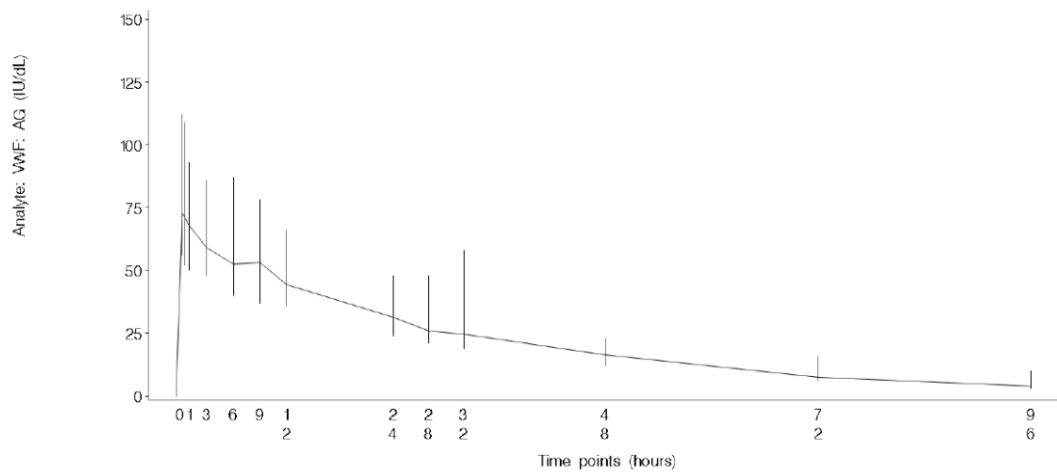


Figure 3: Concentration vs time plot of VWF:CB after administration of rVWF (50 IU/kg)

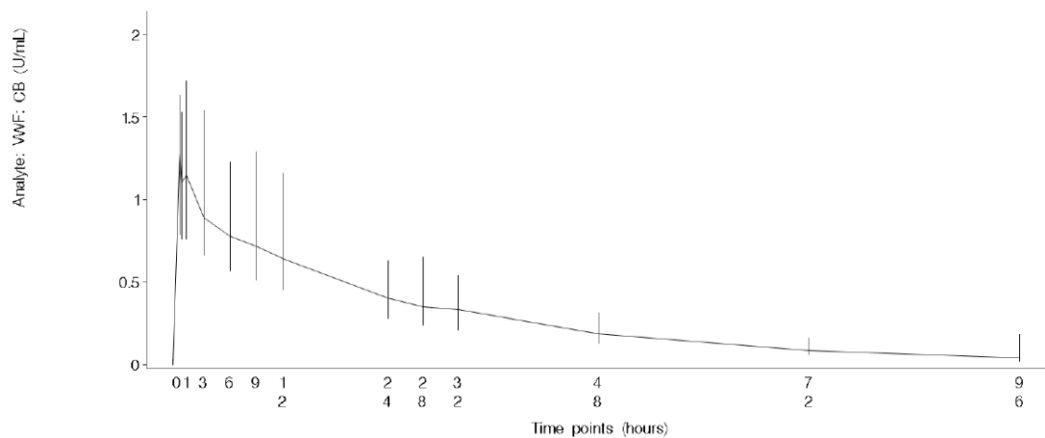
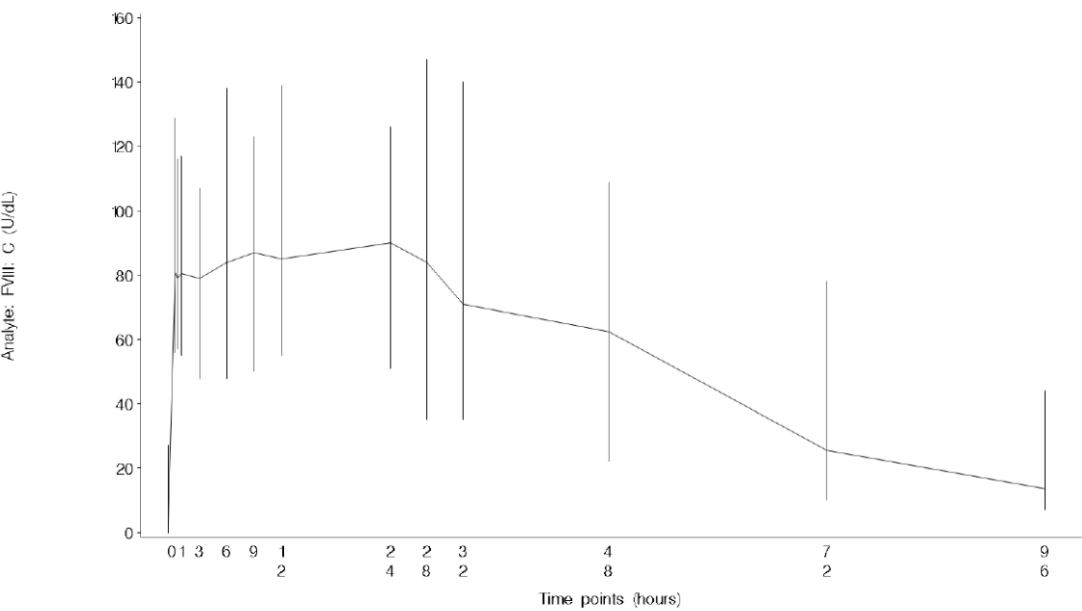


Figure 4: Concentration vs time plot of FVIII:C after administration of rVWF (50 IU/kg)



STUDY #2

Study Title: A Phase 3 clinical study to determine the pharmacokinetics, safety, and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes in subjects diagnosed with von Willebrand disease (Study 071001).

The objectives of this study were:

To compare the PK parameters of rVWF alone or concomitantly with rFVIII (ADVATE) in subjects with type 3 VWD

To examine the PK parameters of rVWF in subjects with severe VWD

To evaluate the hemostatic efficacy, safety, and tolerability of rVWF:rFVIII and rVWF alone in subjects with VWD receiving the investigational product for the treatment of bleeding episodes (BEs)

To evaluate tolerability and safety of rVWF including the development of inhibitory and total binding anti-VWF antibodies and clinically significant changes in laboratory parameters following drug administration

This was a Phase 3, multicenter part-randomized clinical study to assess the PK, safety and efficacy of rVWF:rFVIII and rVWF in the treatment of bleeding episodes (BEs) in adult subjects with severe type 3 and severe non-type 3 Von Willebrand disease (VWD).

The study consisted of four arms that vary with the dose of investigational product (IP) administered and whether the subjects will participate in PK assessments and/or on demand treatment for BEs.

Subjects in Arm 1 (PK50 with treatment of BEs) received 50 IU/kg VWF:RCo rVWF (administered with rFVIII or placebo) for PK assessments and rVWF and/or rVWF:rFVIII for BEs.

Subjects in Arm 2 (PK50 only) received 50 IU/kg VWF:RCo rVWF (administered with rFVIII or placebo) for PK assessment only,

Subjects in Arm 3 (PK80 with treatment of BEs) received 80 IU/kg VWF:RCo rVWF for PK assessment and rVWF and/or rVWF:rFVIII for BEs,

Subjects in Arm 4 (treatment of BEs only) received rVWF and/or rVWF:rFVIII for BEs (no PK assessment).

A total of 49 subjects were enrolled (signed informed consent) and screened, 18 subjects were randomized (Arm 1 and Arm 2 [PK50] only), 37 subjects were treated with IP (all study arms) and 30 subjects completed the study. Subject disposition per treatment arm is as follows:

Arm 1 (PK50 and treatment of a BE): 9 subjects enrolled and randomized; 8 subjects treated with IP; 5 subjects enrolled but discontinued study and 4 subjects completed the study.

Arm 2 (PK50 only): 9 subjects enrolled and randomized; 8 subjects treated with IP; 1 subject enrolled but discontinued study and 8 subjects completed the study.

Arm 3 (PK80 and treatment of a BE): 16 subjects enrolled; 15 subjects treated with IP; 3 subjects enrolled but discontinued study and 13 subjects completed the study.

Arm 4 (treatment of a BE only): 6 subjects enrolled; 6 subjects treated with IP; 1 subject enrolled but discontinued study and 5 subjects completed the study.

Discontinued subjects

A total of 19 subjects discontinued from the study:

Twelve subjects discontinued prior to treatment:

- 6 subjects were screen failures

- 3 subjects withdrew consent

- 1 subject started a dental procedure (oral cavity sanitation) after enrollment, under continuous high amounts of FVIII; the subject was not treated with IP in the study because re-screening had closed by the time the oral sanitation had been completed.

- 1 subject was withdrawn by the physician because the subject appeared to have uncontrolled diabetes, which could however not be verified because the subject did not return phone calls after screening.

- 1 subject signed ICF for the PK50 arm after the arm was closed and was not eligible for the other arms.

Seven subjects discontinued after treatment started:

- 4 subjects withdrew consent

- 1 subject became pregnant

- 1 subject withdrew due to an AE chest discomfort, heart rate increase.

- 1 subject had been treated with an immunomodulatory drug within 30 days prior to enrollment and was included in the PK80 arm but was withdrawn prior to the PK2 infusion.

The main criterion for inclusion was the subject diagnosed with:

- a. Type 1 (VWF:RCo < 20 IU/dL) or,

- b. Type 2A (VWF:RCo < 20 IU/dL), Type 2B (as diagnosed by genotype),

- Type 2N (FVIII:C < 10% and historically documented genetics), Type 2M or,

- c. Type 3 (VWF:Ag ≤ 3 IU/dL) or,

- d. Severe VWD with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding and the subject, who participated in the treatment for BEs, had a minimum of 1 documented bleed (medical history) requiring VWF coagulation factor replacement therapy during the previous 12 months prior to enrollment.

A total of 16 subjects in Arm 1 or Arm 2 included in the PK study (PK50 subjects), were randomized to receive an initial PK infusion of either 50 IU/kg VWF:RCo rVWF co-infused with

38.5 IU/kg rFVIII, or 50 IU/kg VWF:RCo rVWF co-infused with saline (placebo). These subjects then crossed over to the alternative treatment for the second infusion and PK assessment.

A total of 15 subjects in Arm 3 included in the RPK-FAS (PK80 subjects) underwent PK assessment after an initial infusion of 80 IU/kg VWF:RCo rVWF, and underwent a second PK assessment after an infusion of 80 IU/kg VWF:RCo rVWF after 6 months of treatment of BEs. The disposition of subjects is shown in the following Table.

Category	PK50+Treatment (Arm 1) N (%)	PK50 (Arm 2) N (%)	PK80+Treatment (Arm 3) N (%)	Treatment Only (Arm 4) N (%)	No Arm Assigned N (%)	Overall N (%)
Enrolled subjects (i.e. subjects who signed the informed consent)	9 (100.0)	9 (100.0)	16 (100.0)	6 (100.0)	9 (100.0)	49 (100.0)
Subjects randomized	9 (100.0)	9 (100.0)	NA	NA	NA	18 (36.7)
Subjects treated with IP	8 (88.9)	8 (88.9)	15 (93.8)	6 (100.0)	NA	37 (75.5)
Subjects enrolled but discontinued study	5 (55.6)	1 (11.1)	3 (18.8)	1 (16.7)	9 (100.0)	19 (38.8)
Subjects completed study	4 (44.4)	8 (88.9)	13 (81.3)	5 (83.3)	NA	30 (61.2)

Blood samples for PK study were taken at 15, 30, and 60 minutes after drug infusion, and at 3, 6, 9, 12, 24, 28, 32, 48, 72, and 96 hours. Pharmacokinetic parameters of VWF:RCo, VWF:Ag, VWF:CB and FVIII:C levels were estimated by non-compartmental analysis. The PK parameters of rVWF/FVIII in terms of Von Willebrand factor:Ristocetin cofactor activity (VWF:RCo), Von Willebrand factor:antigen (VWF:Ag), Von Willebrand factor:collagen binding (VWF:CB), and Factor VIII:C are summarized in Tables 1-16.

Results

Pharmacokinetics of 50 IU/kg dose (crossover):

VWF Ristocetin Cofactor Activity (VWF:RCo)

A summary of PK parameters of VWF:RCo is provided in Tables 1 and 2. Mean VWF:RCo half-life (19.6 vs 21.9 hours) and clearance (0.033 vs 0.029 dL/hr per kg) were comparable between rVWF alone and co-infused with rFVIII.

VWF Collagen Binding (VWF:CB)

A summary of PK parameters of VWF:CB is provided in Tables 3 and 4. Mean VWF:CB half-life (19.2 vs 19.7 hours) and clearance (0.014 vs 0.013 dL/hr per kg) were comparable between rVWF alone and co-infused with rFVIII.

VWF Antigen (VWF:Ag):

A summary of PK parameters of VWF:Ag is provided in Tables 5 and 6. Mean VWF:Ag half-life (22.7 vs 25.1 hours) and clearance (0.016 vs 0.015 dL/hr per kg) were comparable between rVWF alone and co-infused with rFVIII.

Factor VIII:C

A summary of PK parameters of Factor VIII:C is provided in Tables 7 and 8. Mean Factor VIII:C half-life (32.3 vs 31.2 hours) and clearance (0.008 vs 0.009 dL/hr per kg) were comparable between rVWF alone and co-infused with rFVIII.

Pharmacokinetics of 80 IU/kg dose:

The PK parameters of VWF:RCo, VWF:Ag, VWF:CB and FVIII:C following 50 and 80 IU/kg were similar. The PK parameters of aforementioned moieties (Table 9-16) following single and repeat dosing (after 6 months of treatment) of 80 IU/kg were comparable.

Table 1

Summary of Pharmacokinetic Parameters for VWF:RCo
(Study 071001: Full PK Analysis Set / Crossover: PK50)

Treatment=rVWF:rFVIII							
Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
AUC _{0-96h} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	16	33.3 (27.0 to 39.6)	11.9	31.6 (27.3 to 37.3)	12.7;56.0	10.6 (25.7;36.2)	31.3 (25.7 to 38.2)
AUC _{0-inf} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	16	36.1 (27.5 to 44.7)	16.1	32.4 (27.5 to 40.1)	13.1;77.8	13.8 (25.9;39.7)	33.2 (26.4 to 41.6)
AUMC _{0-inf} /Dose [(h ² *U/dL)/(U VWF: RCo/kg)]	16	1181.4 (461.9 to 1901.0)	1350.4	758.7 (519.3 to 1601.8)	336.8;5851.1	833.0 (476.0;1309.0)	845.9 (566.4 to 1263.3)
T _{1/2} [hours]	16	19.6 (14.1 to 25.1)	10.3	16.6 (14.7 to 20.4)	10.6;50.3	5.5 (14.0;19.5)	17.8 (14.3 to 22.3)
MRT [hours]	16	27.8 (20.1 to 35.4)	14.3	25.2 (20.0 to 30.1)	14.7;75.2	9.4 (19.5;28.9)	25.5 (20.7 to 31.5)
Cl [dL/kg/hours]	16	0.033 (0.025 to 0.041)	0.015	0.031 (0.025 to 0.041)	0.013;0.076	0.014 (0.025;0.039)	0.030 (0.024 to 0.038)
V _{ss} [dL/kg]	16	0.81 (0.63 to 1.00)	0.34	0.70 (0.66 to 0.93)	0.51;1.97	0.28 (0.63;0.91)	0.77 (0.65 to 0.91)
C _{max} [U/dL]	16	92.5 (77.2 to 107.8)	28.6	91.0 (80.0 to 128.0)	31.0;132.0	45.0 (75.0;120.0)	87.4 (71.7 to 106.6)
T _{max} [hours]	16	0.72 (0.57 to 0.86)	0.28	0.68 (0.53 to 0.85)	0.35;1.50	0.29 (0.52;0.81)	0.67 (0.56 to 0.81)
IR at C _{max} [(U/dL)/(U VWF: RCo/kg)]	16	1.8 (1.5 to 2.1)	0.6	1.8 (1.6 to 2.4)	0.6;2.7	0.8 (1.5;2.3)	1.7 (1.4 to 2.1)

Table 2

Summary of Pharmacokinetic Parameters for VWF:RCo
(Study 071001: Full PK Analysis Set / Crossover: PK50)

Treatment=rVWF							
Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
AUC _{0-96h} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	14	34.5 (29.7 to 39.3)	8.3	31.3 (28.4 to 43.7)	23.8;53.5	11.7 (28.4;40.1)	33.6 (29.5 to 38.4)
AUC _{0-inf} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	14	37.5 (31.3 to 43.7)	10.7	32.7 (29.0 to 47.8)	24.9;57.7	18.6 (29.0;47.6)	36.2 (30.9 to 42.4)
AUMC _{0-inf} /Dose [(h ² *U/dL)/(U VWF: RCo/kg)]	14	1197.2 (763.9 to 1630.5)	750.4	913.2 (644.3 to 1818.7)	588.3;3059.0	1073.5 (644.3;1717.8)	1027.8 (748.1 to 1412.0)
T _{1/2} [hours]	14	21.9 (17.1 to 26.8)	8.4	19.4 (15.5 to 31.3)	13.5;42.6	9.1 (15.5;24.6)	20.7 (17.0 to 25.2)
MRT [hours]	14	29.8 (23.8 to 35.9)	10.5	26.7 (22.7 to 36.0)	19.0;55.6	11.9 (22.7;34.5)	28.4 (23.7 to 34.0)
Cl [dL/kg/hours]	14	0.029 (0.024 to 0.033)	0.007	0.031 (0.021 to 0.035)	0.017;0.040	0.013 (0.021;0.034)	0.028 (0.024 to 0.032)
V _{ss} [dL/kg]	14	0.80 (0.71 to 0.89)	0.15	0.83 (0.70 to 0.97)	0.55;1.01	0.20 (0.70;0.90)	0.78 (0.70 to 0.88)
C _{max} [U/dL]	14	90.7 (78.3 to 103.1)	21.5	89.5 (75.0 to 111.0)	54.0;141.0	24.0 (75.0;99.0)	88.4 (77.2 to 101.3)
T _{max} [hours]	14	0.70 (0.53 to 0.86)	0.28	0.58 (0.52 to 0.83)	0.40;1.40	0.32 (0.52;0.83)	0.66 (0.54 to 0.80)
IR at C _{max} [(U/dL)/(U VWF: RCo/kg)]	14	1.8 (1.6 to 2.1)	0.4	1.8 (1.5 to 2.2)	1.1;2.7	0.6 (1.5;2.0)	1.8 (1.6 to 2.0)

Table 3

Summary of Pharmacokinetic Parameters for VWF:CB
(Study 071001: Full PK Analysis Set / Crossover: PK50)

Treatment=rVWF:rFVIII							
Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
AUC _{0-96h} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	16	73.1 (61.0 to 85.2)	22.8	78.7 (66.5 to 90.5)	19.6;107.4	22.3 (66.3;88.7)	68.1 (53.9 to 86.1)
AUC _{0-inf} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	16	77.2 (65.7 to 88.7)	21.6	80.1 (68.4 to 95.0)	31.6;113.1	25.6 (68.2;93.8)	73.7 (61.6 to 88.2)
AUMC _{0-inf} /Dose [(h ² *U/dL)/(U VWF: RCo/kg)]	16	2201.2 (1669.4 to 2732.9)	997.9	2099.2 (1681.3 to 3049.7)	544.6;4172.4	1452.5 (1567.7;3020.2)	1957.2 (1469.2 to 2607.3)
T _{1/2} [hours]	16	19.2 (16.6 to 21.8)	4.9	19.3 (14.9 to 23.4)	12.7;27.0	8.2 (14.6;22.8)	18.6 (16.2 to 21.4)
MRT [hours]	16	27.4 (23.8 to 31.1)	6.9	27.5 (22.7 to 32.1)	13.9;40.5	10.1 (22.0;32.1)	26.6 (23.0 to 30.7)
Cl [dL/kg/hours]	16	0.014 (0.011 to 0.018)	0.006	0.012 (0.011 to 0.015)	0.009;0.032	0.004 (0.011;0.015)	0.014 (0.011 to 0.016)
V _{ss} [dL/kg]	16	0.38 (0.30 to 0.45)	0.14	0.35 (0.31 to 0.40)	0.22;0.86	0.09 (0.31;0.40)	0.36 (0.31 to 0.42)
C _{max} [U/dL]	16	173.4 (146.9 to 200.0)	49.8	174.5 (152.0 to 186.0)	68.0;294.0	35.5 (146.0;181.5)	166.3 (140.6 to 196.6)
T _{max} [hours]	16	0.84 (0.63 to 1.06)	0.41	0.71 (0.50 to 1.30)	0.35;1.52	0.78 (0.49;1.28)	0.76 (0.59 to 0.98)
IR at C _{max} [(U/dL)/(U VWF: RCo/kg)]	16	3.4 (2.9 to 4.0)	1.0	3.4 (3.0 to 3.7)	1.4;5.9	0.8 (2.9;3.7)	3.3 (2.8 to 3.9)

Table 4

Summary of Pharmacokinetic Parameters for VWF:CB
(Study 071001: Full PK Analysis Set / Crossover: PK50)

Treatment=rVWF							
Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
AUC _{0-96h} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	14	78.6 (69.3 to 87.9)	16.2	75.1 (69.2 to 97.0)	55.5;112.0	16.0 (69.2;85.2)	77.1 (68.6 to 86.7)
AUC _{0-inf} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	14	82.1 (71.7 to 92.5)	18.1	81.3 (71.2 to 99.8)	55.9;119.9	18.6 (71.2;89.9)	80.3 (70.8 to 91.0)
AUMC _{0-inf} /Dose [(h ² *U/dL)/(U VWF: RCo/kg)]	14	2374.1 (1863.8 to 2884.5)	883.9	2214.3 (1783.8 to 3185.2)	1099.1;3983.0	1115.1 (1783.8;2898.9)	2227.4 (1796.1 to 2762.2)
T _{1/2} [hours]	14	19.7 (17.4 to 22.1)	4.1	18.3 (17.4 to 24.8)	13.7;25.3	5.5 (17.4;22.9)	19.3 (17.1 to 21.8)
MRT [hours]	14	28.3 (25.0 to 31.6)	5.8	26.1 (25.1 to 33.2)	19.6;38.2	7.3 (25.1;32.3)	27.7 (24.6 to 31.2)
Cl [dL/kg/hours]	14	0.013 (0.011 to 0.014)	0.003	0.012 (0.011 to 0.015)	0.008;0.018	0.003 (0.011;0.014)	0.012 (0.011 to 0.014)
V _{ss} [dL/kg]	14	0.35 (0.31 to 0.39)	0.07	0.36 (0.28 to 0.42)	0.24;0.46	0.12 (0.28;0.40)	0.35 (0.31 to 0.39)
C _{max} [U/dL]	14	166.2 (142.1 to 190.4)	41.8	163.5 (139.0 to 186.0)	124.0;294.0	35.0 (139.0;174.0)	162.4 (143.5 to 183.7)
T _{max} [hours]	14	0.76 (0.57 to 0.96)	0.34	0.68 (0.52 to 0.90)	0.40;1.55	0.32 (0.52;0.83)	0.71 (0.56 to 0.89)
IR at C _{max} [(U/dL)/(U VWF: RCo/kg)]	14	3.3 (2.8 to 3.8)	0.8	3.2 (2.8 to 3.7)	2.5;5.8	0.7 (2.8;3.5)	3.3 (2.9 to 3.7)

Table 5

Summary of Pharmacokinetic Parameters for VWF:AG
(Study 071001: Full PK Analysis Set / Crossover: PK50)

Treatment=rVWF:rFVIII							
Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
AUC _{0-96h} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	16	62.9 (53.4 to 72.4)	17.9	62.1 (52.8 to 74.9)	25.9;100.3	21.5 (52.6;74.1)	60.1 (50.4 to 71.7)
AUC _{0-inf} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	16	67.6 (57.2 to 78.0)	19.5	67.8 (55.1 to 81.7)	27.1;108.9	25.7 (55.0;80.7)	64.6 (54.1 to 77.0)
AUMC _{0-inf} /Dose [(h ² *U/dL)/(U VWF: RCo/kg)]	16	2355.1 (1820.5 to 2889.7)	1003.3	2140.6 (1707.7 to 3249.4)	864.4;4211.4	1535.8 (1700.1;3235.9)	2135.0 (1654.2 to 2755.5)
T _{1/2} [hours]	16	22.7 (19.9 to 25.4)	5.2	21.8 (19.5 to 27.2)	15.7;33.7	8.2 (18.8;26.9)	22.1 (19.6 to 25.0)
MRT [hours]	16	33.8 (30.0 to 37.5)	7.1	32.1 (29.8 to 41.1)	22.5;47.2	11.0 (28.9;39.9)	33.1 (29.5 to 37.0)
Cl [dL/kg/hours]	16	0.016 (0.013 to 0.020)	0.007	0.015 (0.013 to 0.018)	0.009;0.037	0.006 (0.012;0.018)	0.015 (0.013 to 0.018)
V _{ss} [dL/kg]	16	0.54 (0.43 to 0.64)	0.19	0.50 (0.45 to 0.56)	0.34;1.18	0.11 (0.44;0.56)	0.51 (0.44 to 0.60)
C _{max} [U/dL]	16	110.3 (97.8 to 122.8)	23.4	116.0 (101.0 to 126.0)	44.0;138.0	26.0 (99.5;125.5)	107.1 (92.5 to 124.0)
T _{max} [hours]	16	0.75 (0.55 to 0.95)	0.38	0.62 (0.50 to 0.78)	0.35;1.60	0.28 (0.49;0.77)	0.68 (0.54 to 0.86)
IR at C _{max} [(U/dL)/(U VWF: RCo/kg)]	16	2.2 (1.9 to 2.4)	0.5	2.3 (2.0 to 2.5)	0.9;2.9	0.5 (2.0;2.5)	2.1 (1.8 to 2.5)

Table 6

Summary of Pharmacokinetic Parameters for VWF:AG
(Study 071001: Full PK Analysis Set / Crossover: PK50)

Treatment=rVWF							
Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
AUC _{0-96h} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	14	64.4 (57.7 to 71.2)	11.7	62.2 (54.7 to 74.5)	47.2;85.8	18.4 (54.7;73.1)	63.5 (57.2 to 70.4)
AUC _{0-inf} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	14	69.5 (61.0 to 77.9)	14.6	67.1 (55.6 to 80.5)	51.6;98.5	20.9 (55.6;76.5)	68.1 (60.6 to 76.6)
AUMC _{0-inf} /Dose [(h ² *U/dL)/(U VWF: RCo/kg)]	14	2474.3 (1922.9 to 3025.7)	955.0	2155.7 (1699.7 to 3025.3)	1290.5;4449.7	1210.5 (1699.7;2910.1)	2318.9 (1873.1 to 2870.9)
T _{1/2} [hours]	14	25.1 (22.1 to 28.0)	5.1	25.2 (21.9 to 30.3)	15.7;32.0	7.7 (21.9;29.6)	24.5 (21.6 to 27.8)
MRT [hours]	14	34.7 (30.7 to 38.6)	6.8	34.3 (30.4 to 41.4)	23.2;45.2	10.3 (30.4;40.7)	34.0 (30.2 to 38.3)
Cl [dL/kg/hours]	14	0.015 (0.013 to 0.017)	0.003	0.015 (0.013 to 0.018)	0.010;0.019	0.005 (0.013;0.018)	0.015 (0.013 to 0.017)
V _{ss} [dL/kg]	14	0.51 (0.45 to 0.56)	0.09	0.49 (0.45 to 0.58)	0.38;0.71	0.12 (0.45;0.57)	0.50 (0.45 to 0.55)
C _{max} [U/dL]	14	107.2 (96.6 to 117.8)	18.4	110.0 (95.0 to 125.0)	76.0;139.0	26.0 (95.0;121.0)	105.7 (95.5 to 117.0)
T _{max} [hours]	14	1.07 (0.65 to 1.49)	0.73	0.87 (0.53 to 1.55)	0.40;3.12	0.80 (0.53;1.33)	0.90 (0.64 to 1.26)
IR at C _{max} [(U/dL)/(U VWF: RCo/kg)]	14	2.1 (1.9 to 2.4)	0.4	2.2 (1.9 to 2.5)	1.5;2.8	0.5 (1.9;2.4)	2.1 (1.9 to 2.3)

Table 7

Summary of Pharmacokinetic Parameters for FVIII:C
(Study 071001: Full PK Analysis Set / Crossover: PK50)

Treatment=rVWF:rFVIII							
Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
AUC _{0-96h} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	16	128.0 (106.2 to 149.8)	40.9	127.8 (112.3 to 145.1)	48.7;207.1	36.1 (107.8;143.9)	121.2 (100.1 to 146.7)
AUC _{0-inf} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	16	157.3 (119.8 to 194.8)	70.4	145.4 (118.8 to 189.5)	52.0;323.0	69.0 (113.0;182.0)	143.6 (113.2 to 182.2)
AUMC _{0-inf} /Dose [(h ² *U/dL)/(U VWF: RCo/kg)]	16	9808.2 (4822.2 to 14794.2)	9357.0	6403.8 (5004.3 to 13306.5)	1975.9;33331.5	6495.7 (4559.9;11055.6)	7237.8 (4839.9 to 10823.7)
T _{1/2} [hours]	16	32.3 (22.3 to 42.4)	18.9	24.8 (20.1 to 50.5)	13.3;75.8	28.8 (17.7;46.4)	27.9 (20.7 to 37.5)
MRT [hours]	16	54.6 (41.5 to 67.7)	24.6	44.0 (38.0 to 75.0)	33.5;115.0	32.0 (36.6;68.6)	50.4 (40.8 to 62.2)
Cl [dL/kg/hours]	16	0.008 (0.006 to 0.010)	0.004	0.007 (0.006 to 0.009)	0.003;0.019	0.003 (0.006;0.009)	0.007 (0.005 to 0.009)
V _{ss} [dL/kg]	16	0.37 (0.30 to 0.45)	0.14	0.32 (0.29 to 0.44)	0.16;0.73	0.15 (0.29;0.44)	0.35 (0.29 to 0.43)
C _{max} [U/dL]	16	110.9 (93.3 to 128.4)	32.9	114.0 (96.0 to 135.0)	61.0;192.0	39.0 (90.5;129.5)	106.3 (90.5 to 124.9)
T _{max} [hours]	16	9.59 (4.43 to 14.75)	9.69	7.43 (1.18 to 23.43)	0.62;24.47	16.88 (1.02;17.89)	4.28 (1.94 to 9.44)
IR at C _{max} [(U/dL)/(U VWF: RCo/kg)]	16	2.2 (1.9 to 2.5)	0.6	2.3 (1.9 to 2.7)	1.2;3.8	0.8 (1.8;2.6)	2.1 (1.8 to 2.5)

Table 8

Summary of Pharmacokinetic Parameters for FVIII:C
(Study 071001: Full PK Analysis Set / Crossover: PK50)

Treatment=rVWF							
Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
AUC _{0-96h} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	14	104.4 (83.2 to 125.7)	36.9	101.8 (74.4 to 124.4)	58.9;181.8	45.4 (74.4;119.9)	99.0 (81.6 to 120.1)
AUC _{0-inf} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	14	123.9 (100.6 to 147.1)	40.3	113.0 (93.0 to 167.4)	70.9;198.5	73.4 (93.0;166.4)	117.9 (97.7 to 142.4)
AUMC _{0-inf} /Dose [(h ² *U/dL)/(U VWF: RCo/kg)]	14	7912.8 (3829.0 to 11996.6)	7073.0	5838.2 (3880.9 to 9918.5)	3230.6;30543.2	5976.1 (3880.9;9857.1)	6379.6 (4494.6 to 9055.0)
T _{1/2} [hours]	14	31.2 (15.1 to 47.4)	27.9	23.3 (18.1 to 36.0)	12.0;124.0	16.2 (18.1;34.3)	25.6 (18.4 to 35.6)
MRT [hours]	14	60.0 (38.5 to 81.6)	37.3	47.7 (43.3 to 70.7)	35.0;182.5	21.9 (43.3;65.2)	54.1 (42.5 to 68.9)
Cl [dL/kg/hours]	14	0.009 (0.007 to 0.011)	0.003	0.009 (0.006 to 0.012)	0.005;0.014	0.005 (0.006;0.011)	0.008 (0.007 to 0.010)
V _{ss} [dL/kg]	14	0.50 (0.37 to 0.64)	0.23	0.45 (0.34 to 0.70)	0.20;1.09	0.25 (0.34;0.59)	0.46 (0.36 to 0.59)
C _{max} [U/dL]	14	90.5 (70.0 to 111.0)	35.6	87.0 (67.0 to 100.0)	47.0;173.0	31.0 (67.0;98.0)	84.9 (68.8 to 104.8)
T _{max} [hours]	14	28.64 (23.77 to 33.51)	8.43	24.42 (23.90 to 30.55)	22.43;47.62	6.52 (23.90;30.42)	27.73 (24.00 to 32.04)
IR at C _{max} [(U/dL)/(U VWF: RCo/kg)]	14	1.8 (1.4 to 2.2)	0.7	1.7 (1.3 to 2.0)	1.0;3.5	0.6 (1.3;2.0)	1.7 (1.4 to 2.1)

Table 9

Summary of Pharmacokinetic Parameters for VWF:RCo
(Study 071001: Full PK Analysis Set / Repeated: PK80 – All Subjects)

Visit=PK1

Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
AUC _{0-96h} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	15	34.9 (30.3 to 39.4)	8.3	35.6 (28.9 to 41.2)	18.7;47.9	12.3 (28.9;41.2)	33.8 (29.3 to 39.1)
AUC _{0-inf} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	15	36.2 (31.3 to 41.1)	8.9	36.9 (29.2 to 41.7)	19.0;50.4	12.6 (29.2;41.7)	35.0 (30.1 to 40.7)
AUMC _{0-inf} /Dose [(h ² *U/dL)/(U VWF: RCo/kg)]	15	945.6 (749.1 to 1142.1)	354.9	875.5 (669.1 to 1246.3)	420.3;1476.0	577.2 (669.1;1246.3)	880.9 (706.5 to 1098.4)
T _{1/2} [hours]	15	19.1 (16.4 to 21.9)	4.9	18.4 (16.4 to 22.1)	10.3;29.1	5.8 (16.4;22.1)	18.5 (16.0 to 21.5)
MRT [hours]	15	25.7 (22.7 to 28.7)	5.4	26.4 (20.9 to 31.1)	16.9;33.5	10.2 (20.9;31.1)	25.1 (22.2 to 28.4)
Cl [dL/kg/hours]	15	0.030 (0.025 to 0.035)	0.009	0.027 (0.024 to 0.034)	0.020;0.053	0.010 (0.024;0.034)	0.029 (0.025 to 0.033)
V _{ss} [dL/kg]	15	0.75 (0.63 to 0.87)	0.22	0.78 (0.58 to 0.86)	0.43;1.16	0.29 (0.58;0.86)	0.72 (0.61 to 0.85)
C _{max} [U/dL]	15	155.1 (137.9 to 172.4)	31.1	147.0 (133.0 to 175.0)	114.0;230.0	42.0 (133.0;175.0)	152.4 (137.2 to 169.4)
T _{max} [hours]	15	0.57 (0.44 to 0.70)	0.23	0.45 (0.42 to 0.72)	0.40;1.20	0.30 (0.42;0.72)	0.54 (0.44 to 0.65)
IR at C _{max} [(U/dL)/(U VWF: RCo/kg)]	15	1.9 (1.7 to 2.2)	0.4	1.8 (1.7 to 2.2)	1.4;2.9	0.5 (1.7;2.2)	1.9 (1.7 to 2.1)

Table 10

Summary of Pharmacokinetic Parameters for VWF:RCo
(Study 071001: Full PK Analysis Set / Repeated: PK80 – All Subjects)

Visit=PK2

Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
AUC _{0-96h} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	13	34.9 (29.0 to 40.7)	9.7	37.9 (25.9 to 41.8)	20.7;54.2	12.6 (28.1;40.7)	33.6 (28.3 to 39.9)
AUC _{0-inf} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	13	36.7 (30.2 to 43.2)	10.7	38.9 (28.1 to 43.3)	22.3;56.7	15.0 (28.3;43.3)	35.3 (29.5 to 42.2)
AUMC _{0-inf} /Dose [(h ² *U/dL)/(U VWF: RCo/kg)]	13	1050.6 (740.8 to 1360.4)	512.6	922.3 (679.1 to 1518.5)	464.4;2330.0	513.1 (731.6;1244.7)	953.5 (726.5 to 1251.4)
T _{1/2} [hours]	13	21.2 (16.3 to 26.2)	8.2	19.8 (15.2 to 23.6)	10.6;39.3	6.6 (16.4;23.0)	20.0 (16.0 to 24.8)
MRT [hours]	13	27.8 (23.4 to 32.3)	7.4	26.4 (23.7 to 32.8)	16.4;46.2	5.6 (23.7;29.3)	27.0 (23.2 to 31.4)
Cl [dL/kg/hours]	13	0.030 (0.024 to 0.035)	0.009	0.026 (0.023 to 0.036)	0.018;0.045	0.012 (0.023;0.035)	0.028 (0.024 to 0.034)
V _{ss} [dL/kg]	13	0.80 (0.64 to 0.97)	0.27	0.75 (0.58 to 1.01)	0.47;1.47	0.35 (0.59;0.93)	0.77 (0.63 to 0.93)
C _{max} [U/dL]	13	149.0 (127.5 to 170.5)	35.6	139.0 (127.0 to 164.0)	87.0;231.0	30.0 (130.0;160.0)	145.2 (126.0 to 167.4)
T _{max} [hours]	13	0.57 (0.44 to 0.70)	0.22	0.45 (0.42 to 0.82)	0.40;1.10	0.23 (0.43;0.67)	0.54 (0.44 to 0.66)
IR at C _{max} [(U/dL)/(U VWF: RCo/kg)]	13	1.9 (1.6 to 2.1)	0.4	1.8 (1.6 to 2.0)	1.1;2.9	0.4 (1.6;2.0)	1.8 (1.6 to 2.1)

Table 11

Summary of Pharmacokinetic Parameters for VWF:CB
(Study 071001: Full PK Analysis Set / Repeated: PK80 – All Subjects)

Visit=PK1

Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
AUC _{0-96h} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	15	73.5 (62.4 to 84.7)	20.1	71.9 (57.0 to 89.8)	38.1;109.2	32.8 (57.0;89.8)	70.9 (60.6 to 83.0)
AUC _{0-inf} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	15	77.1 (64.9 to 89.4)	22.1	73.9 (57.3 to 96.2)	39.0;115.8	38.9 (57.3;96.2)	74.1 (62.9 to 87.4)
AUMC _{0-inf} /Dose [(h ² *U/dL)/(U VWF: RCo/kg)]	15	2382.1 (1811.5 to 2952.6)	1030.3	2215.4 (1540.2 to 3003.8)	949.0;4344.5	1463.6 (1540.2;3003.8)	2174.7 (1695.1 to 2790.0)
T _{1/2} [hours]	15	20.5 (18.2 to 22.8)	4.2	18.8 (16.6 to 24.9)	14.0;26.3	8.3 (16.6;24.9)	20.1 (17.9 to 22.5)
MRT [hours]	15	29.9 (26.5 to 33.3)	6.2	30.9 (24.3 to 35.0)	22.4;40.8	10.7 (24.3;35.0)	29.3 (26.2 to 32.9)
Cl [dL/kg/hours]	15	0.014 (0.012 to 0.017)	0.004	0.014 (0.010 to 0.017)	0.009;0.026	0.007 (0.010;0.017)	0.013 (0.011 to 0.016)
Vss [dL/kg]	15	0.41 (0.35 to 0.46)	0.10	0.39 (0.34 to 0.46)	0.24;0.62	0.12 (0.34;0.46)	0.40 (0.35 to 0.45)
C _{max} [U/dL]	15	246.0 (219.0 to 273.0)	48.7	245.0 (222.0 to 286.0)	163.0;356.0	64.0 (222.0;286.0)	241.5 (216.3 to 269.7)
T _{max} [hours]	15	0.59 (0.42 to 0.75)	0.30	0.45 (0.42 to 0.55)	0.40;1.25	0.13 (0.42;0.55)	0.54 (0.43 to 0.67)
IR at C _{max} [(U/dL)/(U VWF: RCo/kg)]	15	3.1 (2.7 to 3.4)	0.6	3.1 (2.8 to 3.6)	2.1;4.5	0.8 (2.8;3.6)	3.0 (2.7 to 3.4)

Table 12

Summary of Pharmacokinetic Parameters for VWF:CB
(Study 071001: Full PK Analysis Set / Repeated: PK80 – All Subjects)

Visit=PK2

Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
AUC _{0-96h} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	13	80.7 (69.3 to 92.2)	19.0	88.1 (63.8 to 96.3)	43.9;106.4	29.8 (66.0;95.8)	78.4 (66.8 to 91.9)
AUC _{0-inf} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	13	85.1 (72.2 to 98.1)	21.4	90.8 (66.0 to 105.2)	46.2;110.8	37.6 (66.8;104.3)	82.3 (69.4 to 97.5)
AUMC _{0-inf} /Dose [(h ² *U/dL)/(U VWF: RCo/kg)]	13	2721.9 (2016.1 to 3427.7)	1168.0	2608.4 (1503.7 to 3705.4)	1140.3;4539.1	1853.0 (1711.6;3564.6)	2478.6 (1873.4 to 3279.3)
T _{1/2} [hours]	13	21.1 (18.2 to 24.0)	4.8	20.9 (17.8 to 23.5)	14.5;29.8	5.4 (18.0;23.3)	20.7 (18.0 to 23.6)
MRT [hours]	13	30.9 (26.5 to 35.2)	7.2	28.7 (25.6 to 37.2)	21.1;43.2	9.5 (25.9;35.4)	30.1 (26.2 to 34.6)
Cl [dL/kg/hours]	13	0.013 (0.010 to 0.015)	0.004	0.011 (0.010 to 0.015)	0.009;0.022	0.005 (0.010;0.015)	0.012 (0.010 to 0.014)
Vss [dL/kg]	13	0.37 (0.32 to 0.43)	0.09	0.36 (0.33 to 0.40)	0.24;0.64	0.06 (0.33;0.39)	0.37 (0.32 to 0.42)
C _{max} [U/dL]	13	283.3 (239.7 to 326.9)	72.1	298.0 (211.0 to 324.0)	174.0;448.0	103.0 (217.0;320.0)	274.9 (235.5 to 321.0)
T _{max} [hours]	13	0.76 (0.55 to 0.97)	0.35	0.65 (0.45 to 1.18)	0.42;1.20	0.72 (0.45;1.17)	0.69 (0.52 to 0.91)
IR at C _{max} [(U/dL)/(U VWF: RCo/kg)]	13	3.5 (3.0 to 4.1)	0.9	3.7 (2.7 to 4.0)	2.2;5.6	1.2 (2.7;3.9)	3.4 (3.0 to 4.0)

Table 13

Summary of Pharmacokinetic Parameters for VWF:AG
(Study 071001: Full PK Analysis Set / Repeated: PK80 – All Subjects)

Visit=PK1							
Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
AUC _{0-96h} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	15	63.6 (54.2 to 73.1)	17.0	61.3 (48.8 to 73.7)	42.1;92.3	24.9 (48.8;73.7)	61.6 (53.2 to 71.3)
AUC _{0-inf} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	15	70.4 (59.1 to 81.8)	20.5	66.6 (50.4 to 89.4)	45.7;106.8	39.0 (50.4;89.4)	67.8 (58.0 to 79.3)
AUMC _{0-inf} /Dose [(h ² *U/dL)/(U VWF: RCo/kg)]	15	2811.5 (2085.2 to 3537.9)	1311.6	2503.9 (1922.0 to 3118.9)	1292.8;5216.7	1196.9 (1922.0;3118.9)	2550.9 (1982.5 to 3282.4)
T _{1/2} [hours]	15	27.8 (23.8 to 31.8)	7.2	27.5 (22.5 to 34.0)	17.7;39.7	11.5 (22.5;34.0)	26.9 (23.3 to 31.2)
MRT [hours]	15	38.7 (33.6 to 43.7)	9.2	38.4 (31.9 to 48.1)	24.6;54.2	16.1 (31.9;48.1)	37.6 (32.9 to 43.0)
Cl [dL/kg/hours]	15	0.015 (0.013 to 0.018)	0.004	0.015 (0.011 to 0.020)	0.009;0.022	0.009 (0.011;0.020)	0.015 (0.013 to 0.017)
V _{ss} [dL/kg]	15	0.57 (0.48 to 0.67)	0.17	0.55 (0.46 to 0.61)	0.33;1.00	0.15 (0.46;0.61)	0.55 (0.48 to 0.64)
C _{max} [U/dL]	15	182.1 (159.6 to 204.6)	40.6	175.0 (151.0 to 209.0)	110.0;274.0	58.0 (151.0;209.0)	177.9 (157.1 to 201.4)
T _{max} [hours]	15	0.55 (0.41 to 0.70)	0.26	0.45 (0.42 to 0.55)	0.40;1.22	0.13 (0.42;0.55)	0.52 (0.42 to 0.63)
IR at C _{max} [(U/dL)/(U VWF: RCo/kg)]	15	2.3 (2.0 to 2.6)	0.5	2.2 (1.9 to 2.6)	1.4;3.5	0.7 (1.9;2.6)	2.2 (2.0 to 2.5)

Table 14

Summary of Pharmacokinetic Parameters for VWF:AG
(Study 071001: Full PK Analysis Set / Repeated: PK80 – All Subjects)

Visit=PK2							
Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
AUC _{0-96h} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	13	72.8 (61.5 to 84.1)	18.7	77.4 (53.0 to 87.6)	37.9;102.6	29.0 (54.5;83.5)	70.3 (59.1 to 83.6)
AUC _{0-inf} /Dose [(h*U/dL)/(U VWF: RCo/kg)]	13	80.4 (66.8 to 94.1)	22.6	86.9 (54.9 to 100.5)	40.9;109.9	38.9 (56.3;95.2)	77.1 (63.8 to 93.2)
AUMC _{0-inf} /Dose [(h ² *U/dL)/(U VWF: RCo/kg)]	13	3290.6 (2354.1 to 4227.1)	1549.8	3535.5 (1589.2 to 4556.9)	1426.6;6120.3	2291.0 (1596.0;3887.0)	2941.2 (2165.0 to 3995.8)
T _{1/2} [hours]	13	27.2 (22.8 to 31.6)	7.3	24.8 (21.1 to 37.7)	20.0;40.4	5.8 (21.6;27.4)	26.4 (22.8 to 30.7)
MRT [hours]	13	39.2 (33.3 to 45.0)	9.7	36.9 (30.0 to 50.8)	28.2;56.4	12.6 (30.9;43.5)	38.1 (33.1 to 44.0)
Cl [dL/kg/hours]	13	0.014 (0.011 to 0.016)	0.005	0.012 (0.010 to 0.018)	0.009;0.024	0.007 (0.011;0.018)	0.013 (0.011 to 0.016)
V _{ss} [dL/kg]	13	0.51 (0.43 to 0.58)	0.13	0.50 (0.41 to 0.57)	0.32;0.85	0.12 (0.43;0.55)	0.49 (0.43 to 0.57)
C _{max} [U/dL]	13	192.2 (165.0 to 219.4)	45.0	193.0 (158.0 to 230.0)	126.0;291.0	59.0 (165.0;224.0)	187.5 (162.8 to 215.9)
T _{max} [hours]	13	0.70 (0.52 to 0.88)	0.30	0.65 (0.45 to 1.17)	0.42;1.18	0.35 (0.47;0.82)	0.64 (0.51 to 0.82)
IR at C _{max} [(U/dL)/(U VWF: RCo/kg)]	13	2.4 (2.1 to 2.7)	0.6	2.4 (2.0 to 2.9)	1.6;3.6	0.7 (2.1;2.8)	2.3 (2.0 to 2.7)

Table 15

Summary of Pharmacokinetic Parameters for FVIII:C
(Study 071001: Full PK Analysis Set / Repeated: PK80 – All Subjects)

Visit=PK1

Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
$AUC_{0-96h}/Dose [(h*U/dL)/(U VWF: RCo/kg)]$	15	80.3 (63.3 to 97.4)	30.8	81.7 (54.7 to 104.3)	31.9;133.1	49.5 (54.7;104.3)	74.0 (57.8 to 94.6)
$AUC_{0-inf}/Dose [(h*U/dL)/(U VWF: RCo/kg)]$	15	100.1 (76.6 to 123.6)	42.5	96.8 (64.0 to 126.5)	37.0;174.7	62.4 (64.0;126.5)	91.0 (70.1 to 118.1)
$AUMC_{0-inf}/Dose [(h^2*U/dL)/(U VWF: RCo/kg)]$	15	6621.7 (4125.5 to 9117.9)	4507.5	5430.6 (3400.2 to 8258.3)	1724.8;19450.8	4858.1 (3400.2;8258.3)	5521.8 (3924.2 to 7769.7)
$T_{1/2}$ [hours]	15	34.1 (27.0 to 41.1)	12.8	28.3 (26.3 to 40.4)	18.3;67.3	14.1 (26.3;40.4)	32.2 (26.6 to 38.9)
MRT [hours]	15	62.5 (52.9 to 72.1)	17.4	55.9 (53.1 to 71.0)	43.5;113.5	17.9 (53.1;71.0)	60.7 (52.9 to 69.5)
Cl [dL/kg/hours]	15	0.012 (0.009 to 0.016)	0.006	0.010 (0.008 to 0.016)	0.006;0.027	0.008 (0.008;0.016)	0.011 (0.008 to 0.014)
Vss [dL/kg]	15	0.73 (0.53 to 0.93)	0.35	0.66 (0.45 to 0.93)	0.40;1.64	0.48 (0.45;0.93)	0.67 (0.53 to 0.84)
C_{max} [U/dL]	15	108.5 (91.9 to 125.2)	30.1	105.0 (82.0 to 132.0)	53.0;159.0	50.0 (82.0;132.0)	104.4 (88.5 to 123.1)
T_{max} [hours]	15	29.61 (24.32 to 34.91)	9.56	24.37 (24.13 to 29.88)	23.72;48.20	5.75 (24.13;29.88)	28.46 (24.42 to 33.17)
IR at C_{max} [(U/dL)/(U VWF: RCo/kg)]	15	1.4 (1.2 to 1.6)	0.4	1.3 (1.0 to 1.7)	0.7;2.0	0.6 (1.0;1.7)	1.3 (1.1 to 1.5)

Table 16

Summary of Pharmacokinetic Parameters for FVIII:C
(Study 071001: Full PK Analysis Set / Repeated: PK80 – All Subjects)

Visit=PK2

Parameter [unit]	N	Mean (95% CI)	SD	Median (95% CI)	Min;Max	IQR (Q1;Q3)	Geometric Mean (95% CI)
$AUC_{0-96h}/Dose [(h*U/dL)/(U VWF: RCo/kg)]$	13	67.7 (55.6 to 79.8)	20.0	71.8 (49.6 to 89.2)	31.6;96.1	26.2 (56.3;82.5)	64.5 (52.7 to 79.1)
$AUC_{0-inf}/Dose [(h*U/dL)/(U VWF: RCo/kg)]$	13	97.7 (63.7 to 131.7)	56.3	94.8 (60.4 to 106.5)	35.3;266.8	31.2 (68.7;99.9)	87.2 (65.3 to 116.4)
$AUMC_{0-inf}/Dose [(h^2*U/dL)/(U VWF: RCo/kg)]$	13	9384.0 (1098.3 to 17669.6)	13711.4	6400.6 (3538.6 to 8216.4)	1632.0;54337.3	3635.9 (3766.4;7402.3)	6080.3 (3698.7 to 9995.2)
$T_{1/2}$ [hours]	13	42.9 (26.6 to 59.3)	27.1	37.0 (28.5 to 41.5)	16.9;127.3	5.6 (35.3;40.9)	38.1 (28.7 to 50.6)
MRT [hours]	13	76.2 (51.2 to 101.1)	41.3	67.5 (52.1 to 78.9)	41.1;203.7	13.5 (58.6;72.1)	69.7 (54.8 to 88.7)
Cl [dL/kg/hours]	13	0.013 (0.009 to 0.016)	0.006	0.011 (0.009 to 0.017)	0.004;0.028	0.005 (0.010;0.015)	0.011 (0.009 to 0.015)
Vss [dL/kg]	13	0.84 (0.67 to 1.00)	0.27	0.76 (0.55 to 1.06)	0.52;1.34	0.32 (0.65;0.97)	0.80 (0.66 to 0.97)
C_{max} [U/dL]	13	91.3 (76.8 to 105.8)	24.0	98.0 (72.0 to 112.0)	48.0;126.0	39.0 (73.0;112.0)	87.9 (73.4 to 105.3)
T_{max} [hours]	13	29.20 (22.10 to 36.30)	11.75	28.92 (23.85 to 46.35)	11.67;48.25	6.22 (23.95;30.17)	26.87 (20.55 to 35.12)
IR at C_{max} [(U/dL)/(U VWF: RCo/kg)]	13	1.1 (1.0 to 1.3)	0.3	1.2 (0.9 to 1.4)	0.6;1.6	0.5 (0.9;1.4)	1.1 (0.9 to 1.3)

STUDY #3

Study Title: Co-infusion of recombinant von Willebrand Factor/recombinant Factor VIII (rVWF:rFVIII): a phase 1 study evaluating the pharmacokinetics, safety and tolerability in severe hemophilia A (study # 071104).

The purpose of the study was to evaluate whether co-infusion of BAX 111 can extend half-life of rFVIII in subjects with severe hemophilia A and to assess the immediate safety and tolerability of BAX 111 in subjects with hemophilia A.

The objectives of this study were to:

- Evaluate the immediate tolerability and safety after single doses of 50 IU/kg FVIII alone or in combination with BAX 111 at 10 or 50 IU/kg VWF:RCo.
- Evaluate the pharmacokinetics after single doses of 50 IU/kg rFVIII alone or in combination with BAX 111 at 10 or 50 IU/kg (VWF:RCo).

This study was a phase 1, prospective, uncontrolled, non-randomized, multicenter proof of concept study to assess safety and pharmacokinetics of the addition of BAX 111 to rFVIII treatment in 12 evaluable subjects with severe hemophilia A. All subjects underwent 3 PK analyses: the first with rFVIII alone, the second with rFVIII plus 10 IU/kg BAX 111, and the third rFVIII with 50 IU/kg BAX 111. Three infusions of rFVIII (50 IU/kg) without or with BAX 111 10 IU/kg or BAX 111 50 IU/kg were given approximately 8 to 14 days apart.

The subjects were male and 21 to 56 years old, had severe hemophilia A (FVIII:C <1%) and had received previous treatment with plasma-derived FVIII concentrates or recombinant FVIII (≥ 150 exposure days (EDs)). The results of the pharmacokinetic study ((b) (4) assay) are summarized in Table 1. A similar result was obtained with the chromogenic assay.

**Table 1: Summary of pharmacokinetic parameters of factor VIII
with and without BAX 111 ((b) (4) assay)**

Parameters	rFVIII (50 IU/kg)	rFVIII + 10 IU/kg BAX 111	rFVIII + 50 IU/kg BAX 111
AUC (U*hr/dL)	1636 \pm 589	1834 \pm 725	2070 \pm 542
CL (mL/hr/kg)	0.05 \pm 0.07	0.042 \pm 0.051	0.026 \pm 0.009
Half-life (hrs)	13.5 \pm 5.0	12.2 \pm 4.5	14.2 \pm 4.2

Comments and conclusion: Co-administration of rFVIII with BAX 111 did not improve the half-life of rFVIII at both 10 and 50 IU/kg BAX 111 dose. However, based on arithmetic mean, co-administration of rFVIII with BAX 111 at 50 IU/kg dose led to a 26% increase in the AUC of rFVIII and a decrease in clearance by 50%. Based on geometric mean, co-administration of rFVIII with BAX 111 at 50 IU/kg dose led to a 41% increase in the AUC of rFVIII and a

decrease in clearance by 28%. This is a substantial change in the PK of rFVIII which may impact the dose of rFVIII if given with BAX 111 at 50 IU/kg dose.

Comments sent to the applicant:

Co-administration of rFVIII with BAX 111 did not improve the half-life of rFVIII at both 10 and 50 IU/kg BAX 111 dose. However, based on arithmetic mean, co-administration of rFVIII with BAX 111 at 50 IU/kg dose led to a 26% increase in the AUC of rFVIII and a decrease in clearance by 50%. Based on geometric mean, co-administration of rFVIII with BAX 111 at 50 IU/kg dose led to a 41% increase in the AUC of rFVIII and a decrease in clearance by 28%. This is a substantial change in the PK of rFVIII which may impact the dose of rFVIII if given with BAX 111 at 50 IU/kg dose. Please comment.

Baxter Response

The data quoted above refer to the exploratory study (071104) in which the PK of rFVIII when administered with or without rVWF was assessed in patients with hemophilia A. In the pivotal study of the use of rVWF in severe VWD patients (study 071001), the co-administration of BAX111 should and did affect the half-life of the infused rFVIII which would otherwise be only a few hours in patients with severe VWF deficiency. In fact, the PK of rFVIII observed in the pivotal study appeared to be slightly better than that seen with pdVWF concentrates, which may serve to limit the need for a second rFVIII infusion in most cases.

Administration of rVWF at a dose of 50 IU/kg resulted in initial levels of rFVIII consistent with those observed in previous studies of hemophilia A patients, who have normal levels of VWF. Sustained levels of FVIII seen thereafter in the pivotal study represent contributions from both the infused rFVIII and stabilization of endogenous FVIII, which is synthesized normally in VWD patients. Based on the pivotal study data, Baxter recommends to infuse rVWF with rFVIII at a ratio of 1.3:1 for the initial infusion, if baseline factor VIII levels are below 40% or are unknown, to ensure rapid hemostasis. Also, based on the pivotal study data, it is predicted that co-administration of rFVIII will only be needed with the first dose of rVWF in most clinical circumstances.

Reviewer's Comment: The applicant has not provided a satisfactory response to the comment which is mainly related to the dose of von Willebrand factor. Since the observation is based on an exploratory study and may not be of clinical significance, this issue will not be pursued further.