TREATMENT OF COAGULATION DISEASE BY ADMINISTRATION OF RECOMBINANT VWF

BACKGROUND OF THE INVENTION

[0001] Coagulation diseases, such as von Willebrand Disease (VWD) and Hemophilia, generally result from a deficiency in the coagulation cascade. "von Willebrand Disease" refers to the group of diseases caused by a deficiency of von Willebrand factor. Von Willebrand factor helps blood platelets clump together and stick to the blood vessel wall, which is necessary for normal blood clotting. Hemophilia A refers to a deficiency of Factor VIII activity, whereas Hemophilia B refers to a Factor IX deficiency. Current treatment for these coagulopathies includes a replacement therapy using pharmaceutical preparations comprising the normal coagulation factor.

[0002] Replacement therapy in VWD and Hemophilia A patients involves the repeated administration of preparations containing normal coagulation factors via intravenous infusion, which can constitute a heavy load on the life of these patients, particularly when venous access is difficult to achieve. It would be advantageous if the frequency of infusions could be reduced. One potentially viable therapy is to stabilize Factor VIII through its association with a second molecule, such as von Willebrand Factor (VWF), with the result that plasma half-life of Factor VIII is increased.

[0003] VWF is a glycoprotein circulating in plasma as a series of multimers ranging in size from about 500 to 20,000 kD. The full length of cDNA of VWF has been cloned; the propolypeptide corresponds to amino acid residues 23 to 764 of the full length prepro-VWF (Eikenboom et al (1995) Haemophilia 1, 77 90). Multimeric forms of VWF are composed of 250 kD polypeptide subunits linked together by disulfide bonds. VWF mediates the initial platelet adhesion to the sub-endothelium of the damaged vessel wall, with the larger multimers exhibiting enhanced hemostatic activity. Multimerized VWF binds to the platelet surface glycoprotein Gp1bα, through an interaction in the A1 domain of VWF, facilitating platelet adhesion. Other sites on VWF mediate binding to the blood vessel wall. Thus, VWF forms a bridge between the platelet and the vessel wall that is essential to platelet adhesion and primary hemostasis under conditions of high shear stress. Normally, endothelial cells secrete large polymeric forms of VWF and those forms of VWF that have a lower molecular weight arise from proteolytic cleavage. The multimers of exceptionally large molecular masses are stored in the Weibel-Pallade bodies of the endothelial cells and liberated upon stimulation by agonists such as thrombin and histamine.

[0004] That FVIII pharmacokinetics are a function of VWF levels is supported by several previous observations. Reduction of FVIII binding activity in von Willebrand Disease (VWD), due to either reduced VWF protein levels or lowered FVIII binding affinity, results in reduced steady-state levels of endogenous FVIII (summarized in Castaman *et al.*, Disorders of Hemostasis 88(1):94-108 (2003), and improving survival of VWF has been proposed as a viable strategy for improving FVIII stability (Denis et al., Thromb Haemost. 2008 Feb;99(2):271-8; Turecek et al., Blood, 2006, 108(11): Abstract 1002). Among severe Hemophilia A patients, a correlation between pre-infusion VWF levels and the half-life of infused FVIII has been demonstrated by Fijnvandraat and colleagues (Fijnvandraat, et al., Br J Haematol. 1995 Oct;91(2):474-6). In that study, patients with 200-300% of average VWF levels were seen to have a FVIII half-life of 15-29 hours compared to a mean of 12.5 hours in patients with normal VWF levels. In another study, patients with blood group O were demonstrated to have significantly lower VWF levels and shorter FVIII half-lives (15.3 hours) compared with those with blood group A (19.7 hours) (Vlot, et al. Thromb Haemost. 2000 Jan;83(1):65-9). Chemically modified VWF has been shown to prolong survival of rFVIII (Turecek et al., J. Thromb. Haemost. 2007 Jul 9; 5(2) abstract available at: http/www.blackwellpublishing.com/isth2007/abstract.asp?id=64898). As such, co-administration of rVWF and rFVIII is a viable strategy for the treatment of coagulation diseases such as von Willebrand Disease and Hemophilia A.

BRIEF SUMMARY OF THE INVENTION

[0005] Accordingly, the present invention provides methods and combinations for treating coagulation disease by administering recombinant von Willebrand Factor (rVWF) alone or in combination with recombinant Factor VIII (rFVIII) to a subject in need thereof, with the result that the *in-vivo* half-life of Factor VIII is increased.

[0006] In one aspect, the present invention provides a method for treating Von Willebrand Disease or Hemophilia A in a subject in need thereof, the method comprising: administering to the subject recombinant Von Willebrand Factor (rVWF) such that Factor VIII half-life is extended as compared to a subject administered plasma derived Von Willebrand Factor, wherein the rVWF is a high molecular weight VWF multimer composition comprising at least 20% VWF decamers or higher order multimers, and wherein the rVWF has a higher specific activity than plasma derived Von Willebrand Factor.

[0007] In further embodiments and in accordance with the above, methods of the invention include co-administering to the subject recombinant Von Willebrand Factor (rVWF) and recombinant Factor VIII (rFVIII).

[0008] In further embodiments and in accordance with any of the above, the rVWF and rFVIII are administered together in a single composition.

[0009] In further embodiments and in accordance with any of the above, the subject is administered between 1.0 IU/kg VWF:RCo and 150 IU/kg VWF:RCo per dose.

[0010] In further embodiments and in accordance with any of the above, the subject is administered between 2 IU/kg VWF:RCo and 50 IU/kg VWF:RCo per dose.

[0011] In further embodiments and in accordance with any of the above, the subject is administered between 5 IU/kg VWF:RCo and 40 IU/kg VWF:RCo per dose.

[0012] In further embodiments and in accordance with any of the above, the subject is administered between 10 IU/kg VWF:RCo and 20 IU/kg VWF:RCo per dose.

[0013] In further embodiments and in accordance with any of the above, the rVWF used in methods of the invention is matured in vitro by treatment with Furin.

[0014] In further embodiments and in accordance with any of the above, the rVWF is produced through expression in a Chinese Hamster Ovary (CHO cell culture).

[0015] In further embodiments and in accordance with any of the above, the rFVIII and rVWF are produced through expression in the same cell culture.

[0016] In further embodiments, and in accordance with any of the above, the subject is administered rVWF no more than once every other day.

[0017] In further embodiments and in accordance with any of the above, the subject is administered rVWF no more than twice a week.

[0018] In further aspects and in accordance with any of the above, the high molecular weight VWF multimer composition maintains the at least 20% VWF decamers or higher order multimers for at least 3 hours post-administration.

[0019] In further embodiments and in accordance with any of the above, the Factor VIII half-life is extended by about 5 hours.

[0020] In further embodiments and in accordance with any of the above, the Factor VIII half-life is extended for at least 12 hours.

[0021] In further embodiments and in accordance with any of the above, the Factor VIII half-life is extended for at least 24 hours.

[0022] In further embodiments and in accordance with any of the above, the Factor VIII half-life is extended for at least 36 hours.

[0023] In further embodiments and in accordance with any of the above, the Factor VIII half-life is extended for at least 48 hours.

[0024] In further embodiments and in accordance with any of the above, wherein the Factor VIII half-life is extended for at least 72 hours.

[0025] In further embodiments and in accordance with any of the above, the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 2:1 and 1:4.

[0026] In further embodiments and in accordance with any of the above, the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 3:2 and 1:3.

[0027] In further embodiments and in accordance with any of the above, the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 1:1 and 1:2.

[0028] In further embodiments and in accordance with any of the above, 23 the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is about 3:4.

[0029] In further embodiments and in accordance with any of the above, the rVWF has a specific activity of about 20-150 mU/μg.

[0030] In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition comprises at least 30% VWF decamers or higher order multimers.

[0031] In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition comprises at least 40% VWF decamers or higher order multimers.

[0032] In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition comprises at least 50% VWF decamers or higher order multimers.

[0033] In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition comprises at least 60% VWF decamers or higher order multimers.

[0034] In further embodiments and in accordance with any of the above, the high molecular weight VWF multimer composition comprises at least 70% VWF decamers or higher order multimers.

[0035] In further aspects and in accordance with any of the above, the present invention provides a method for treating Hemophilia A or Von Willebrand Disease in a subject in need thereof, the method comprising: administering to the subject recombinant Von Willebrand Factor (rVWF) such that Factor VIII half-life is extended as compared to a subject administered plasma derived Von Willebrand Factor, wherein: (a) the rVWF has a higher specific activity than plasma derived Von Willebrand Factor, wherein the specific activity of

rVWF is about 20-150 mU/µg; and (b) the FVIII half-life is at least 1.5 times higher as compared to FVIII half-life in a subject administered plasma derived Von Willebrand Factor.

[0036] In further aspects and in accordance with any of the above, the present invention provides a method for treating Hemophilia A or Von Willebrand Disease in a subject in need thereof, the method comprising: administering to the subject recombinant Von Willebrand Factor (rVWF) such that Factor VIII half-life is extended as compared to a subject administered plasma derived Von Willebrand Factor, wherein: (a) the rVWF is a high molecular weight VWF multimer composition comprising at least 20% VWF decamers or higher order multimers, (b) the rVWF has a higher specific activity than plasma derived Von Willebrand Factor, wherein the specific activity of rVWF is at least about 20-150 mU/µg; and (c) the FVIII half-life is at least 1.5 times higher as compared to FVIII half-life in a subject administered plasma derived Von Willebrand Factor.

[0037] In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 24 hours post-administration of the rVWF is at least 90% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

[0038] In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 24 hours post-administration is at least 100% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

[0039] In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 36 hours post-administration is at least 80% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

[0040] In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 48 hours post-administration is at least 50% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

[0041] In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 6 hours post-administration.

[0042] In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 12 hours post-administration.

[0043] In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 18 hours post-administration.

[0044] In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 24 hours post-administration.

[0045] In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 36 hours post-administration.

[0046] In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 48 hours post-administration.

[0047] In further embodiments and in accordance with any of the above, the higher order rVWF multimers are stable for at least 72 hours post-administration.

[0048] In further aspects and in accordance with any of the above, the present invention provides a method for treating Hemophilia A or Von Willebrand Disease in a subject in need thereof, the method comprising: administering to the subject recombinant Von Willebrand Factor (rVWF).

[0049] In further embodiments and in accordance with any of the above, the method comprises co-administering to the subject recombinant Factor VIII (rFVIII) and recombinant Von Willebrand Factor (rVWF).

[0050] In further embodiments and in accordance with any of the above, the rFVIII and rVWF are administered together in a single composition.

[0051] In further embodiments and in accordance with any of the above, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 2:1 and 1:4.

[0052] In further embodiments and in accordance with any of the above, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 3:2 and 1:3.

[0053] In further embodiments and in accordance with any of the above, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is between 1:1 and 1:2.

[0054] In further embodiments and in accordance with any of the above, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) administered to the subject is about 3:4.

[0055] In further embodiments and in accordance with any of the above, the rVWF is matured *in vitro* by treatment with Furin.

[0056] In further embodiments and in accordance with any of the above, the rVWF is expressed in mammalian cell culture.

[0057] In further embodiments and in accordance with any of the above, the rFVIII is expressed in mammalian cell culture.

[0058] In further embodiments and in accordance with any of the above, the mammalian culture comprises CHO cells.

[0059] In further embodiments and in accordance with any of the above, the rFVIII and rVWF are co-expressed in the same culture.

[0060] In further embodiments and in accordance with any of the above, the rFVIII and rVWF are co-purified.

[0061] In further embodiments and in accordance with any of the above, the rFVIII and rVWF are purified separately.

[0062] In further embodiments and in accordance with any of the above, a rFVIII/rVWF complex is reconstituted prior to administration.

[0063] In further embodiments and in accordance with any of the above, rVWF is treated with Furin prior to reconstituting the rFVIII/rVWF complex.

[0064] In further embodiments and in accordance with any of the above, the reconstituted rFVIII/rVWF complex is treated with Furin.

[0065] In further embodiments and in accordance with any of the above, the Furin is recombinant Furin.

[0066] In further embodiments and in accordance with any of the above, the subject is administered rVWF no more than once daily.

[0067] In further embodiments and in accordance with any of the above, the subject is administered rVWF no more than once every other day.

[0068] In further embodiments and in accordance with any of the above, the subject is co-administered rVWF no more than once every third day.

[0069] In further embodiments and in accordance with any of the above, the subject is administered rVWF no more than once every fourth day.

[0070] In further embodiments and in accordance with any of the above, the subject is administered between 1.5 IU/kg FVIII:C and 150 IU/kg FVIII:C per dose.

[0071] In further embodiments and in accordance with any of the above, the subject is administered between 10 IU/kg FVIII:C and 100 IU/kg FVIII:C per dose.

[0072] In further embodiments and in accordance with any of the above, the subject is administered between 25 IU/kg FVIII:C and 75 IU/kg FVIII:C per dose.

[0073] In further embodiments and in accordance with any of the above, the subject is administered between 40 IU/kg FVIII:C and 60 IU/kg FVIII:C per dose.

[0074] In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 24 hours post-administration

is at least 90% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

[0075] In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 24 hours post-administration is at least 100% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

[0076] In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 36 hours post-administration is at least 80% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

[0077] In further embodiments and in accordance with any of the above, the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 48 hours post-administration is at least 50% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

[0078] In further embodiments and in accordance with any of the above, the rVWF administered to the subject has a HMW VWF multimer composition comprising at least 10% VWF decamers or higher order multimers.

[0079] In further embodiments and in accordance with any of the above, the rVWF administered to the subject has a HMW VWF multimer composition comprising at least 20% VWF decamers or higher order multimers.

[0080] In further embodiments and in accordance with any of the above, the rVWF administered to the subject has a HMW VWF multimer composition comprising at least 30% VWF decamers or higher order multimers.

[0081] In further embodiments and in accordance with any of the above, the rVWF administered to the subject has a HMW VWF multimer composition comprising at least 40% VWF decamers or higher order multimers.

[0082] In further embodiments and in accordance with any of the above, the rVWF administered to the subject has a HMW VWF multimer composition comprising at least 50% VWF decamers or higher order multimers.

[0083] In further embodiments and in accordance with any of the above, higher order rVWF multimers are stable *in vitro* for at least 3 hours post-administration.

[0084] In further embodiments and in accordance with any of the above, higher order rVWF multimers are stable *in vitro* for at least 6 hours post-administration.

[0085] In further embodiments and in accordance with any of the above, wherein higher order rVWF multimers are stable *in vitro* for at least 12 hours post-administration.

[0086] In further embodiments and in accordance with any of the above, wherein higher order rVWF multimers are stable *in vitro* for at least 18 hours post-administration.

[0087] In further embodiments and in accordance with any of the above, higher order rVWF multimers are stable *in vitro* for at least 24 hours post-administration.

[0088] In further embodiments and in accordance with any of the above, higher order rVWF multimers are stable *in vitro* for at least 36 hours post-administration.

[0089] In further embodiments and in accordance with any of the above, wherein higher order rVWF multimers are stable *in vitro* for at least 48 hours post-administration.

[0090] In further embodiments and in accordance with any of the above, higher order rVWF multimers are stable *in vitro* for at least 72 hours post-administration.

[0091] In further embodiments and in accordance with any of the above, endogenous FVIII activity is stabilized for at least 12 hours.

[0092] In further embodiments and in accordance with any of the above, endogenous FVIII activity is stabilized for at least 24 hours.

[0093] In further embodiments and in accordance with any of the above, endogenous FVIII activity is stabilized for at least 36 hours.

[0094] In further embodiments and in accordance with any of the above, endogenous FVIII activity is stabilized for at least 48 hours.

[0095] In further embodiments and in accordance with any of the above, endogenous FVIII activity is stabilized for at least 72 hours.

[0096] In further embodiments and in accordance with any of the above, wherein co-administered rFVIII activity is stabilized for at least 12 hours.

[0097] In further embodiments and in accordance with any of the above, co-administered rFVIII activity is stabilized for at least 24 hours.

[0098] In further embodiments and in accordance with any of the above, co-administered rFVIII activity is stabilized for at least 36 hours.

[0099] In further embodiments and in accordance with any of the above, co-administered rFVIII activity is stabilized for at least 48 hours.

[00100] In further embodiments and in accordance with any of the above, co-administered rFVIII activity is stabilized for at least 72 hours.

[00101] In further embodiments and in accordance with any of the above, co-administered rFVIII activity is stabilized by extending the half-life of the rFVIII *in vivo*.

[00102] In further embodiments and in accordance with any of the above, FVIII half-life is extended by about five hours as compared to a patient administered pdFVIII.

[00103] In further embodiments and in accordance with any of the above, at least 1% of the co-administered rFVIII activity is maintained for at least 36 hours in a patient administered said rFVIII.

[00104] In further embodiments and in accordance with any of the above, at least 1% of the co-administered rFVIII activity is maintained for at least 48 hours in a patient administered said rFVIII.

[00105] In further embodiments and in accordance with any of the above, at least 1% of the co-administered rFVIII activity is maintained for at least 72 hours in a patient administered said rFVIII.

[00106] In further embodiments and in accordance with any of the above, at least 1% of the co-administered rFVIII activity is maintained for at least 90 hours in a patient administered said rFVIII.

[00107] In further embodiments and in accordance with any of the above, at least 1% of the co-administered rFVIII activity is maintained for at least 120 hours in a patient administered said rFVIII.

[00108] In further embodiments and in accordance with any of the above, at least 1% of the co-administered rFVIII activity is maintained for at least 168 hours in a patient administered said rFVIII.

BRIEF DESCRIPTION OF THE DRAWINGS

[00109] Figure 1. A schematic of the study design assessing tolerability and safety after single doses of rVWF:rFVIII.

[00110] Figure 2. Pharmacokinetic data. (A) provides PK data for rVWF/rFVIII and pdVWF/pdFVIII. (B) provides data on progressive loss of high molecular weight rVWF upon exposure to ADAMTS13.

[00111] Figure 3. Pharmacokinetic data showing FVIII PK for rVWF/rFVIII and pdVWF/pdFVIII.

[00112] Figure 4. Table summarizing patient demographics for the study.

[00113] Figure 5. Pharmacokinetic data of rVWF/rFVIII and pdVWF/pdFVIII treatment of Cohort 4A.

[00114] Figure 6. SDS-PAGE data on VWF multimer cleavage by ADAMTS13.

[00115] Figure 7. Pharmacokinetic data of rVWF/rFVIII and pdVWF/pdFVIII treatment of Cohort 4A.

[00116] Figure 8. Summary of adverse events from the study.

[00117] Figure 9. rVWF PK parameters data from the study.

[00118] Figure 10. rVWF PK data from Patient 1.

[00119] Figure 11. rVWF PK data from Patient 2.

[00120] Figure 12. rVWF PK data from Patient 3.

[00121] Figure 13. Comparison of rVWF PK in Patients 1, 2 and 3 – comparison of the VWF parameters and FVIII activity.

[00122] Figure 14. FVIII activity across all cohorts in the study.

[00123] Figure 15. rVWF PK in patients of Cohort 2 – comparison of VWF parameters and FVIII activity.

[00124] Figure 16. Summary of pharmacokinetic parameters for Factor VIII procoagulant activity (FVIII:C) for patients in Cohort 2.

[00125] Figure 17. rVWF PK in all patients of Cohort 3 – comparison of plasma parameters for VWF and FVIII.

[00126] Figure 18. Summary of pharmacokinetic parameters for Factor VIII procoagulant activity (FVIII:C) for patients in Cohort 3.

[00127] Figure 19. Data from patients in Cohort 4.

[00128] Figure 20. Summary of pharmacokinetic parameters for Factor VIII procoagulant activity (FVIII:C) for patients in Cohort 4A.

[00129] Figure 21. Pharmacokinetic data of FVIII:C comparing co-administered rVWF and rFVIII to Advate Pivotal.

[00130] Figure 22. Antibody summary for a subject receiving co-administered pdVWF/pdFVIII or rVWF/rFVIII.

DETAILED DESCRIPTION OF THE INVENTION

Overview

[00131] The present invention provides compositions and methods for treating coagulation disease in a subject by administering recombinant von Willebrand Factor (rVWF) alone or in combination with Factor VIII (which can be recombinant or plasma derived). In some aspects, the compositions and methods of the present invention are used for treating coagulation diseases such as von Willebrand Disease (VWD) or Hemophilia A.

[00132] In one aspect, rVWF administered to the subject provides increased stability for *in vivo* Factor VIII (FVIII) activity as compared to FVIII stability due to administered plasma derived VWF, allowing for lower doses and/or frequency of treatment than in traditional treatments for coagulation diseases. Increased stability of FVIII activity and levels of FVIII can be measured using methods known in the art and described herein, including standard

assays such as one-stage clotting assays, chromogenic assays, and immunoassays (see for example Lippi et al., Blood Coagulation & Fibrinolysis, 2009, 20(1):1-3 and Chandler et al., Am J. Clin. Pathol., 2003, 120:34-39, each of which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings related to assays of FVIII level and activity). As shown in FIG. 20, average FVIII half-life was increased by rVWF by 5.2 hours over the half-life for patients receiving pdVWF. FIGs. 2 and 7 also show increases in FVIII activity in patients administered rVWF as compared to those administered pdVWF: FIG. 2 shows that average FVIII half-life was increased by 4.7 hours for patients administered rVWF as compared to patients administered pdVWF, and the data from Cohort 4A in FIG. 7 shows an increase in FVIII half-life of 5.3 hours for patients administered rVWF as compared to patients administered pdVWF. In addition, as shown in FIG. 21, the half-life of plasma FVIII is increased by 12.27 hours in VWD patients receiving rVWF in combination with rFVIII as compared to patients receiving FVIII (i.e., Advate) alone.

[00133] In a further aspect, the administration of rVWF stabilizes endogenous and/or co-administered FVIII activity, with the result that the *in vivo* half-life and/or activity of FVIII is increased. In embodiments in which rVWF and FVIII are co-administered, the rVWF and FVIII can be administered to the subject together in a single composition. In further embodiments, neither rVWF nor FVIII are modified with a water soluble polymer. In other embodiments, either the rVWF or FVIII or both are modified with a water soluble polymer. As will be appreciated, in embodiments in which rVWF is co-administered with FVIII, the FVIII may be recombinant or plasma derived.

[00134] In further aspects and in accordance with any of the above, the rVWF administered to the subject is a high molecular weight multimer composition comprising decamers or higher order multimers of rVWF. As discussed above, the use of rVWF compositions of the invention provide therapeutic flexibility to dose (or re-dose) with or without FVIII (recombinant or plasma derived). In further embodiments, the rVWF administered to the subject is a high molecular weight VWF multimer composition comprising at least 20% VWF decamers or higher order multimers. In specific embodiments, the rVWF administered to subjects is not modified with a water soluble polymer.

[00135] In still further aspects, the rVWF administered to the subject has a higher specific activity than pdVWF.

[00136] In a still further aspect, the rVWF alone or in combination with pdFVIII or rFVIII is administered to the subject no more than twice a week.

[00137] In a yet further aspect, the rVWF is processed with Furin prior to administration to the subject. In certain embodiments, the rVWF is processed with recombinant Furin.

[00138] In further aspects, the rVWF of use in the present invention is produced in accordance with methods known in the art and described for example in US 2012/0035110, filed July 8, 2011 and US Patent No. 8,173,597, issued May 8, 2012, each of which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings related to rVWF compositions and methods for producing those compositions.

[00139] In accordance with any of the above, rVWF alone or in combination with FVIII is used to treat patients with coagulation diseases, such as VWD and Hemophilia A. Patients with VWD have some level of FVIII, but the stability of that FVIII is generally compromised because these patients lack VWF. Treatment of VWD patients may in some embodiments involve an initial treatment with both rVWF and rFVIII followed by repeated administrations of rVWF alone. In other embodiments, the initial treatment may be with rVWF alone while subsequent repeated administrations are with both rVWF and rFVIII, or the initial and subsequent repeat administrations may all include a co-administration of both rVWF and rFVIII. Similarly, Hemophilia A patients (who lack FVIII) may receive an initial treatment of both rVWF and rFVIII, and subsequent repeat treatments may comprise the administration of rFVIII alone or rVWF alone. In other embodiments, the initial treatment may be rFVIII alone while the subsequent repeat treatments involve co-administration of rVWF and rFVIII.

Definitions

[00140] As used herein, "rVWF" refers to recombinant VWF.

[00141] As used herein, "rFVIII" refers to recombinant FVIII.

[00142] The term "recombinant" when used with reference, e.g., to a cell, or nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the cell is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all.

[00143] As used herein, "recombinant VWF" includes VWF obtained via recombinant DNA technology. In certain embodiments, VWF proteins of the invention can comprise a construct, for example, prepared as in WO 1986/06096 published on Oct. 23, 1986 and U.S. patent application Ser. No. 07/559,509, filed on Jul. 23, 1990, in the name of Ginsburg *et al.*, which is incorporated herein by reference with respect to the methods of producing recombinant VWF. The VWF in the present invention can include all potential forms, including the monomeric and multimeric forms. It should also be understood that the present

invention encompasses different forms of VWF to be used in combination. For example, the VWF of the present invention may include different multimers, different derivatives and both biologically active derivatives and derivatives not biologically active.

[00144] In the context of the present invention, the recombinant VWF embraces any member of the VWF family from, for example, a mammal such as a primate, human, monkey, rabbit, pig, rodent, mouse, rat, hamster, gerbil, canine, feline, and biologically active derivatives thereof. Mutant and variant VWF proteins having activity are also embraced, as are functional fragments and fusion proteins of the VWF proteins. Furthermore, the VWF of the invention may further comprise tags that facilitate purification, detection, or both. The VWF described herein may further be modified with a therapeutic moiety or a moiety suitable imaging *in vitro* or *in vivo*.

[00145] As used herein, "plasma-derived VWF (pdVWF)" includes all forms of the protein found in blood including the mature VWF obtained from a mammal having the property of in vivo-stabilizing, e.g. binding, of at least one FVIII molecule.

[00146] The term “highly multimeric VWF” or “high molecular weight VWF” refers to VWF comprising at least 10 subunits, or 12, 14, or 16 subunits, to about 20, 22, 24 or 26 subunits or more**.** The term “subunit” refers to a monomer of VWF. As is known in the art, it is generally dimers of VWF that polymerize to form the larger order multimers. (*see* Turecek et al., Semin. Thromb. Hemost. 2010, 36(5): 510-521 which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings regarding multimer analysis of VWF).

[00147] As used herein, the term "factor VIII" or "FVIII" refers to any form of factor VIII molecule with the typical characteristics of blood coagulation factor VIII, whether endogenous to a patient, derived from blood plasma, or produced through the use of recombinant DNA techniques, and including all modified forms of factor VIII. Factor VIII (FVIII) exists naturally and in therapeutic preparations as a heterogeneous distribution of polypeptides arising from a single gene product (*see, e.g.,* Andersson et al., *Proc. Natl. Acad. Sci. USA*, 83:2979-2983 (1986)). Commercially available examples of therapeutic preparations containing Factor VIII include those sold under the trade names of HEMOFIL M, ADVATE, and RECOMBINATE (available from Baxter Healthcare Corporation, Deerfield, Ill., U.S.A.).

[00148] As used herein, “plasma FVIII activity” and “in vivo FVIII activity” are used interchangeably. The in vivo FVIII activity measured using standard assays may be endogenous FVIII activity, the activity of a therapeutically administered FVIII (recombinant

or plasma derived), or both endogenous and administered FVIII activity. Similarly, "plasma FVIII" refers to endogenous FVIII or administered recombinant or plasma derived FVIII.

[00149] As used herein "von Willebrand Disease" refers to the group of diseases caused by a deficiency of von Willebrand factor. Von Willebrand factor helps blood platelets clump together and stick to the blood vessel wall, which is necessary for normal blood clotting. As described in further detail herein, there are several types of Von Willebrand disease.

[00150] As used herein, the terms "hemophilia" or "haemophilia" refer to a group of disease states broadly characterized by reduced blood clotting or coagulation. Hemophilia may refer to Type A, Type B, or Type C hemophilia, or to the composite of all three diseases types. Type A hemophilia (hemophilia A) is caused by a reduction or loss of factor VIII (FVIII) activity and is the most prominent of the hemophilia subtypes. Type B hemophilia (hemophilia B) results from the loss or reduction of factor IX (FIX) clotting function. Type C hemophilia (hemophilia C) is a consequence of the loss or reduction in factor XI (FXI) clotting activity. Hemophilia A and B are X-linked diseases, while hemophilia C is autosomal. Common treatments for hemophilia include both prophylactic and on-demand administration of clotting factors, such as FVIII, FIX, including Bebulin®–VH, and FXI, as well as FEIBA-VH, desmopressin, and plasma infusions.

[00151] The terms "isolated," "purified," or "biologically pure" refer to material that is substantially or essentially free from components that normally accompany it as found in its native state. Purity and homogeneity are typically determined using analytical chemistry techniques such as polyacrylamide gel electrophoresis or high performance liquid chromatography. VWF is the predominant species present in a preparation is substantially purified. The term "purified" in some embodiments denotes that a nucleic acid or protein gives rise to essentially one band in an electrophoretic gel. In other embodiments, it means that the nucleic acid or protein is at least 50% pure, more preferably at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more pure. "Purify" or "purification" in other embodiments means removing at least one contaminant from the composition to be purified. In this sense, purification does not require that the purified compound be homogenous, *e.g.*, 100% pure.

[00152] As used herein, "administering" (and all grammatical equivalents) includes intravenous administration, intramuscular administration, subcutaneous administration, oral administration, administration as a suppository, topical contact, intraperitoneal, intralesional, or intranasal administration, or the implantation of a slow-release device, *e.g.*, a mini-osmotic pump, to a subject. Administration is by any route including parenteral, and transmucosal (*e.g.*, oral, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.*,

intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc*.

[00153] The terms "therapeutically effective amount or dose" or "therapeutically sufficient amount or dose" or "effective or sufficient amount or dose" refer to a dose that produces therapeutic effects for which it is administered. For example, a therapeutically effective amount of a drug useful for treating hemophilia can be the amount that is capable of preventing or relieving one or more symptoms associated with hemophilia. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see, e.g.*, Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[00154] As used herein, the terms “patient” and “subject” are used interchangeably and refer to a mammal (preferably human) that has a disease or has the potential of contracting a disease.

[00155] As used herein, the term "about" denotes an approximate range of plus or minus 10% from a specified value. For instance, the language "about 20%" encompasses a range of 18-22%.

[00156] As used herein, the term “half-life” refers to the period of time it takes for the amount of a substance undergoing decay (or clearance from a sample or from a patient) to decrease by half.

Compositions of the invention

[00157] The present invention utilizes compositions comprising recombinant von Willebrand Factor (rVWF) for treatment of coagulation disease, such as VWD and Hemophilia A. In some embodiments, the present invention utilizes rVWF in combination with Factor VIII (FVIII). The co-administered FVIII may be recombinant (rFVIII) or plasma derived (pdFVIII). In preferred aspects, the compositions of the present invention stabilize *in vivo* Factor VIII activity (also referred to herein as plasma Factor VIII activity) such that the *in vivo* half-life of Factor VIII is extended as compared to that in subjects that have not been administered rVWF or that have been administered pdVWF. Measuring the extent to which rVWF stabilizes FVIII activity (including extension of FVIII half-life) can be carried out using methods known in the art. The level of FVIII activity can be measured by, for instance, one-stage clotting assays, chromogenic assays, and immunoassays (see for example Lippi et

al., Blood Coagulation & Fibrinolysis, 2009, 20(1):1-3, European Pharmacopoeia (Ph. Eur., 3.sup.rd Ed. 1997:2.7.4), and Chandler et al., Am J. Clin. Pathol., 2003, 120:34-39, each of which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings related to assays of FVIII level and activity).

[00158] In certain embodiments, VWF proteins of the invention may comprise a construct, for example, prepared as in WO 1986/06096 published on Oct. 23, 1986 and U.S. patent application Ser. No. 07/559,509, filed on Jul. 23, 1990, in the name of Ginsburg et al., which is incorporated herein by reference with respect to the methods of producing recombinant VWF. The VWF useful for the present invention includes all potential forms, including the monomeric and multimeric forms. One particularly useful form of VWF are homo-multimers of at least two VWFs. The VWF proteins may be either a biologically active derivative, or when to be used solely as a stabilizer for FVIII the VWF may be of a form not biologically active. It should also be understood that the present invention encompasses different forms of VWF to be used in combination. For example, a composition useful for the present invention may include different multimers, different derivatives and both biologically active derivatives and derivatives not biologically active.

[00159] In primary hemostasis VWF serves as a bridge between platelets and specific components of the extracellular matrix, such as collagen. The biological activity of VWF in this process can be measured by different in vitro assays (Turecek et al., Semin. Thromb. Hemost. 28: 149-160, 2002). The ristocetin cofactor assay is based on the agglutination of fresh or formalin-fixed platelets induced by the antibiotic ristocetin in the presence of VWF. The degree of platelet agglutination depends on the VWF concentration and can be measured by the turbidimetric method, e.g. by use of an aggregometer (Weiss et al., J. Clin. Invest. 52: 2708-2716, 1973; Macfarlane et al., Thromb. Diath. Haemorrh. 34: 306-308, 1975). The second method is the collagen binding assay, which is based on ELISA technology (Brown et Bosak, Thromb. Res. 43: 303-311, 1986; Favaloro, Thromb. Haemost. 83: 127-135, 2000). A microtiter plate is coated with type I or III collagen. Then the VWF is bound to the collagen surface and subsequently detected with an enzyme-labeled polyclonal antibody. The last step is the substrate reaction, which can be photometrically monitored with an ELISA reader. As provided herein, the specific Ristocetin Cofactor activity of the VWF (VWF:RCo) of the present invention is generally described in terms of mU/μg of VWF, as measured using *in vitro* assays.

[00160] An advantage of the rVWF compositions of the present invention over pdVWF is that rVWF exhibits a higher specific activity than pdVWF. In some embodiments, the rVWF of the invention has a specific activity of at least about 20, 22.5, 25, 27.5, 30, 32.5, 35,

37.5, 40, 42.5, 45, 47.5, 50, 52.5, 55, 57.5, 60, 62.5, 65, 67.5, 70, 72.5, 75, 77.5, 80, 82.5, 85, 87.5, 90, 92.5, 95, 97.5, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150 or more mU/µg. In one embodiment, rVWF used in the methods described herein has a specific activity of from 20 mU/µg to 150 mU/µg. In another embodiment, the VWF has a specific activity of from 30 mU/µg to 120 mU/µg. In another embodiment, the rVWF has a specific activity from 40 mU/µg to 90 mU/µg. In yet another embodiment, the rVWF has a specific activity selected from variations 1 to 133 found in **Table 1**.

Table 1. Exemplary embodiments for the specific activity of rVWF found in the compositions and used in the methods provided herein.

(mU/µg)		(mU/µg)		(mU/µg)		(mU/µg)	
20	Var. 1	110	Var. 35	40-150	Var. 68	70-120	Var. 101
22.5	Var. 2	115	Var. 36	40-140	Var. 69	70-110	Var. 102
25	Var. 3	120	Var. 37	40-130	Var. 70	70-100	Var. 103
27.5	Var. 4	125	Var. 38	40-120	Var. 71	70-90	Var. 104
30	Var. 5	130	Var. 39	40-110	Var. 72	70-80	Var. 105
32.5	Var. 6	135	Var. 40	40-100	Var. 73	80-150	Var. 106
35	Var. 7	140	Var. 41	40-90	Var. 74	80-140	Var. 107
37.5	Var. 8	145	Var. 42	40-80	Var. 75	80-130	Var. 108
40	Var. 9	150	Var. 43	40-70	Var. 76	80-120	Var. 109
42.5	Var. 10	20-150	Var. 44	40-60	Var. 77	80-110	Var. 110
45	Var. 11	20-140	Var. 45	40-50	Var. 78	80-100	Var. 111
47.5	Var. 12	20-130	Var. 46	50-150	Var. 79	80-90	Var. 112
50	Var. 13	20-120	Var. 47	50-140	Var. 80	90-150	Var. 113
52.5	Var. 14	20-110	Var. 48	50-130	Var. 81	90-140	Var. 114
55	Var. 15	20-100	Var. 49	50-120	Var. 82	90-130	Var. 115
57.5	Var. 16	20-90	Var. 50	50-110	Var. 83	90-120	Var. 116
60	Var. 17	20-80	Var. 51	50-100	Var. 84	90-110	Var. 117
62.5	Var. 18	20-70	Var. 52	50-90	Var. 85	90-100	Var. 118
65	Var. 19	20-60	Var. 53	50-80	Var. 86	100-150	Var. 119
67.5	Var. 20	20-50	Var. 54	50-70	Var. 87	100-140	Var. 120
70	Var. 21	20-40	Var. 55	50-60	Var. 88	100-130	Var. 121
72.5	Var. 22	30-150	Var. 56	60-150	Var. 89	100-120	Var. 122
75	Var. 23	30-140	Var. 57	60-140	Var. 90	100-110	Var. 123
77.5	Var. 24	30-130	Var. 58	60-130	Var. 91	110-150	Var. 124
80	Var. 25	30-120	Var. 59	60-120	Var. 92	110-140	Var. 125
82.5	Var. 26	30-110	Var. 60	60-110	Var. 93	110-130	Var. 126
85	Var. 27	30-100	Var. 61	60-100	Var. 94	110-120	Var. 127
87.5	Var. 28	30-90	Var. 62	60-90	Var. 95	120-150	Var. 128
90	Var. 29	30-80	Var. 63	60-80	Var. 96	120-140	Var. 129
92.5	Var. 30	30-70	Var. 64	60-70	Var. 97	120-130	Var. 130
95	Var. 31	30-60	Var. 65	70-150	Var. 98	130-150	Var. 131
97.5	Var. 32	30-50	Var. 66	70-140	Var. 99	130-140	Var. 132
100	Var. 33	30-40	Var. 67	70-130	Var. 100	140-150	Var. 133
105	Var. 34						

Var. = Variation

[00161] The rVWF of the present invention is highly multimeric comprising about 10 to about 40 subunits. In further embodiments, the multimeric rVWF produced using methods of the present invention comprise about 10-30, 12-28, 14-26, 16-24, 18-22, 20-21 subunits. In further embodiments, the rVWF is present in multimers varying in size from dimers to multimers of over 40 subunits (> 10 million Daltons). The largest multimers provide multiple binding sites that can interact with both platelet receptors and subendothelial matrix sites of injury, and are the most hemostatically active form of VWF. As shown in the multimer analysis in FIG. 2 (bottom panel), application of ADAMTS13 will cleave the ultra-large rVWF multimers over time, but during production (generally through expression in cell culture), rVWF compositions of the present invention are generally not exposed to ADAMTS13 and retain their highly multimeric structure.

[00162] In one embodiment, a rVWF composition used in the methods described herein has a distribution of rVWF oligomers characterized in that 95% of the oligomers have between 6 subunits and 20 subunits. In other embodiments, the a rVWF composition has a distribution of rVWF oligomers characterized in that 95% of the oligomers have a range of subunits selected from variations 458 to 641 found in **Table 2**.

Table 2. Exemplary embodiments for the distribution of rVWF oligomers found in the compositions and used in the methods provided herein.

Subunits		**Subunits**		**Subunits**		**Subunits**	
2-40	Var. 458	6-16	Var. 504	12-20	Var. 550	20-28	Var. 596
2-38	Var. 459	6-14	Var. 505	12-18	Var. 551	20-26	Var. 597
2-36	Var. 460	6-12	Var. 506	12-16	Var. 552	20-24	Var. 598
2-34	Var. 461	6-10	Var. 507	12-14	Var. 553	20-22	Var. 599
2-32	Var. 462	6-8	Var. 508	14-40	Var. 554	22-40	Var. 600
2-30	Var. 463	8-40	Var. 509	14-38	Var. 555	22-38	Var. 601
2-28	Var. 464	8-38	Var. 510	14-36	Var. 556	22-36	Var. 602
2-26	Var. 465	8-36	Var. 511	14-34	Var. 557	22-34	Var. 603
2-24	Var. 466	8-34	Var. 512	14-32	Var. 558	22-32	Var. 604
2-22	Var. 467	8-32	Var. 513	14-30	Var. 559	22-30	Var. 605
2-20	Var. 468	8-30	Var. 514	14-28	Var. 560	22-28	Var. 606
2-18	Var. 469	8-28	Var. 515	14-26	Var. 561	22-26	Var. 607
2-16	Var. 470	8-26	Var. 516	14-24	Var. 562	22-24	Var. 608
2-14	Var. 471	8-24	Var. 517	14-22	Var. 563	24-40	Var. 609
2-12	Var. 472	8-22	Var. 518	14-20	Var. 564	24-38	Var. 610
2-10	Var. 473	8-20	Var. 519	14-18	Var. 565	24-36	Var. 611
2-8	Var. 474	8-18	Var. 520	14-16	Var. 566	24-34	Var. 612
4-40	Var. 475	8-16	Var. 521	16-40	Var. 567	24-32	Var. 613
4-38	Var. 476	8-14	Var. 522	16-38	Var. 568	24-30	Var. 614
4-36	Var. 477	8-12	Var. 523	16-36	Var. 569	24-28	Var. 615
4-34	Var. 478	8-10	Var. 524	16-34	Var. 570	24-26	Var. 616
4-32	Var. 479	10-40	Var. 525	16-32	Var. 571	26-40	Var. 617

4-30	Var. 480	10-38	Var. 526	16-30	Var. 572	26-38	Var. 618
4-28	Var. 481	10-36	Var. 527	16-28	Var. 573	26-36	Var. 619
4-26	Var. 482	10-34	Var. 528	16-26	Var. 574	26-34	Var. 620
4-24	Var. 483	10-32	Var. 529	16-24	Var. 575	26-32	Var. 621
4-22	Var. 484	10-30	Var. 530	16-22	Var. 576	26-30	Var. 622
4-20	Var. 485	10-28	Var. 531	16-20	Var. 577	26-28	Var. 623
4-18	Var. 486	10-26	Var. 532	16-18	Var. 578	28-40	Var. 624
4-16	Var. 487	10-24	Var. 533	18-40	Var. 579	28-38	Var. 625
4-14	Var. 488	10-22	Var. 534	18-38	Var. 580	28-36	Var. 626
4-12	Var. 489	10-20	Var. 535	18-36	Var. 581	28-34	Var. 627
4-10	Var. 490	10-18	Var. 536	18-34	Var. 582	28-32	Var. 628
4-8	Var. 491	10-16	Var. 537	18-32	Var. 583	28-30	Var. 629
6-40	Var. 492	10-14	Var. 538	18-30	Var. 584	30-40	Var. 630
6-38	Var. 493	10-12	Var. 539	18-28	Var. 585	30-38	Var. 631
6-36	Var. 494	12-40	Var. 540	18-26	Var. 586	30-36	Var. 632
6-34	Var. 495	12-38	Var. 541	18-24	Var. 587	30-34	Var. 633
6-32	Var. 496	12-36	Var. 542	18-22	Var. 588	30-32	Var. 634
6-30	Var. 497	12-34	Var. 543	18-20	Var. 589	32-40	Var. 635
6-28	Var. 498	12-32	Var. 544	20-40	Var. 590	32-38	Var. 636
6-26	Var. 499	12-30	Var. 545	20-38	Var. 591	32-36	Var. 637
6-24	Var. 500	12-28	Var. 546	20-36	Var. 592	32-34	Var. 638
6-22	Var. 501	12-26	Var. 547	20-34	Var. 593	34-40	Var. 639
6-20	Var. 502	12-24	Var. 548	20-32	Var. 594	36-38	Var. 640
6-18	Var. 503	12-22	Var. 549	20-30	Var. 595	38-40	Var. 641

Var. = Variation

[00163] In one embodiment, a rVWF composition can be characterized according to the percentage of rVWF molecules that are present in a particular higher order rVWF multimer or larger multimer. For example, in one embodiment, at least 20% of rVWF molecules in a rVWF composition used in the methods described herein are present in an oligomeric complex of at least 10 subunits. In another embodiment, at least 20% of rVWF molecules in a rVWF composition used in the methods described herein are present in an oligomeric complex of at least 12 subunits. In yet other embodiments, a rVWF composition used in the methods provided herein has a minimal percentage (*e.g.*, has at least X%) of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer (*e.g.*, a multimer of at least Y subunits) according to any one of variations 134 to 457 found in **Table 3** to **Table 5**.

Table 3. Exemplary embodiments for the percentage of rVWF molecules that are present in a particular higher order rVWF multimer or larger multimer found in the compositions and used in the methods provided herein.

		Minimal Number of Subunits in rVWF Multimer					
		6	**8**	**10**	**12**	**14**	**16**
Minimal Percentage of rVWF Molecules Present in Multimer	**10%**	Var. 134	Var. 152	Var. 170	Var. 188	Var. 206	Var. 224

	15%	Var. 135	Var. 153	Var. 171	Var. 189	Var. 207	Var. 225
	20%	Var. 136	Var. 154	Var. 172	Var. 190	Var. 208	Var. 226
	25%	Var. 137	Var. 155	Var. 173	Var. 191	Var. 209	Var. 227
	30%	Var. 138	Var. 156	Var. 174	Var. 192	Var. 210	Var. 228
	35%	Var. 139	Var. 157	Var. 175	Var. 193	Var. 211	Var. 229
	40%	Var. 140	Var. 158	Var. 176	Var. 194	Var. 212	Var. 230
	45%	Var. 141	Var. 159	Var. 177	Var. 195	Var. 213	Var. 231
	50%	Var. 142	Var. 160	Var. 178	Var. 196	Var. 214	Var. 232
	55%	Var. 143	Var. 161	Var. 179	Var. 197	Var. 215	Var. 233
	60%	Var. 144	Var. 162	Var. 180	Var. 198	Var. 216	Var. 234
	65%	Var. 145	Var. 163	Var. 181	Var. 199	Var. 217	Var. 235
	70%	Var. 146	Var. 164	Var. 182	Var. 200	Var. 218	Var. 236
	75%	Var. 147	Var. 165	Var. 183	Var. 201	Var. 219	Var. 237
	80%	Var. 148	Var. 166	Var. 184	Var. 202	Var. 220	Var. 238
	85%	Var. 149	Var. 167	Var. 185	Var. 203	Var. 221	Var. 239
	90%	Var. 150	Var. 168	Var. 186	Var. 204	Var. 222	Var. 240
	95%	Var. 151	Var. 169	Var. 187	Var. 205	Var. 223	Var. 241

Var. = Variation

Table 4. Exemplary embodiments for the percentage of rVWF molecules that are present in a particular higher order rVWF multimer or larger multimer found in the compositions and used in the methods provided herein.

		Minimal Number of Subunits in rVWF Multimer					
		18	**20**	**22**	**24**	**26**	**28**
Minimal Percentage of rVWF Molecules	**10%**	Var. 242	Var. 260	Var. 278	Var. 296	Var. 314	Var. 332
	15%	Var. 243	Var. 261	Var. 279	Var. 297	Var. 315	Var. 333
	20%	Var. 244	Var. 262	Var. 280	Var. 298	Var. 316	Var. 334
	25%	Var. 245	Var. 263	Var. 281	Var. 299	Var. 317	Var. 335
	30%	Var. 246	Var. 264	Var. 282	Var. 300	Var. 318	Var. 336
	35%	Var. 247	Var. 265	Var. 283	Var. 301	Var. 319	Var. 337
	40%	Var. 248	Var. 266	Var. 284	Var. 302	Var. 320	Var. 338
	45%	Var. 249	Var. 267	Var. 285	Var. 303	Var. 321	Var. 339
	50%	Var. 250	Var. 268	Var. 286	Var. 304	Var. 322	Var. 340
	55%	Var. 251	Var. 269	Var. 287	Var. 305	Var. 323	Var. 341
	60%	Var. 252	Var. 270	Var. 288	Var. 306	Var. 324	Var. 342
	65%	Var. 253	Var. 271	Var. 289	Var. 307	Var. 325	Var. 343
	70%	Var. 254	Var. 272	Var. 290	Var. 308	Var. 326	Var. 344
	75%	Var. 255	Var. 273	Var. 291	Var. 309	Var. 327	Var. 345
	80%	Var. 256	Var. 274	Var. 292	Var. 310	Var. 328	Var. 346
	85%	Var. 257	Var. 275	Var. 293	Var. 311	Var. 329	Var. 347
	90%	Var. 258	Var. 276	Var. 294	Var. 312	Var. 330	Var. 348
	95%	Var. 259	Var. 277	Var. 295	Var. 313	Var. 331	Var. 349

Var. = Variation

Table 5. Exemplary embodiments for the percentage of rVWF molecules that are present in a particular higher order rVWF multimer or larger multimer found in the compositions and used in the methods provided herein.

		Minimal Number of Subunits in rVWF Multimer					
		30	**32**	**34**	**36**	**38**	**40**
Minimal Percentage of rVWF Molecules	**10%**	Var. 350	Var. 368	Var. 386	Var. 404	Var. 422	Var. 440
	15%	Var. 351	Var. 369	Var. 387	Var. 405	Var. 423	Var. 441
	20%	Var. 352	Var. 370	Var. 388	Var. 406	Var. 424	Var. 442
	25%	Var. 353	Var. 371	Var. 389	Var. 407	Var. 425	Var. 443
	30%	Var. 354	Var. 372	Var. 390	Var. 408	Var. 426	Var. 444
	35%	Var. 355	Var. 373	Var. 391	Var. 409	Var. 427	Var. 445
	40%	Var. 356	Var. 374	Var. 392	Var. 410	Var. 428	Var. 446
	45%	Var. 357	Var. 375	Var. 393	Var. 411	Var. 429	Var. 447
	50%	Var. 358	Var. 376	Var. 394	Var. 412	Var. 430	Var. 448
	55%	Var. 359	Var. 377	Var. 395	Var. 413	Var. 431	Var. 449
	60%	Var. 360	Var. 378	Var. 396	Var. 414	Var. 432	Var. 450
	65%	Var. 361	Var. 379	Var. 397	Var. 415	Var. 433	Var. 451
	70%	Var. 362	Var. 380	Var. 398	Var. 416	Var. 434	Var. 452
	75%	Var. 363	Var. 381	Var. 399	Var. 417	Var. 435	Var. 453
	80%	Var. 364	Var. 382	Var. 400	Var. 418	Var. 436	Var. 454
	85%	Var. 365	Var. 383	Var. 401	Var. 419	Var. 437	Var. 455
	90%	Var. 366	Var. 384	Var. 402	Var. 420	Var. 438	Var. 456
	95%	Var. 367	Var. 385	Var. 403	Var. 421	Var. 439	Var. 457

Var. = Variation

[00164] In accordance with the above, the rVWF composition administered to the subject (with or without FVIII) generally comprises a significant percentage of high molecular weight (HMW) rVWF multimers. In further embodiments, the HMW rVWF multimer composition comprises at least 10% - 80% rVWF decamers or higher order multimers. In further embodiments, the composition comprises about 10-95%, 20-90%, 30-85%, 40-80%, 50-75%, 60-70% decamers or higher order multimers. In further embodiments, the HMW rVWF multimer composition comprises at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% decamers or higher order multimers.

[00165] Assessment of the number and percentage of rVWF multimers can be conducted using methods known in the art, including without limitation methods using electrophoresis and size exclusion chromatography methods to separate VWF multimers by size, for example as discussed by Cumming et al, (J Clin Pathol. 1993 May; 46(5): 470–473, which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings related to assessment of VWF multimers). Such techniques may further include immunoblotting techniques (such as Western Blot), in which the gel is immunoblotted with a radiolabelled antibody against VWF followed by chemiluminescent detection (see for

example Wen et al., (1993), J. Clin. Lab. Anal., 7: 317–323, which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings related to assessment of VWF multimers). Further assays for VWF include VWF:Antigen (VWF:Ag), VWF:Ristocetin Cofactor (VWF:RCof), and VWF:Collagen Binding Activity assay (VWF:CBA), which are often used for diagnosis and classification of Von Willebrand Disease. (see for example Favaloro et al., Pathology, 1997, 29(4): 341-456, which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings related to assays for VWF).

[00166] In further embodiments, higher order rVWF multimers of the invention are stable for about 1 to about 90 hours post-administration. In still further embodiments, the higher order rVWF multimers are stable for about 5-80, 10-70, 15-60, 20-50, 25-40, 30-35 hours post-administration. In yet further embodiments, the higher order rVWF multimers are stable for at least 3, 6, 12, 18, 24, 36, 48, 72 hours post-administration. In certain embodiments the stability of the rVWF multimers is assessed *in vitro*.

[00167] In one embodiment, higher order rVWF multimers used in the compositions and methods provided herein have a half life of at least 12 hour post administration. In another embodiment, the higher order rVWF multimers have a half life of at least 24 hour post administration. In yet other embodiments, the higher order rVWF multimers have a half life selected from variations 642 to 1045 found in **Table 6**.

Table 6. Exemplary embodiments for the half-life of higher order rVWF multimers found in the compositions and used in the methods provided herein.

Hours		**Hours**		**Hours**		**Hours**	
at least 1	Var. 642	4-22	Var. 743	14-78	Var. 844	24-30	Var. 945
at least 2	Var. 643	4-20	Var. 744	14-72	Var. 845	24-27	Var. 946
at least 3	Var. 644	4-18	Var. 745	14-66	Var. 846	27-90	Var. 947
at least 4	Var. 645	4-16	Var. 746	14-60	Var. 847	27-84	Var. 948
at least 5	Var. 646	4-14	Var. 747	14-54	Var. 848	27-78	Var. 949
at least 6	Var. 647	4-12	Var. 748	14-48	Var. 849	27-72	Var. 950
at least 7	Var. 648	4-10	Var. 749	14-45	Var. 850	27-66	Var. 951
at least 8	Var. 649	4-8	Var. 750	14-42	Var. 851	27-60	Var. 952
at least 9	Var. 650	4-6	Var. 751	14-39	Var. 852	27-54	Var. 953
at least 10	Var. 651	6-90	Var. 752	14-36	Var. 853	27-48	Var. 954
at least 11	Var. 652	6-84	Var. 753	14-33	Var. 854	30-90	Var. 955
at least 12	Var. 653	6-78	Var. 754	14-30	Var. 855	30-84	Var. 956
at least 14	Var. 654	6-72	Var. 755	14-27	Var. 856	30-78	Var. 957
at least 16	Var. 655	6-66	Var. 756	14-24	Var. 857	30-72	Var. 958
at least 18	Var. 656	6-60	Var. 757	14-22	Var. 858	30-66	Var. 959
at least 20	Var. 657	6-54	Var. 758	14-20	Var. 859	30-60	Var. 960
at least 22	Var. 658	6-48	Var. 759	14-18	Var. 860	30-54	Var. 961
at least 24	Var. 659	6-45	Var. 760	14-16	Var. 861	30-48	Var. 962

at least 27	Var. 660	6-42	Var. 761	16-90	Var. 862	30-45	Var. 963
at least 30	Var. 661	6-39	Var. 762	16-84	Var. 863	30-42	Var. 964
at least 33	Var. 662	6-36	Var. 763	16-78	Var. 864	30-39	Var. 965
at least 36	Var. 663	6-33	Var. 764	16-72	Var. 865	30-36	Var. 966
at least 39	Var. 664	6-30	Var. 765	16-66	Var. 866	30-33	Var. 967
at least 42	Var. 665	6-27	Var. 766	16-60	Var. 867	33-90	Var. 968
at least 45	Var. 666	6-24	Var. 767	16-54	Var. 868	33-84	Var. 969
at least 48	Var. 667	6-22	Var. 768	16-48	Var. 869	33-78	Var. 970
at least 54	Var. 668	6-20	Var. 769	16-45	Var. 870	33-72	Var. 971
at least 60	Var. 669	6-18	Var. 770	16-42	Var. 871	33-66	Var. 972
at least 66	Var. 670	6-16	Var. 771	16-39	Var. 872	33-60	Var. 973
at least 72	Var. 671	6-14	Var. 772	16-36	Var. 873	33-54	Var. 974
at least 78	Var. 672	6-12	Var. 773	16-33	Var. 874	33-48	Var. 975
at least 84	Var. 673	6-10	Var. 774	16-30	Var. 875	33-45	Var. 976
at least 90	Var. 674	6-8	Var. 775	16-27	Var. 876	33-42	Var. 977
2-90	Var. 675	8-90	Var. 776	16-24	Var. 877	33-29	Var. 978
2-84	Var. 676	8-84	Var. 777	16-22	Var. 878	33-36	Var. 979
2-78	Var. 677	8-78	Var. 778	16-20	Var. 879	36-90	Var. 980
2-72	Var. 678	8-72	Var. 779	16-18	Var. 880	36-84	Var. 981
2-66	Var. 679	8-66	Var. 780	18-90	Var. 881	36-78	Var. 982
2-60	Var. 680	8-60	Var. 781	18-84	Var. 882	36-72	Var. 983
2-54	Var. 681	8-54	Var. 782	18-78	Var. 883	36-66	Var. 984
2-48	Var. 682	8-48	Var. 783	18-72	Var. 884	36-60	Var. 985
2-45	Var. 683	8-45	Var. 784	18-66	Var. 885	36-54	Var. 986
2-42	Var. 684	8-42	Var. 785	18-60	Var. 886	36-48	Var. 987
2-39	Var. 685	8-39	Var. 786	18-54	Var. 887	36-45	Var. 988
2-36	Var. 686	8-36	Var. 787	18-48	Var. 888	36-42	Var. 989
2-33	Var. 687	8-33	Var. 788	18-45	Var. 889	36-39	Var. 990
2-30	Var. 688	8-30	Var. 789	18-42	Var. 890	39-90	Var. 991
2-27	Var. 689	8-27	Var. 790	18-39	Var. 891	39-84	Var. 992
2-24	Var. 690	8-24	Var. 791	18-36	Var. 892	39-78	Var. 993
2-22	Var. 691	8-22	Var. 792	18-33	Var. 893	39-72	Var. 994
2-20	Var. 692	8-20	Var. 793	18-30	Var. 894	39-66	Var. 995
2-18	Var. 693	8-18	Var. 794	18-27	Var. 895	39-60	Var. 996
2-16	Var. 694	8-16	Var. 795	18-24	Var. 896	39-54	Var. 997
2-14	Var. 695	8-14	Var. 796	18-22	Var. 897	39-48	Var. 998
2-12	Var. 696	8-12	Var. 797	18-20	Var. 898	39-45	Var. 999
2-10	Var. 697	8-10	Var. 798	20-90	Var. 899	39-42	Var. 1000
2-8	Var. 698	10-90	Var. 799	20-84	Var. 900	42-90	Var. 1001
2-6	Var. 699	10-84	Var. 800	20-78	Var. 901	42-84	Var. 1002
2-4	Var. 700	10-78	Var. 801	20-72	Var. 902	42-78	Var. 1003
3-90	Var. 701	10-72	Var. 802	20-66	Var. 903	42-72	Var. 1004
3-84	Var. 702	10-66	Var. 803	20-60	Var. 904	42-66	Var. 1005
3-78	Var. 703	10-60	Var. 804	20-54	Var. 905	42-60	Var. 1006
3-72	Var. 704	10-54	Var. 805	20-48	Var. 906	42-54	Var. 1007
3-66	Var. 705	10-48	Var. 806	20-45	Var. 907	42-48	Var. 1008
3-60	Var. 706	10-45	Var. 807	20-42	Var. 908	42-45	Var. 1009
3-54	Var. 707	10-42	Var. 808	20-39	Var. 909	45-90	Var. 1010
3-48	Var. 708	10-39	Var. 809	20-36	Var. 910	45-84	Var. 1011

3-45	Var. 709	10-36	Var. 810	20-33	Var. 911	45-78	Var. 1012
3-42	Var. 710	10-33	Var. 811	20-30	Var. 912	45-72	Var. 1013
3-39	Var. 711	10-30	Var. 812	20-27	Var. 913	45-66	Var. 1014
3-36	Var. 712	10-27	Var. 813	20-24	Var. 914	45-60	Var. 1015
3-33	Var. 713	10-24	Var. 814	20-22	Var. 915	45-54	Var. 1016
3-30	Var. 714	10-22	Var. 815	22-90	Var. 916	45-48	Var. 1017
3-27	Var. 715	10-20	Var. 816	22-84	Var. 917	48-90	Var. 1018
3-24	Var. 716	10-18	Var. 817	22-78	Var. 918	48-84	Var. 1019
3-22	Var. 717	10-16	Var. 818	22-72	Var. 919	48-78	Var. 1020
3-20	Var. 718	10-14	Var. 819	22-66	Var. 920	48-72	Var. 1021
3-18	Var. 719	10-12	Var. 820	22-60	Var. 921	48-66	Var. 1022
3-16	Var. 720	12-90	Var. 821	22-54	Var. 922	48-60	Var. 1023
3-14	Var. 721	12-84	Var. 822	22-48	Var. 923	48-54	Var. 1024
3-12	Var. 722	12-78	Var. 823	22-45	Var. 924	54-90	Var. 1025
3-10	Var. 723	12-72	Var. 824	22-42	Var. 925	54-84	Var. 1026
3-8	Var. 724	12-66	Var. 825	22-39	Var. 926	54-78	Var. 1027
3-6	Var. 725	12-60	Var. 826	22-36	Var. 927	54-72	Var. 1028
3-4	Var. 726	12-54	Var. 827	22-33	Var. 928	54-66	Var. 1029
4-90	Var. 727	12-48	Var. 828	22-30	Var. 929	54-60	Var. 1030
4-84	Var. 728	12-45	Var. 829	22-27	Var. 930	60-90	Var. 1031
4-78	Var. 729	12-42	Var. 830	22-24	Var. 931	60-84	Var. 1032
4-72	Var. 730	12-39	Var. 831	24-90	Var. 932	60-78	Var. 1033
4-66	Var. 731	12-36	Var. 832	24-84	Var. 933	60-72	Var. 1034
4-60	Var. 732	12-33	Var. 833	24-78	Var. 934	60-66	Var. 1035
4-54	Var. 733	12-30	Var. 834	24-72	Var. 935	66-90	Var. 1036
4-48	Var. 734	12-27	Var. 835	24-66	Var. 936	66-84	Var. 1037
4-45	Var. 735	12-24	Var. 836	24-60	Var. 937	66-78	Var. 1038
4-42	Var. 736	12-22	Var. 837	24-54	Var. 938	66-72	Var. 1039
4-39	Var. 737	12-20	Var. 838	24-48	Var. 939	72-90	Var. 1040
4-36	Var. 738	12-18	Var. 839	24-45	Var. 940	72-84	Var. 1041
4-33	Var. 739	12-16	Var. 840	24-42	Var. 941	72-78	Var. 1042
4-30	Var. 740	12-14	Var. 841	24-39	Var. 942	78-90	Var. 1043
4-27	Var. 741	14-90	Var. 842	24-36	Var. 943	78-84	Var. 1044
4-24	Var. 742	14-84	Var. 843	24-33	Var. 944	84-90	Var. 1045

Var. = Variation

[00168] In further aspects, rVWF of use in the present invention increases stability of plasma FVIII, which, as will be appreciated, may include pdFVII or rFVIII which has been administered to the patient or it may include FVIII endogenous to the patient, or any combination thereof. For example, as shown in FIG. 22, the half-life of plasma FVIII is increased in VWD patients receiving rVWF in combination with rFVIII as compared to patients receiving FVIII (i.e., Advate) alone. In further embodiments, rVWF increases half-life of FVIII by about 1.5 – 5-fold as compared to the half-life seen with patients receiving FVIII alone. In still further embodiments, rVWF increases half-life of FVIII by about 1.0 - 4.5, 1.5 - 4.0, 2.0 – 3.5, 2.5 – 3.0 fold. In one embodiment, administration of rVWF increases the stability of plasma FVIII, as compared to the administration of plasma-derived

VWF, by an amount selected from variations 1046 to 1089 found in **Table 7**. In a specific embodiment, administration of a rVWF/FVIII complex increases the stability of plasma FVIII, as compared to the administration of plasma-derived VWF, by an amount selected from variations 1046 to 1089 found in **Table 7**.

Table 7. Exemplary embodiments for the increase in half-life experienced by plasma FVIII after administration of rVWF and rVWF/FVIII complexes, as compared to after administration of plasma-derived VWF and plasma-derived VWF/FVIII complexes.

Increase in plasma FVIII half-life		**Increase in plasma FVIII half-life**		**Increase in plasma FVIII half-life**		**Increase in plasma FVIII half-life**	
at least 1.5-fold	Var. 1046	3.0-fold	Var. 1057	1.5-2.0 fold	Var. 1068	2.5-3.0 fold	Var. 1079
at least 2.0-fold	Var. 1047	3.5-fold	Var. 1058	2-5.0 fold	Var. 1069	3-5.0 fold	Var. 1080
at least 2.5-fold	Var. 1048	4.0-fold	Var. 1059	2-4.5 fold	Var. 1070	3-4.5 fold	Var. 1081
at least 3.0-fold	Var. 1049	4.5-fold	Var. 1060	2-4.0 fold	Var. 1071	3-4.0 fold	Var. 1082
at least 3.5-fold	Var. 1050	5.0-fold	Var. 1061	2-3.5 fold	Var. 1072	3-3.5 fold	Var. 1083
at least 4.0-fold	Var. 1051	1.5-5.0 fold	Var. 1062	2-3.0 fold	Var. 1073	3.5-5.0 fold	Var. 1084
at least 4.5 fold	Var. 1052	1.5-4.5 fold	Var. 1063	2-2.5 fold	Var. 1074	3.5-4.5 fold	Var. 1085
at least 5.0-fold	Var. 1053	1.5-4.0 fold	Var. 1064	2.5-5.0 fold	Var. 1075	3.5-4.0 fold	Var. 1086
1.5-fold	Var. 1054	1.5-3.5 fold	Var. 1065	2.5-4.5 fold	Var. 1076	4-5.0 fold	Var. 1087
2.0-fold	Var. 1055	1.5-3.0 fold	Var. 1066	2.5-4.0 fold	Var. 1077	4-4.5 fold	Var. 1088
2.5-fold	Var. 1056	1.5-2.5 fold	Var. 1067	2.5-3.5 fold	Var. 1078	4.5-5.0 fold	Var. 1089

Var. = Variation

[00169] In still further embodiments, the increase in FVIII half-life is maintained at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 hours after administration of rVWF. In yet further embodiments, the increase in FVIII half-life is maintained at least 5-125, 10-115, 15-105, 20-95, 25-85, 30-75, 35-65, 40-55 hours after administration of rVWF.

[00170] In one embodiment, the increase in the mean residence time (MRT) plasma FVIII is maintained for a time selected from variations 1090 to 1299 found in Table 8, after administration of rVWF. In a specific embodiment, the increase in the half life of plasma FVIII is maintained for a time selected from variations 1090 to 1299 found in **Table 8**, after administration of a rVWF/FVIII complex.

Table 8. Exemplary embodiments for the time plasma FVIII stability is maintained after administration of rVWF and rVWF/FVIII complexes.

Hours		**Hours**		**Hours**		**Hours**	

at least 6	Var. 1090	12-36	Var. 1143	36-114	Var. 1196	60-102	Var. 1248
at least 12	Var. 1091	12-30	Var. 1144	36-108	Var. 1197	60-96	Var. 1249
at least 18	Var. 1092	12-24	Var. 1145	36-102	Var. 1198	60-90	Var. 1250
at least 24	Var. 1093	12-18	Var. 1146	36-96	Var. 1199	60-84	Var. 1251
at least 30	Var. 1094	18-120	Var. 1147	36-90	Var. 1200	60-78	Var. 1252
at least 36	Var. 1095	18-114	Var. 1148	36-84	Var. 1201	60-72	Var. 1253
at least 42	Var. 1096	18-108	Var. 1149	36-78	Var. 1202	60-66	Var. 1254
at least 48	Var. 1097	18-102	Var. 1150	36-72	Var. 1203	66-120	Var. 1255
at least 54	Var. 1098	18-96	Var. 1151	36-66	Var. 1204	66-114	Var. 1256
at least 60	Var. 1099	18-90	Var. 1152	36-60	Var. 1205	66-108	Var. 1257
at least 66	Var. 1100	18-84	Var. 1153	36-54	Var. 1206	66-102	Var. 1258
at least 72	Var. 1101	18-78	Var. 1154	36-48	Var. 1207	66-96	Var. 1259
at least 78	Var. 1102	18-72	Var. 1155	36-42	Var. 1208	66-90	Var. 1260
at least 84	Var. 1103	18-66	Var. 1156	42-120	Var. 1209	66-84	Var. 1261
at least 90	Var. 1104	18-60	Var. 1157	42-114	Var. 1210	66-78	Var. 1262
at least 96	Var. 1105	18-54	Var. 1158	42-108	Var. 1211	66-72	Var. 1263
at least 102	Var. 1106	18-48	Var. 1159	42-102	Var. 1212	72-120	Var. 1264
at least 108	Var. 1107	18-42	Var. 1160	42-96	Var. 1213	72-114	Var. 1265
at least 114	Var. 1108	18-36	Var. 1161	42-90	Var. 1214	72-108	Var. 1266
at least 120	Var. 1109	18-30	Var. 1162	42-84	Var. 1215	72-102	Var. 1267
6-120	Var. 1110	18-24	Var. 1163	42-78	Var. 1216	72-96	Var. 1268
6-114	Var. 1111	24-120	Var. 1164	42-72	Var. 1217	72-90	Var. 1269
6-108	Var. 1112	24-114	Var. 1165	42-66	Var. 1218	72-84	Var. 1270
6-102	Var. 1113	24-108	Var. 1166	42-60	Var. 1219	72-78	Var. 1271
6-96	Var. 1114	24-102	Var. 1167	42-54	Var. 1220	78-120	Var. 1272
6-90	Var. 1115	24-96	Var. 1168	42-48	Var. 1221	78-114	Var. 1273
6-84	Var. 1116	24-90	Var. 1169	48-120	Var. 1222	78-108	Var. 1274
6-78	Var. 1117	24-84	Var. 1170	48-114	Var. 1223	78-102	Var. 1275
6-72	Var. 1118	24-78	Var. 1171	48-108	Var. 1224	78-96	Var. 1276
6-66	Var. 1119	24-72	Var. 1172	48-102	Var. 1225	78-90	Var. 1277
6-60	Var. 1120	24-66	Var. 1173	48-96	Var. 1226	78-84	Var. 1278
6-54	Var. 1121	24-60	Var. 1174	48-90	Var. 1227	84-120	Var. 1279
6-48	Var. 1122	24-54	Var. 1175	48-84	Var. 1228	84-114	Var. 1280
6-42	Var. 1123	24-48	Var. 1176	48-78	Var. 1229	84-108	Var. 1281
6-36	Var. 1124	24-42	Var. 1177	48-72	Var. 1230	84-102	Var. 1282
6-30	Var. 1125	24-36	Var. 1178	48-66	Var. 1231	84-96	Var. 1283
6-24	Var. 1126	24-30	Var. 1179	48-60	Var. 1232	84-90	Var. 1284
6-18	Var. 1127	30-120	Var. 1180	48-54	Var. 1233	90-120	Var. 1285
6-12	Var. 1128	30-114	Var. 1181	54-120	Var. 1234	90-114	Var. 1286
12-120	Var. 1129	30-108	Var. 1182	54-114	Var. 1235	90-108	Var. 1287
12-114	Var. 1130	30-102	Var. 1183	54-108	Var. 1236	90-102	Var. 1288
12-108	Var. 1131	30-96	Var. 1184	54-102	Var. 1237	90-96	Var. 1289
12-102	Var. 1132	30-90	Var. 1185	54-96	Var. 1238	96-120	Var. 1290
12-96	Var. 1133	30-84	Var. 1186	54-90	Var. 1239	96-114	Var. 1291
12-90	Var. 1134	30-78	Var. 1187	54-84	Var. 1240	96-108	Var. 1292
12-84	Var. 1135	30-72	Var. 1188	54-78	Var. 1241	96-102	Var. 1293
12-78	Var. 1136	30-66	Var. 1189	54-72	Var. 1242	102-120	Var. 1294
12-72	Var. 1137	30-60	Var. 1190	54-66	Var. 1243	102-114	Var. 1295
12-66	Var. 1138	30-54	Var. 1191	54-60	Var. 1244	102-108	Var. 1296

12-60	Var. 1139	30-48	Var. 1192	60-120	Var. 1245	108-120	Var. 1297
12-54	Var. 1140	30-42	Var. 1193	60-114	Var. 1246	108-114	Var. 1298
12-48	Var. 1141	30-36	Var. 1194	60-108	Var. 1247	114-120	Var. 1299
12-42	Var. 1142	36-120	Var. 1195				

Var. = Variation

[00171] In further aspects, the rVWF of the invention shows an increased effect on the stability of FVIII as compared to the effect of pdVWF. For example, as shown in FIG. 20, average FVIII half-life was increased by rVWF by 5.2 hours over the half-life for patients receiving pdVWF. In further embodiments, rVWF increases average FVIII half-life by about 1-15, 2-14, 3-13, 4-12, 5-11, 6-10, 5-9, 6-8 hours. In still further embodiments, rVWF increases FVIII half-life by about 10% to about 75% as compared to pdVWF. In yet further embodiments, rVWF increases FVIII half-life by about 10-80%, 15-65%, 20-60%, 25-55%, 30-50%, 35-45% as compared to pdVWF. In certain embodiments, the administration of rVWF increases the half life of FVIII by an amount selected from variations 1300 to 1643 found in **Table 9**, as compared to administration of plasma-derived VWF. In yet further embodiments, the average or percentage increase in FVIII half-life is maintained at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 hours after administration of rVWF. In yet further embodiments, the increase in FVIII half-life is maintained at least 5-125, 10-115, 15-105, 20-95, 25-85, 30-75, 35-65, 40-55 hours after administration of rVWF.

Table 9. Exemplary embodiments for the increase in half-life experienced by plasma FVIII after administration of rVWF and rVWF/FVIII complexes.

Increase in half life		**Increase in half life**		**Increase in half life**		**Increase in half life**	
at least 1 hr	Var. 1300	5-8 hr	Var. 1387	10-95%	Var. 1474	35-60%	Var. 1561
at least 2 hr	Var. 1301	5-7 hr	Var. 1388	10-90%	Var. 1475	35-55%	Var. 1562
at least 3 hr	Var. 1302	5-6 hr	Var. 1389	10-85%	Var. 1476	35-50%	Var. 1563
at least 4 hr	Var. 1303	6-15 hr	Var. 1390	10-80%	Var. 1477	35-45%	Var. 1564
at least 5 hr	Var. 1304	6-14 hr	Var. 1391	10-75%	Var. 1478	35-40%	Var. 1565
at least 6 hr	Var. 1305	6-13 hr	Var. 1392	10-70%	Var. 1479	40-100%	Var. 1566
at least 7 hr	Var. 1306	6-12 hr	Var. 1393	10-65%	Var. 1480	40-95%	Var. 1567
at least 8 hr	Var. 1307	6-11 hr	Var. 1394	10-60%	Var. 1481	40-90%	Var. 1568
at least 9 hr	Var. 1308	6-10 hr	Var. 1395	10-55%	Var. 1482	40-85%	Var. 1569
at least 10 hr	Var. 1309	6-9 hr	Var. 1396	10-50%	Var. 1483	40-80%	Var. 1570
at least 11 hr	Var. 1310	6-8 hr	Var. 1397	10-45%	Var. 1484	40-75%	Var. 1571
at least 12 hr	Var. 1311	6-7 hr	Var. 1398	10-40%	Var. 1485	40-70%	Var. 1572
at least 13 hr	Var. 1312	7-15 hr	Var. 1399	10-35%	Var. 1486	40-65%	Var. 1573
at least 14 hr	Var. 1313	7-14 hr	Var. 1400	10-30%	Var. 1487	40-60%	Var. 1574
at least 15 hr	Var. 1314	7-13 hr	Var. 1401	10-25%	Var. 1488	40-55%	Var. 1575
1 hr	Var. 1315	7-12 hr	Var. 1402	10-20%	Var. 1489	40-50%	Var. 1576
2 hr	Var. 1316	7-11 hr	Var. 1403	10-15%	Var. 1490	40-45%	Var. 1577
3 hr	Var. 1317	7-10 hr	Var. 1404	15-100%	Var. 1491	45-100%	Var. 1578
4 hr	Var. 1318	7-9 hr	Var. 1405	15-95%	Var. 1492	45-95%	Var. 1579

5 hr	Var. 1319	7-8 hr	Var. 1406	15-90%	Var. 1493	45-90%	Var. 1580
6 hr	Var. 1320	8-15 hr	Var. 1407	15-85%	Var. 1494	45-85%	Var. 1581
7 hr	Var. 1321	8-14 hr	Var. 1408	15-80%	Var. 1495	45-80%	Var. 1582
8 hr	Var. 1322	8-13 hr	Var. 1409	15-75%	Var. 1496	45-75%	Var. 1583
9 hr	Var. 1323	8-12 hr	Var. 1410	15-70%	Var. 1497	45-70%	Var. 1584
10 hr	Var. 1324	8-11 hr	Var. 1411	15-65%	Var. 1498	45-65%	Var. 1585
11 hr	Var. 1325	8-10 hr	Var. 1412	15-60%	Var. 1499	45-60%	Var. 1586
12 hr	Var. 1326	8-9 hr	Var. 1413	15-55%	Var. 1500	45-55%	Var. 1587
13 hr	Var. 1327	9-15 hr	Var. 1414	15-50%	Var. 1501	45-50%	Var. 1588
14 hr	Var. 1328	9-14 hr	Var. 1415	15-45%	Var. 1502	50-100%	Var. 1589
15 hr	Var. 1329	9-13 hr	Var. 1416	15-40%	Var. 1503	50-95%	Var. 1590
1-15 hr	Var. 1330	9-12 hr	Var. 1417	15-35%	Var. 1504	50-90%	Var. 1591
1-14 hr	Var. 1331	9-11 hr	Var. 1418	15-30%	Var. 1505	50-85%	Var. 1592
1-13 hr	Var. 1332	9-10 hr	Var. 1419	15-25%	Var. 1506	50-80%	Var. 1593
1-12 hr	Var. 1333	10-15 hr	Var. 1420	15-20%	Var. 1507	50-75%	Var. 1594
1-11 hr	Var. 1334	10-14 hr	Var. 1421	20-100%	Var. 1508	50-70%	Var. 1595
1-10 hr	Var. 1335	10-13 hr	Var. 1422	20-95%	Var. 1509	50-65%	Var. 1596
1-9 hr	Var. 1336	10-12 hr	Var. 1423	20-90%	Var. 1510	50-60%	Var. 1597
1-8 hr	Var. 1337	10-11 hr	Var. 1424	20-85%	Var. 1511	50-55%	Var. 1598
1-7 hr	Var. 1338	11-15 hr	Var. 1425	20-80%	Var. 1512	55-100%	Var. 1599
1-6 hr	Var. 1339	11-14 hr	Var. 1426	20-75%	Var. 1513	55-95%	Var. 1600
1-5 hr	Var. 1340	11-13 hr	Var. 1427	20-70%	Var. 1514	55-90%	Var. 1601
1-4 hr	Var. 1341	11-12 hr	Var. 1428	20-65%	Var. 1515	55-85%	Var. 1602
1-3 hr	Var. 1342	12-15 hr	Var. 1429	20-60%	Var. 1516	55-80%	Var. 1603
1-2 hr	Var. 1343	12-14 hr	Var. 1430	20-55%	Var. 1517	55-75%	Var. 1604
2-15 hr	Var. 1344	12-13 hr	Var. 1431	20-50%	Var. 1518	55-70%	Var. 1605
2-14 hr	Var. 1345	13-15 hr	Var. 1432	20-45%	Var. 1519	55-65%	Var. 1606
2-13 hr	Var. 1346	13-14 hr	Var. 1433	20-40%	Var. 1520	55-60%	Var. 1607
2-12 hr	Var. 1347	14-15 hr	Var. 1434	20-35%	Var. 1521	60-100%	Var. 1608
2-11 hr	Var. 1348	at least 10%	Var. 1435	20-30%	Var. 1522	60-95%	Var. 1609
2-10 hr	Var. 1349	at least 15%	Var. 1436	20-25%	Var. 1523	60-90%	Var. 1610
2-9 hr	Var. 1350	at least 20%	Var. 1437	25-100%	Var. 1524	60-85%	Var. 1611
2-8 hr	Var. 1351	at least 25%	Var. 1438	25-95%	Var. 1525	60-80%	Var. 1612
2-7 hr	Var. 1352	at least 30%	Var. 1439	25-90%	Var. 1526	60-75%	Var. 1613
2-6 hr	Var. 1353	at least 35%	Var. 1440	25-85%	Var. 1527	60-70%	Var. 1614
2-5 hr	Var. 1354	at least 40%	Var. 1441	25-80%	Var. 1528	60-65%	Var. 1615
2-4 hr	Var. 1355	at least 45%	Var. 1442	25-75%	Var. 1529	65-100%	Var. 1616
2-3 hr	Var. 1356	at least 50%	Var. 1443	25-70%	Var. 1530	65-95%	Var. 1617
3-15 hr	Var. 1357	at least 55%	Var. 1444	25-65%	Var. 1531	65-90%	Var. 1618
3-14 hr	Var. 1358	at least 60%	Var. 1445	25-60%	Var. 1532	65-85%	Var. 1619
3-13 hr	Var. 1359	at least 65%	Var. 1446	25-55%	Var. 1533	65-80%	Var. 1620
3-12 hr	Var. 1360	at least 70%	Var. 1447	25-50%	Var. 1534	65-75%	Var. 1621
3-11 hr	Var. 1361	at least 75%	Var. 1448	25-45%	Var. 1535	65-70%	Var. 1622
3-10 hr	Var. 1362	at least 80%	Var. 1449	25-40%	Var. 1536	70-100%	Var. 1623
3-9 hr	Var. 1363	at least 85%	Var. 1450	25-35%	Var. 1537	70-95%	Var. 1624
3-8 hr	Var. 1364	at least 90%	Var. 1451	25-30%	Var. 1538	70-90%	Var. 1625
3-7 hr	Var. 1365	at least 95%	Var. 1452	30-100%	Var. 1539	70-85%	Var. 1626
3-6 hr	Var. 1366	at least 100%	Var. 1453	30-95%	Var. 1540	70-80%	Var. 1627
3-5 hr	Var. 1367	10%	Var. 1454	30-90%	Var. 1541	70-75%	Var. 1628

3-4 hr	Var. 1368	15%	Var. 1455	30-85%	Var. 1542	75-100%	Var. 1629
4-15 hr	Var. 1369	20%	Var. 1456	30-80%	Var. 1543	75-95%	Var. 1630
4-14 hr	Var. 1370	25%	Var. 1457	30-75%	Var. 1544	75-90%	Var. 1631
4-13 hr	Var. 1371	30%	Var. 1458	30-70%	Var. 1545	75-85%	Var. 1632
4-12 hr	Var. 1372	35%	Var. 1459	30-65%	Var. 1546	75-80%	Var. 1633
4-11 hr	Var. 1373	40%	Var. 1460	30-60%	Var. 1547	80-100%	Var. 1634
4-10 hr	Var. 1374	45%	Var. 1461	30-55%	Var. 1548	80-95%	Var. 1635
4-9 hr	Var. 1375	50%	Var. 1462	30-50%	Var. 1549	80-90%	Var. 1636
4-8 hr	Var. 1376	55%	Var. 1463	30-45%	Var. 1550	80-85%	Var. 1637
4-7 hr	Var. 1377	60%	Var. 1464	30-40%	Var. 1551	85-100%	Var. 1638
4-6 hr	Var. 1378	65%	Var. 1465	30-35%	Var. 1552	85-95%	Var. 1639
4-5 hr	Var. 1379	70%	Var. 1466	35-100%	Var. 1553	85-90%	Var. 1640
5-15 hr	Var. 1380	75%	Var. 1467	35-95%	Var. 1554	90-100%	Var. 1641
5-14 hr	Var. 1381	80%	Var. 1468	35-90%	Var. 1555	90-95%	Var. 1642
5-13 hr	Var. 1382	85%	Var. 1469	35-85%	Var. 1556	95%-100%	Var. 1643
5-12 hr	Var. 1383	90%	Var. 1470	35-80%	Var. 1557		
5-11 hr	Var. 1384	95%	Var. 1471	35-75%	Var. 1558		
5-10 hr	Var. 1385	100%	Var. 1472	35-70%	Var. 1559		
5-9 hr	Var. 1386	10-100%	Var. 1473	35-65%	Var. 1560		

Var. = Variation

[00172] In still further aspects and in accordance with any of the above, the stabilization of FVIII activity by rVWF as compared to pdVWF can be measured by metrics in addition to FVIII half-life, including mean residence time (MRT) and area under curve (AUC). In exemplary embodiments, rVWF increases MRT by about 1-15 hours as compared to pdVWF. In further embodiments, rVWF increases MRT by about 1-25, 2-20, 3-15, 4-10, 5-9, 6-8 hours as compared to pdVWF. In still further embodiments, rVWF increases FVIII MRT by about 10-80%, 15-65%, 20-60%, 25-55%, 30-50%, 35-45% as compared to pdVWF. In yet further embodiments, the average or percentage increase in FVIII half-life is maintained at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 hours after administration of rVWF. In certain embodiments, the administration of rVWF increases the MRT of FVIII by an amount selected from variations 1644 to 1987 found in **Table 10**, as compared to administration of plasma-derived VWF.

[00173] In yet further embodiments, the increase in MRT is maintained at least 5-125, 10-115, 15-105, 20-95, 25-85, 30-75, 35-65, 40-55 hours after administration of rVWF. In certain embodiments, the increase in MRT of FVIII caused by administration of rVWF is maintained for a time selected from variations 1090 to 1299 found in **Table 8**.

Table 10. Exemplary embodiments for the increase in FVIII mean residence time after administration of rVWF and rVWF/FVIII complexes, as compared to after administration of plasma-derived VWF and plasma-derived VWF/FVIII complexes.

Increase in half life		**Increase in half life**		**Increase in half life**		**Increase in half life**	
at least 1 hr	Var. 1644	5-9 hr	Var. 1730	100%	Var. 1816	35-75%	Var. 1902
at least 2 hr	Var. 1645	5-8 hr	Var. 1731	10-100%	Var. 1817	35-70%	Var. 1903
at least 3 hr	Var. 1646	5-7 hr	Var. 1732	10-95%	Var. 1818	35-65%	Var. 1904
at least 4 hr	Var. 1647	5-6 hr	Var. 1733	10-90%	Var. 1819	35-60%	Var. 1905
at least 5 hr	Var. 1648	6-15 hr	Var. 1734	10-85%	Var. 1820	35-55%	Var. 1906
at least 6 hr	Var. 1649	6-14 hr	Var. 1735	10-80%	Var. 1821	35-50%	Var. 1907
at least 7 hr	Var. 1650	6-13 hr	Var. 1736	10-75%	Var. 1822	35-45%	Var. 1908
at least 8 hr	Var. 1651	6-12 hr	Var. 1737	10-70%	Var. 1823	35-40%	Var. 1909
at least 9 hr	Var. 1652	6-11 hr	Var. 1738	10-65%	Var. 1824	40-100%	Var. 1910
at least 10 hr	Var. 1653	6-10 hr	Var. 1739	10-60%	Var. 1825	40-95%	Var. 1911
at least 11 hr	Var. 1654	6-9 hr	Var. 1740	10-55%	Var. 1826	40-90%	Var. 1912
at least 12 hr	Var. 1655	6-8 hr	Var. 1741	10-50%	Var. 1827	40-85%	Var. 1913
at least 13 hr	Var. 1656	6-7 hr	Var. 1742	10-45%	Var. 1828	40-80%	Var. 1914
at least 14 hr	Var. 1657	7-15 hr	Var. 1743	10-40%	Var. 1829	40-75%	Var. 1915
at least 15 hr	Var. 1658	7-14 hr	Var. 1744	10-35%	Var. 1830	40-70%	Var. 1916
1 hr	Var. 1659	7-13 hr	Var. 1745	10-30%	Var. 1831	40-65%	Var. 1917
2 hr	Var. 1660	7-12 hr	Var. 1746	10-25%	Var. 1832	40-60%	Var. 1918
3 hr	Var. 1661	7-11 hr	Var. 1747	10-20%	Var. 1833	40-55%	Var. 1919
4 hr	Var. 1662	7-10 hr	Var. 1748	10-15%	Var. 1834	40-50%	Var. 1920
5 hr	Var. 1663	7-9 hr	Var. 1749	15-100%	Var. 1835	40-45%	Var. 1921
6 hr	Var. 1664	7-8 hr	Var. 1750	15-95%	Var. 1836	45-100%	Var. 1922
7 hr	Var. 1665	8-15 hr	Var. 1751	15-90%	Var. 1837	45-95%	Var. 1923
8 hr	Var. 1666	8-14 hr	Var. 1752	15-85%	Var. 1838	45-90%	Var. 1924
9 hr	Var. 1667	8-13 hr	Var. 1753	15-80%	Var. 1839	45-85%	Var. 1925
10 hr	Var. 1668	8-12 hr	Var. 1754	15-75%	Var. 1840	45-80%	Var. 1926
11 hr	Var. 1669	8-11 hr	Var. 1755	15-70%	Var. 1841	45-75%	Var. 1927
12 hr	Var. 1670	8-10 hr	Var. 1756	15-65%	Var. 1842	45-70%	Var. 1928
13 hr	Var. 1671	8-9 hr	Var. 1757	15-60%	Var. 1843	45-65%	Var. 1929
14 hr	Var. 1672	9-15 hr	Var. 1758	15-55%	Var. 1844	45-60%	Var. 1930
15 hr	Var. 1673	9-14 hr	Var. 1759	15-50%	Var. 1845	45-55%	Var. 1931
1-15 hr	Var. 1674	9-13 hr	Var. 1760	15-45%	Var. 1846	45-50%	Var. 1932
1-14 hr	Var. 1675	9-12 hr	Var. 1761	15-40%	Var. 1847	50-100%	Var. 1933
1-13 hr	Var. 1676	9-11 hr	Var. 1762	15-35%	Var. 1848	50-95%	Var. 1934
1-12 hr	Var. 1677	9-10 hr	Var. 1763	15-30%	Var. 1849	50-90%	Var. 1935
1-11 hr	Var. 1678	10-15 hr	Var. 1764	15-25%	Var. 1850	50-85%	Var. 1936
1-10 hr	Var. 1679	10-14 hr	Var. 1765	15-20%	Var. 1851	50-80%	Var. 1937
1-9 hr	Var. 1680	10-13 hr	Var. 1766	20-100%	Var. 1852	50-75%	Var. 1938
1-8 hr	Var. 1681	10-12 hr	Var. 1767	20-95%	Var. 1853	50-70%	Var. 1939
1-7 hr	Var. 1682	10-11 hr	Var. 1768	20-90%	Var. 1854	50-65%	Var. 1940
1-6 hr	Var. 1683	11-15 hr	Var. 1769	20-85%	Var. 1855	50-60%	Var. 1941
1-5 hr	Var. 1684	11-14 hr	Var. 1770	20-80%	Var. 1856	50-55%	Var. 1942
1-4 hr	Var. 1685	11-13 hr	Var. 1771	20-75%	Var. 1857	55-100%	Var. 1943

1-3 hr	Var. 1686	11-12 hr	Var. 1772	20-70%	Var. 1858	55-95%	Var. 1944
1-2 hr	Var. 1687	12-15 hr	Var. 1773	20-65%	Var. 1859	55-90%	Var. 1945
2-15 hr	Var. 1688	12-14 hr	Var. 1774	20-60%	Var. 1860	55-85%	Var. 1946
2-14 hr	Var. 1689	12-13 hr	Var. 1775	20-55%	Var. 1861	55-80%	Var. 1947
2-13 hr	Var. 1690	13-15 hr	Var. 1776	20-50%	Var. 1862	55-75%	Var. 1948
2-12 hr	Var. 1691	13-14 hr	Var. 1777	20-45%	Var. 1863	55-70%	Var. 1949
2-11 hr	Var. 1692	14-15 hr	Var. 1778	20-40%	Var. 1864	55-65%	Var. 1950
2-10 hr	Var. 1693	at least 10%	Var. 1779	20-35%	Var. 1865	55-60%	Var. 1951
2-9 hr	Var. 1694	at least 15%	Var. 1780	20-30%	Var. 1866	60-100%	Var. 1952
2-8 hr	Var. 1695	at least 20%	Var. 1781	20-25%	Var. 1867	60-95%	Var. 1953
2-7 hr	Var. 1696	at least 25%	Var. 1782	25-100%	Var. 1868	60-90%	Var. 1954
2-6 hr	Var. 1697	at least 30%	Var. 1783	25-95%	Var. 1869	60-85%	Var. 1955
2-5 hr	Var. 1698	at least 35%	Var. 1784	25-90%	Var. 1870	60-80%	Var. 1956
2-4 hr	Var. 1699	at least 40%	Var. 1785	25-85%	Var. 1871	60-75%	Var. 1957
2-3 hr	Var. 1700	at least 45%	Var. 1786	25-80%	Var. 1872	60-70%	Var. 1958
3-15 hr	Var. 1701	at least 50%	Var. 1787	25-75%	Var. 1873	60-65%	Var. 1959
3-14 hr	Var. 1702	at least 55%	Var. 1788	25-70%	Var. 1874	65-100%	Var. 1960
3-13 hr	Var. 1703	at least 60%	Var. 1789	25-65%	Var. 1875	65-95%	Var. 1961
3-12 hr	Var. 1704	at least 65%	Var. 1790	25-60%	Var. 1876	65-90%	Var. 1962
3-11 hr	Var. 1705	at least 70%	Var. 1791	25-55%	Var. 1877	65-85%	Var. 1963
3-10 hr	Var. 1706	at least 75%	Var. 1792	25-50%	Var. 1878	65-80%	Var. 1964
3-9 hr	Var. 1707	at least 80%	Var. 1793	25-45%	Var. 1879	65-75%	Var. 1965
3-8 hr	Var. 1708	at least 85%	Var. 1794	25-40%	Var. 1880	65-70%	Var. 1966
3-7 hr	Var. 1709	at least 90%	Var. 1795	25-35%	Var. 1881	70-100%	Var. 1967
3-6 hr	Var. 1710	at least 95%	Var. 1796	25-30%	Var. 1882	70-95%	Var. 1968
3-5 hr	Var. 1711	at least 100%	Var. 1797	30-100%	Var. 1883	70-90%	Var. 1969
3-4 hr	Var. 1712	10%	Var. 1798	30-95%	Var. 1884	70-85%	Var. 1970
4-15 hr	Var. 1713	15%	Var. 1799	30-90%	Var. 1885	70-80%	Var. 1971
4-14 hr	Var. 1714	20%	Var. 1800	30-85%	Var. 1886	70-75%	Var. 1972
4-13 hr	Var. 1715	25%	Var. 1801	30-80%	Var. 1887	75-100%	Var. 1973
4-12 hr	Var. 1716	30%	Var. 1802	30-75%	Var. 1888	75-95%	Var. 1974
4-11 hr	Var. 1717	35%	Var. 1803	30-70%	Var. 1889	75-90%	Var. 1975
4-10 hr	Var. 1718	40%	Var. 1804	30-65%	Var. 1890	75-85%	Var. 1976
4-9 hr	Var. 1719	45%	Var. 1805	30-60%	Var. 1891	75-80%	Var. 1977
4-8 hr	Var. 1720	50%	Var. 1806	30-55%	Var. 1892	80-100%	Var. 1978
4-7 hr	Var. 1721	55%	Var. 1807	30-50%	Var. 1893	80-95%	Var. 1979
4-6 hr	Var. 1722	60%	Var. 1808	30-45%	Var. 1894	80-90%	Var. 1980
4-5 hr	Var. 1723	65%	Var. 1809	30-40%	Var. 1895	80-85%	Var. 1981
5-15 hr	Var. 1724	70%	Var. 1810	30-35%	Var. 1896	85-100%	Var. 1982
5-14 hr	Var. 1725	75%	Var. 1811	35-100%	Var. 1897	85-95%	Var. 1983
5-13 hr	Var. 1726	80%	Var. 1812	35-95%	Var. 1898	85-90%	Var. 1984
5-12 hr	Var. 1727	85%	Var. 1813	35-90%	Var. 1899	90-100%	Var. 1985
5-11 hr	Var. 1728	90%	Var. 1814	35-85%	Var. 1900	90-95%	Var. 1986
5-10 hr	Var. 1729	95%	Var. 1815	35-80%	Var. 1901	95%-100%	Var. 1987

Var. = Variation

[00174] Further exemplary differences between pdVWF and rVWF are provided in the following table:

pdVWF	rVWF
• Synthesized in endothelial cells and megakaryocytes	• Expressed in CHO cells
• Post-translational modification of propeptide removal occurs intracellularly: during passage of the protein to the Golgi and post-Golgi compartments	• Propeptide removal mediated in vitro through exposure of the pro-VWF to recombinant Furin
• Glycosylation / ABO blood group glycans present	• Fully glycosylated / ABO blood group gylcans absent
• Consists of VWF subunits that have been exposed to plasma ADAMTS13 → Ultra-large VWF multimers absent → Subunits cleaved at TYR^{1605}-MET^{1606}	• No exposure to ADAMTS13 → Intact VWF subunits → Ultra-large VWF multimers present → Subunit cleavage occurs upon ADAMTS13 exposure
• Plasma-derived VWF concentrates contain other proteins incl. ADAMTS13, hemagglutinins	• Higher specific activity than pdVWF

[00175] In some embodiments, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) is between 3:1 and 1:5. In further embodiments, the ratio is between 2:1 and 1:4. In still further embodiments, the ratio is between 5:2 and 1:4. In further embodiments, the ratio is between 3:2 and 1:3. In still further embodiments, the ratio is about 1:1, 1:2, 1:3, 1:4, 1:5, 2:1, 2:3, 2:4, 2:5, 3:1, 3:2, 3:4, or 3:5. In further embodiments, the ratio is between 1:1 and 1:2. In yet further embodiments, the ratio is 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.6:1, 1.7:1, 1.8:1, 1.9:1, or 2:1. In certain embodiments, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in a composition useful for a method described herein is selected from variations 1988 to 2140 found in **Table 11**.

Table 11. Exemplary embodiments for the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in compositions and used in methods provided herein.

(IU rFVIII:C) to (IU rVWF:RCo)		(IU rFVIII:C) to (IU rVWF:RCo)		(IU rFVIII:C) to (IU rVWF:RCo)		(IU rFVIII:C) to (IU rVWF:RCo)	
4:1	Var. 1988	3:1-3:5	Var. 2027	4:3-1:4	Var. 2065	4:5-2:3	Var. 2103
3:1	Var. 1989	3:1-2:3	Var. 2028	4:3-1:3	Var. 2066	4:5-3:4	Var. 2104
2:1	Var. 1990	3:1-3:4	Var. 2029	4:3-2:5	Var. 2067	3:4-1:6	Var. 2105
3:2	Var. 1991	3:1-4:5	Var. 2030	4:3-1:2	Var. 2068	3:4-1:5	Var. 2106

4:3	Var. 1992	3:1-5:6	Var. 2031	4:3-3:5	Var. 2069	3:4-1:4	Var. 2107
1:1	Var. 1993	3:1-1:1	Var. 2032	4:3-2:3	Var. 2070	3:4-1:3	Var. 2108
5:6	Var. 1994	3:1-4:3	Var. 2033	4:3-3:4	Var. 2071	3:4-2:5	Var. 2109
4:5	Var. 1995	3:1-3:2	Var. 2034	4:3-4:5	Var. 2072	3:4-1:2	Var. 2110
3:4	Var. 1996	3:1-2:1	Var. 2035	4:3-5:6	Var. 2073	3:4-3:5	Var. 2111
2:3	Var. 1997	2:1-1:6	Var. 2036	4:3-1:1	Var. 2074	3:4-2:3	Var. 2112
3:5	Var. 1998	2:1-1:5	Var. 2037	1:1-1:6	Var. 2075	2:3-1:6	Var. 2113
1:2	Var. 1999	2:1-1:4	Var. 2038	1:1-1:5	Var. 2076	2:3-1:5	Var. 2114
2:5	Var. 2000	2:1-1:3	Var. 2039	1:1-1:4	Var. 2077	2:3-1:4	Var. 2115
1:3	Var. 2001	2:1-2:5	Var. 2040	1:1-1:3	Var. 2078	2:3-1:3	Var. 2116
1:4	Var. 2002	2:1-1:2	Var. 2041	1:1-2:5	Var. 2079	2:3-2:5	Var. 2117
1:5	Var. 2003	2:1-3:5	Var. 2042	1:1-1:2	Var. 2080	2:3-1:2	Var. 2118
1:6	Var. 2004	2:1-2:3	Var. 2043	1:1-3:5	Var. 2081	2:3-3:5	Var. 2119
4:1-1:6	Var. 2005	2:1-3:4	Var. 2044	1:1-2:3	Var. 2082	3:5-1:6	Var. 2120
4:1-1:5	Var. 2006	2:1-4:5	Var. 2045	1:1-3:4	Var. 2083	3:5-1:5	Var. 2121
4:1-1:4	Var. 2007	2:1-5:6	Var. 2046	1:1-4:5	Var. 2084	3:5-1:4	Var. 2122
4:1-1:3	Var. 2008	2:1-1:1	Var. 2047	1:1-5:6	Var. 2085	3:5-1:3	Var. 2123
4:1-2:5	Var. 2009	2:1-4:3	Var. 2048	5:6-1:6	Var. 2086	3:5-2:5	Var. 2124
4:1-1:2	Var. 2010	2:1-3:2	Var. 2049	5:6-1:5	Var. 2087	3:5-1:2	Var. 2125
4:1-3:5	Var. 2011	3:2-1:6	Var. 2050	5:6-1:4	Var. 2088	1:2-1:6	Var. 2126
4:1-2:3	Var. 2012	3:2-1:5	Var. 2051	5:6-1:3	Var. 2089	1:2-1:5	Var. 2127
4:1-3:4	Var. 2013	3:2-1:4	Var. 2052	5:6-2:5	Var. 2090	1:2-1:4	Var. 2128
4:1-4:5	Var. 2014	3:2-1:3	Var. 2053	5:6-1:2	Var. 2091	1:2-1:3	Var. 2129
4:1-5:6	Var. 2015	3:2-2:5	Var. 2054	5:6-3:5	Var. 2092	1:2-2:5	Var. 2130
4:1-1:1	Var. 2016	3:2-1:2	Var. 2055	5:6-2:3	Var. 2093	2:5-1:6	Var. 2131
4:1-4:3	Var. 2017	3:2-3:5	Var. 2056	5:6-3:4	Var. 2094	2:5-1:5	Var. 2132
4:1-3:2	Var. 2018	3:2-2:3	Var. 2057	5:6-4:5	Var. 2095	2:5-1:4	Var. 2133
4:1-2:1	Var. 2019	3:2-3:4	Var. 2058	4:5-1:6	Var. 2096	2:5-1:3	Var. 2134
4:1-3:1	Var. 2020	3:2-4:5	Var. 2059	4:5-1:5	Var. 2097	1:3-1:6	Var. 2135
3:1-1:6	Var. 2021	3:2-5:6	Var. 2060	4:5-1:4	Var. 2098	1:3-1:5	Var. 2136

3:1-1:5	Var. 2022	3:2-1:1	Var. 2061	4:5-1:3	Var. 2099	1:3-1:4	Var. 2137
3:1-1:4	Var. 2023	3:2-4:3	Var. 2062	4:5-2:5	Var. 2100	1:4-1:6	Var. 2138
3:1-1:3	Var. 2024	4:3-1:6	Var. 2063	4:5-1:2	Var. 2101	1:4-1:5	Var. 2139
3:1-2:5	Var. 2025	4:3-1:5	Var. 2064	4:5-3:5	Var. 2102	1:5-1:6	Var. 2140
3:1-1:2	Var. 2026						

Var. = Variation

[00176] In specific aspects, the rVWF and/or the FVIII (recombinant or plasma derived) used in accordance with the present invention are not modified with any conjugation, post-translation or covalent modifications. In particular embodiments, the rVWF and/or FVIII of the present invention are not modified with a water soluble polymer, including without limitation, a polyethylene glycol (PEG), a polypropylene glycol, a polyoxyalkylene, a polysialic acid, hydroxyl ethyl starch, a poly-carbohydrate moiety, and the like.

[00177] In other aspects, the rVWF and/or the FVIII (recombinant or plasma derived) used in accordance with the present invention are modified through conjugation, post-translation modification, or covalent modification, including modifications of the N- or C- terminal residues as well as modifications of selected side chains, for example, at free sulfhydryl-groups, primary amines, and hydroxyl-groups. In one embodiment, a water soluble polymer is linked to the protein (directly or via a linker) by a lysine group or other primary amine. In one embodiment, the rVWF and/or FVIII proteins of the present invention may be modified by conjugation of a water soluble polymer, including without limitation, a polyethylene glycol (PEG), a polypropylene glycol, a polyoxyalkylene, a polysialic acid, hydroxyl ethyl starch, a poly-carbohydrate moiety, and the like.

[00178] Water soluble polymers that may be used to modify the rVWF and/or FVIII include linear and branched structures. The conjugated polymers may be attached directly to the coagulation proteins of the invention, or alternatively may be attached through a linking moiety. Non-limiting examples of protein conjugation with water soluble polymers can be found in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192, and 4,179,337, as well as in Abuchowski and Davis "Enzymes as Drugs," Holcenberg and Roberts, Eds., pp. 367 383, John Wiley and Sons, New York (1981), and Hermanson G., Bioconjugate Techniques 2nd Ed., Academic Press, Inc. 2008.

[00179] Protein conjugation may be performed by a number of well known techniques in the art, for example, see Hermanson G., Bioconjugate Techniques 2nd Ed., Academic Press, Inc. 2008. Examples include linkage through the peptide bond between a carboxyl group on one

of either the coagulation protein or water-soluble polymer moiety and an amine group of the other, or an ester linkage between a carboxyl group of one and a hydroxyl group of the other. Another linkage by which a coagulation protein of the invention could be conjugated to a water-soluble polymer compound is via a Schiff base, between a free amino group on the polymer moiety being reacted with an aldehyde group formed at the non-reducing end of the polymer by periodate oxidation (Jennings and Lugowski, J. Immunol. 1981; 127:1011-8; Femandes and Gregonradis, Biochim Biophys Acta. 1997; 1341; 26-34). The generated Schiff Base can be stabilized by specific reduction with $NaCNBH_3$ to form a secondary amine. An alternative approach is the generation of terminal free amino groups on the polymer by reductive amination with NH_4Cl after prior oxidation. Bifunctional reagents can be used for linking two amino or two hydroxyl groups. For example a polymer containing an amino group can be coupled to an amino group of the coagulation protein with reagents like BS3 (Bis(sulfosuccinimidyl)suberate/Pierce, Rockford, Ill.). In addition heterobifunctional cross linking reagents like Sulfo-EMCS (N-ε-Maleimidocaproyloxy) sulfosuccinimide ester/Pierce) can be used for instance to link amine and thiol groups. In other embodiments, an aldehyde reactive group, such as PEG alkoxide plus diethyl acetal of bromoacetaldehyde; PEG plus DMSO and acetic anhydride, and PEG chloride plus the phenoxide of 4-hydroxybenzaldehyde, succinimidyl active esters, activated dithiocarbonate PEG, 2,4,5-trichlorophenylcloroformate and P-nitrophenylcloroformate activated PEG, may be used in the conjugation of a coagulation protein.

[00180] In some aspects, the rVWF used in methods of the present invention has been matured *in vitro* with Furin. In further embodiments, the Furin is recombinant Furin.

[00181] In further aspects, the rVWF and/or rFVIII used in the methods of the present invention are produced by expression in a mammalian cell culture using methods known in the art. In particular embodiments, the mammalian culture comprises CHO cells. In further embodiments, the rVWF and the rFVIII are co-expressed in the same culture. In such embodiments, the rVWF and the rFVIII are purified together (co-purified) or separately using methods known in the art. In other embodiments, the rVWF and the rFVIII are expressed in different cultures.

[00182] In an exemplary embodiment, the rVWF of the invention comprises rVWF protein isolated from a CHO cell expression system. In a further embodiment, the propeptide removal is mediated *in vitro* through exposure of the pro-VWF to Furin – in a still further embodiment, the Furin used for propeptide removal is recombinant Furin. In as yet further embodiment, fully glycosylated/ABO blood group glycans are absent.

[00183] In yet further embodiments, the rVWF used in methods and compositions of the present invention by expression in a suitable eukaryotic host system. Examples of eukaryotic cells include, without limitation, mammalian cells, such as CHO, COS, HEK 293, BHK, SK-Hep, and HepG2; insect cells, e.g., SF9 cells, SF21 cells, S2 cells, and High Five cells; and yeast cells, e.g., *Saccharomyces* or *Schizosaccharomyces* cells. In one embodiment, the VWF can be expressed in yeast cells, insect cells, avian cells, mammalian cells, and the like. For example, in a human cell line, a hamster cell line, or a murine cell line. In one particular embodiment, the cell line is a CHO, BHK, or HEK cell line. Typically, mammalian cells, e.g., CHO cell from a continuous cell line, can be used to express the VWF of the present invention.

[00184] In certain embodiments, the nucleic acid sequence comprising a sequence coding for VWF can be a vector. The vector can be delivered by a virus or can be a plasmid. The nucleic acid sequence coding for the protein can be a specific gene or a biologically functional part thereof. In one embodiment, the protein is at least a biologically active part of VWF.

[00185] A wide variety of vectors can be used for the expression of the VWF and can be selected from eukaryotic expression vectors. Examples of vectors for eukaryotic expression include: (i) for expression in yeast, vectors such as pAO, pPIC, pYES, pMET, using promoters such as AOX1, GAP, GAL1, AUG1, etc; (ii) for expression in insect cells, vectors such as pMT, pAc5, pIB, pMIB, pBAC, etc., using promoters such as PH, p10, MT, Ac5, OpIE2, gp64, polh, etc., and (iii) for expression in mammalian cells, vectors such as pSVL, pCMV, pRc/RSV, pcDNA3, pBPV, etc., and vectors derived from viral systems such as vaccinia virus, adeno-associated viruses, herpes viruses, retroviruses, etc., using promoters such as CMV, SV40, EF-1, UbC, RSV, ADV, BPV, and β-actin.

[00186] In some embodiments of the present invention, the nucleic acid sequence further comprises other sequences suitable for a controlled expression of a protein such as promoter sequences, enhancers, TATA boxes, transcription initiation sites, polylinkers, restriction sites, poly-A-sequences, protein processing sequences, selection markers, and the like which are generally known to a person of ordinary skill in the art.

[00187] In certain embodiments, the cell-culture methods of the invention may comprise the use of a microcarrier. In some embodiments, the cell-cultures of the embodiments can be performed in large bioreactors under conditions suitable for providing high volume-specific culture surface areas to achieve high cell densities and protein expression. One means for providing such growth conditions is to use microcarriers for cell-culture in stirred tank bioreactors. The concept of cell-growth on microcarriers was first described by van Wezel

(van Wezel, A.L., Nature 216:64-5 (1967)) and allows for cell attachment on the surface of small solid particles suspended in the growth medium. These methods provide for high surface-to-volume ratios and thus allow for efficient nutrient utilization. Furthermore, for expression of secreted proteins in eukaryotic cell lines, the increased surface-to-volume ratio allows for higher levels of secretion and thus higher protein yields in the supernatant of the culture. Finally, these methods allow for the easy scale-up of eukaryotic expression cultures.

[00188] The cells expressing VWF can be bound to a spherical or a porous microcarrier during cell culture growth. The microcarrier can be a microcarrier selected from the group of microcarriers based on dextran, collagen, plastic, gelatine and cellulose and others as described in Butler (1988. In: Spier & Griffiths, Animal Cell Biotechnology 3:283-303). It is also possible to grow the cells to a biomass on spherical microcarriers and subculture the cells when they have reached final fermenter biomass and prior to production of the expressed protein on a porous microcarrier or vice versa. Suitable spherical microcarriers can include smooth surface microcarriers, such as Cytodex™ 1, Cytodex™ 2, and Cytodex™ 3 (GE Healthcare) and macroporous microcarriers such as Cytopore™ 1, Cytopore™ 2, Cytoline™ 1, and Cytoline™ 2 (GE Healthcare).

[00189] In certain embodiments, rVWF is expressed in cells cultured in cell culture media that produces high molecular weight rVWF. The terms "cell culture solution," "cell culture medium or media," and "cell culture supernatant" refer to aspects of cell culture processes generally well known in the art. In the context of the present invention, a cell culture solution can include cell culture media and cell culture supernatant. The cell culture media are externally added to the cell culture solution, optionally together with supplements, to provide nutrients and other components for culturing the cells expressing VWF. The cell culture supernatant refers to a cell culture solution comprising the nutrients and other components from the cell culture medium as well as products released, metabolized, and/or excreted from the cells during culture. In further embodiments , the media can be animal protein-free and chemically defined. Methods of preparing animal protein-free and chemically defined culture media are known in the art, for example in US 2008/0009040 and US 2007/0212770, which are both incorporated herein for all purposes and in particular for all teachings related to cell culture media. "Protein free" and related terms refers to protein that is from a source exogenous to or other than the cells in the culture, which naturally shed proteins during growth. In another embodiment, the culture medium is polypeptide free. In another embodiment, the culture medium is serum free. In another embodiment the culture medium is animal protein free. In another embodiment the culture medium is animal component free. In another embodiment, the culture medium contains protein, e.g., animal protein from serum

such as fetal calf serum. In another embodiment, the culture has recombinant proteins exogenously added. In another embodiment, the proteins are from a certified pathogen free animal. The term "chemically defined" as used herein shall mean, that the medium does not comprise any undefined supplements, such as, for example, extracts of animal components, organs, glands, plants, or yeast. Accordingly, each component of a chemically defined medium is accurately defined. In a preferred embodiment, the media are animal-component free and protein free.

[00190] In certain embodiments, the culture of cells expressing VWF can be maintained for at least about 7 days, or at least about 14 days, 21 days, 28 days, or at least about 5 weeks, 6 weeks, 7 weeks, or at least about 2 months, or 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 months or longer. The cell density at which a cell-culture is maintained at for production of a recombinant VWF protein will depend upon the culture-conditions and medium used for protein expression. One of skill in the art will readily be able to determine the optimal cell density for a cell-culture producing an VWF. In one embodiment, the culture is maintained at a cell density of between about $0.5x10^6$ and $4x10^7$ cells/ml for an extended period of time. In other embodiments, the cell density is maintained at a concentration of between about $1.0x10^6$ and about $1.0x10^7$ cells/ml for an extended period of time. In other embodiments, the cell density is maintained at a concentration of between about $1.0x10^6$ and about $4.0x10^6$ cells/ml for an extended period of time. In other embodiments, the cell density is maintained at a concentration of between about $1.0x10^6$ and about $4.0x10^6$ cells/ml for an extended period of time. In yet other embodiments, the cell density may be maintained at a concentration between about $2.0x10^6$ and about $4.0x10^6$, or between about $1.0x10^6$ and about $2.5x10^6$, or between about $1.5x10^6$ and about $3.5x10^6$, or any other similar range, for an extended period of time. After an appropriate time in cell culture, the rVWF can be isolated from the expression system using methods known in the art.

[00191] In a specific embodiment, the cell density of the continuous cell culture for production of rVWF is maintained at a concentration of no more than $2.5x10^6$ cells/mL for an extended period. In other specific embodiments, the cell density is maintained at no more than $2.0x10^6$ cells/mL, $1.5x10^6$ cells/mL, $1.0x10^6$ cells/mL, $0.5x10^6$ cells/mL, or less. In one embodiment, the cell density is maintained at between $1.5x10^6$ cells/mL and $2.5x10^6$ cells/mL.

[00192] In one specific embodiment of the cell cultures described above, the cell culture solution comprises a medium supplement comprising copper. Such cell culture solutions are described for example in US 2012/0035110, filed July 8, 2011, which is hereby incorporated

by reference in its entirety for all purposes and in particular for all teachings related to cell culture methods and compositions for producing recombinant VWF.

[00193] In further embodiments, subsequent to purification (separately or together) from a mammalian cell culture, the rFVIII/rVWF complex is reconstituted prior to administration. In still further embodiments, the rVWF is treated with Furin prior to or subsequent to reconstitution of the rFVIII/rVWF complex. In further embodiments, the Furin is recombinant Furin.

[00194] In still further embodiments, the rVWF of the invention is not exposed to ADAMTS13, with the result that ultra large (i.e., comprising 10 or more subunits) are present in rVWF compositions of the invention.

[00195] In specific aspects, the rVWF and/or the rFVIII used in methods of the present invention are contained in a formulation containing a buffer, a sugar and/or a sugar alcohol (including without limitation trehalose and mannitol), a stabilizer (such as glycine), and a surfactant (such as Polysorbate 80). In further embodiments, for formulations containing rFVIII, the formulation may further include sodium, histidine, calcium, and glutathione.

[00196] In one aspect, the formulations comprising rVWF and/or rFVIII are lyophilized prior to administration. Lyophilization is carried out using techniques common in the art and should be optimized for the composition being developed [Tang et al., Pharm Res. 21:191-200, (2004) and Chang et al., Pharm Res. 13:243-9 (1996)].

[00197] Methods of preparing pharmaceutical formulations can include one or more of the following steps: adding a stabilizing agent as described herein to said mixture prior to lyophilizing, adding at least one agent selected from a bulking agent, an osmolarity regulating agent, and a surfactant, each of which as described herein, to said mixture prior to lyophilization. A lyophilized formulation is, in one aspect, at least comprised of one or more of a buffer, a bulking agent, and a stabilizer. In this aspect, the utility of a surfactant is evaluated and selected in cases where aggregation during the lyophilization step or during reconstitution becomes an issue. An appropriate buffering agent is included to maintain the formulation within stable zones of pH during lyophilization.

[00198] The standard reconstitution practice for lyophilized material is to add back a volume of pure water or sterile water for injection (WFI) (typically equivalent to the volume removed during lyophilization), although dilute solutions of antibacterial agents are sometimes used in the production of pharmaceuticals for parenteral administration [Chen, Drug Development and Industrial Pharmacy, 18:1311-1354 (1992)]. Accordingly, methods are provided for preparation of reconstituted recombinant VWF (with or without recombinant Factor VIII)

compositions comprising the step of adding a diluent to a lyophilized recombinant VWF composition of the invention.

[00199] The lyophilized material may be reconstituted as an aqueous solution. A variety of aqueous carriers, e.g., sterile water for injection, water with preservatives for multi dose use, or water with appropriate amounts of surfactants (for example, an aqueous suspension that contains the active compound in admixture with excipients suitable for the manufacture of aqueous suspensions). In various aspects, such excipients are suspending agents, for example and without limitation, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents are a naturally-occurring phosphatide, for example and without limitation, lecithin, or condensation products of an alkylene oxide with fatty acids, for example and without limitation, polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example and without limitation, heptadecaethyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example and without limitation, polyethylene sorbitan monooleate. In various aspects, the aqueous suspensions also contain one or more preservatives, for example and without limitation, ethyl, or n-propyl, p-hydroxybenzoate.

[00200] In certain embodiments, compositions of the present invention are liquid formulations for administration with the use of a syringe or other storage vessel. In further embodiments, these liquid formulations are produced from lyophilized material described herein reconstituted as an aqueous solution.

[00201] In a further aspect, the compositions of the invention further comprise one or more pharmaceutically acceptable carriers. The phrases "pharmaceutically" or "pharmacologically" acceptable refer to molecular entities and compositions that are stable, inhibit protein degradation such as aggregation and cleavage products, and in addition do not produce allergic, or other adverse reactions when administered using routes well-known in the art, as described below. "Pharmaceutically acceptable carriers" include any and all clinically useful solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like, including those agents disclosed above.

Administration of compositions of the invention for methods of treating disease

[00202] One of the advantages of administering rVWF to subjects to treat coagulation disease is that the higher specific activity of rVWF as compared to pdVWF allows flexibility

in the amount of rVWF administered and the number of times the subject is re-dosed with rVWF (with or without co-administered FVIII). In addition, rVWF compositions provide the further flexibility of re-dosing with rVWF alone after an initial co-administration of rVWF and FVIII, without need for additional dosing with FVIII. As will be appreciated and as is discussed in further detail herein, the co-administered FVIII may be recombinant or plasma derived.

[00203] In one aspect, the administration of rVWF in accordance with the invention results in higher plasma FVIII levels and/or activity in the subject than is seen with a subject administered pdVWF. As discussed above, increases in FVIII levels and activity can be measured using methods standard in the art, thus allowing for determination of appropriate dosages for rVWF with or without FVIII.

[00204] Single or multiple administrations of rVWF (with or without FVIII) are carried out with the dose levels and pattern being selected by the treating physician. For the prevention or treatment of disease, the appropriate dosage depends on the type of disease to be treated (e.g., von Willebrand disease), the severity and course of the disease, whether drug is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the drug, and the discretion of the attending physician.

[00205] In further embodiments and in accordance with any of the above, treatment of coagulation diseases such as VWD or Hemophilia A may involve an initial treatment of rVWF alone or in combination with FVIII, followed by one or more repeat doses of rVWF alone, rVWF plus FVIII together, or FVIII alone. The nature of the initial and then the subsequent repeat administrations will depend in part on the disease being treated. For example, patients with VWD have some level of FVIII, but the stability of that FVIII is generally compromised because these patients lack VWF. Treatment of VWD patients may thus in some embodiments involve an initial treatment with both rVWF and rFVIII followed by repeated administrations of rVWF alone. In other embodiments, the initial treatment may be with rVWF alone while subsequent repeated administrations are with both rVWF and rFVIII. In still other embodiments, the initial and subsequent repeat administrations may all include a co-administration of both rVWF and rFVIII. Similarly, Hemophilia A patients (who lack FVIII) may receive an initial treatment of both rVWF and rFVIII, and subsequent repeat treatments may comprise the administration of rFVIII alone or rVWF alone. In other embodiments, the initial treatment may be rFVIII alone while the subsequent repeat treatments involve co-administration of rVWF and rFVIII.

[00206] In further aspects, rVWF is administered to a subject in doses ranging from 0.5 IU/kg – 200 IU/kg. In some embodiments, rVWF is administered in doses ranging from 1-

190, 5-180, 10-170, 15-160, 20-150, 25-140, 30-130, 35-120, 40-110, 45-100, 50-90, 55-80, or 60-70 IU/kg. In further embodiments and in accordance with any of the above , rVWF (with or without FVIII) is administered to a subject at doses of between about 1 IU/kg to about 150 IU/kg rVWF. In still further embodiments, the rVWF and rFVIII is administered at doses of between 1.5 IU/kg to 150 IU/kg, 2 IU/kg to 50 IU/kg, 5 IU/kg to 40 IU/kg, 10 IU/kg to 20 IU/kg, 10 IU/kg to 100 IU/kg, 25 IU/kg to 75 IU/kg, and 40 IU/kg to 75 IU/kg. In still further embodiments, rVWF is administered at 2, 5, 7.5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 IU/kg. As will be appreciated and as is discussed further herein, appropriate dosages of rVWF (or rVWF together with FVIII) may be ascertained through use of established assays for determining blood level dosages in conjunction with appropriate dose-response data. In one embodiment, rVWF is administered to a subject in a dose selected from variations 2141 to 2338 in **Table 12**.

Table 12. Exemplary embodiments for the dosage of rVWF administered to a subject according to the methods provided herein.

IU/kg		**IU/kg**		**IU/kg**		**IU/kg**	
About 0.5	Var. 2141	0.5-75	Var. 2191	5-40	Var. 2241	20-50	Var. 2290
About 1	Var. 2142	0.5-50	Var. 2192	5-30	Var. 2242	20-40	Var. 2291
About 2	Var. 2143	0.5-40	Var. 2193	5-25	Var. 2243	20-30	Var. 2292
About 3	Var. 2144	0.5-30	Var. 2194	5-20	Var. 2244	20-25	Var. 2293
About 4	Var. 2145	0.5-25	Var. 2195	5-15	Var. 2245	25-200	Var. 2294
About 5	Var. 2146	0.5-20	Var. 2196	5-10	Var. 2246	25-175	Var. 2295
About 10	Var. 2147	0.5-15	Var. 2197	5-7.5	Var. 2247	25-150	Var. 2296
About 15	Var. 2148	0.5-10	Var. 2198	7.5-200	Var. 2248	25-125	Var. 2297
About 20	Var. 2149	0.5-7.5	Var. 2199	7.5-175	Var. 2249	25-100	Var. 2298
About 25	Var. 2150	0.5-5	Var. 2200	7.5-150	Var. 2250	25-75	Var. 2299
About 30	Var. 2151	0.5-2.5	Var. 2201	7.5-125	Var. 2251	25-50	Var. 2300
About 35	Var. 2152	0.5-1	Var. 2202	7.5-100	Var. 2252	25-40	Var. 2301
About 40	Var. 2153	1-200	Var. 2203	7.5-75	Var. 2253	25-30	Var. 2302
About 45	Var. 2154	1-175	Var. 2204	7.5-50	Var. 2254	30-200	Var. 2303
About 50	Var. 2155	1-150	Var. 2205	7.5-40	Var. 2255	30-175	Var. 2304
About 55	Var. 2156	1-125	Var. 2206	7.5-30	Var. 2256	30-150	Var. 2305
About 60	Var. 2157	1-100	Var. 2207	7.5-25	Var. 2257	30-125	Var. 2306
About 65	Var. 2158	1-75	Var. 2208	7.5-20	Var. 2258	30-100	Var. 2307
About 70	Var. 2159	1-50	Var. 2209	7.5-15	Var. 2259	30-75	Var. 2308
About 75	Var. 2160	1-40	Var. 2210	7.5-10	Var. 2260	30-50	Var. 2309
About 80	Var. 2161	1-30	Var. 2211	10-200	Var. 2261	30-40	Var. 2310
About 85	Var. 2162	1-25	Var. 2212	10-175	Var. 2262	40-200	Var. 2311
About 90	Var. 2163	1-20	Var. 2213	10-150	Var. 2263	40-175	Var. 2312
About 95	Var. 2164	1-15	Var. 2214	10-125	Var. 2264	40-150	Var. 2313
About 100	Var. 2165	1-10	Var. 2215	10-100	Var. 2265	40-125	Var. 2314
About 105	Var. 2166	1-7.5	Var. 2216	10-75	Var. 2266	40-100	Var. 2315
About 110	Var. 2167	1-5	Var. 2217	10-50	Var. 2267	40-75	Var. 2316
About 115	Var. 2168	1-2.5	Var. 2218	10-40	Var. 2268	40-50	Var. 2317

About 120	Var. 2169	2.5-200	Var. 2219	10-30	Var. 2269	50-200	Var. 2318
About 125	Var. 2170	2.5-175	Var. 2220	10-25	Var. 2270	50-175	Var. 2319
About 130	Var. 2171	2.5-150	Var. 2221	10-20	Var. 2271	50-150	Var. 2320
About 135	Var. 2172	2.5-125	Var. 2222	10-15	Var. 2272	50-125	Var. 2321
About 140	Var. 2173	2.5-100	Var. 2223	15-200	Var. 2273	50-100	Var. 2322
About 145	Var. 2174	2.5-75	Var. 2224	15-175	Var. 2274	50-75	Var. 2323
About 150	Var. 2175	2.5-50	Var. 2225	15-150	Var. 2275	75-200	Var. 2324
About 155	Var. 2176	2.5-40	Var. 2226	15-125	Var. 2276	75-175	Var. 2325
About 160	Var. 2177	2.5-30	Var. 2227	15-100	Var. 2277	75-150	Var. 2326
About 165	Var. 2178	2.5-25	Var. 2228	15-75	Var. 2278	75-125	Var. 2327
About 170	Var. 2179	2.5-20	Var. 2229	15-50	Var. 2279	75-100	Var. 2328
About 175	Var. 2180	2.5-15	Var. 2230	15-40	Var. 2280	100-200	Var. 2329
About 180	Var. 2181	2.5-10	Var. 2231	15-30	Var. 2281	100-175	Var. 2330
About 185	Var. 2182	2.5-7.5	Var. 2232	15-25	Var. 2282	100-150	Var. 2331
About 190	Var. 2183	2.5-5	Var. 2233	15-20	Var. 2283	100-125	Var. 2332
About 195	Var. 2184	5-200	Var. 2234	20-200	Var. 2284	125-200	Var. 2333
About 200	Var. 2185	5-175	Var. 2235	20-175	Var. 2285	125-175	Var. 2334
0.5-200	Var. 2186	5-150	Var. 2236	20-150	Var. 2286	125-150	Var. 2335
0.5-175	Var. 2187	5-125	Var. 2237	20-125	Var. 2287	150-200	Var. 2336
0.5-150	Var. 2188	5-100	Var. 2238	20-100	Var. 2288	150-200	Var. 2337
0.5-125	Var. 2189	5-75	Var. 2239	20-75	Var. 2289	175-200	Var. 2338
0.5-100	Var. 2190	5-50	Var. 2240				

Var. = Variation

[00207] In still further embodiments, rVWF is administered at a dose such that it increases half-life of plasma FVIII by about 1.0 - 4.5, 1.5 - 4.0, 2.0 – 3.5, 2.5 – 3.0 fold. In still further embodiments, the dose and/or frequency of rVWF administration is such that the increase in FVIII half-life is maintained at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 hours after administration of rVWF. In yet further embodiments, the dose and/or frequency of rVWF administration is such that the increase in FVIII half-life is maintained at least 5-125, 10-115, 15-105, 20-95, 25-85, 30-75, 35-65, 40-55 hours after administration of rVWF. In one embodiment, rVWF is administered at a dose such that it increases the half-life of plasma FVIII by a value selected from variations 1046 to 1089 found in **Table 7**.

[00208] As discussed above, the rVWF of the invention shows an increased effect on the stability of FVIII as compared to the effect of pdVWF. In certain aspects, rVWF is administered at a dose and/or with a frequency such that it increases average FVIII half-life by about 1-15, 2-14, 3-13, 4-12, 5-11, 6-10, 5-9, 6-8 hours. In still further embodiments, rVWF is administered at a dose and/or frequency such that it increases FVIII half-life by about 10% to about 75% as compared to pdVWF. In yet further embodiments, rVWF increases FVIII half-life by about 10-80%, 15-65%, 20-60%, 25-55%, 30-50%, 35-45% as compared to pdVWF. In yet further embodiments, the average or percentage increase in

FVIII half-life is maintained at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 hours after administration of rVWF. In yet further embodiments, the increase in FVIII half-life is maintained at least 5-125, 10-115, 15-105, 20-95, 25-85, 30-75, 35-65, 40-55 hours after administration of rVWF. As will be appreciated, the increase in FVIII stability, half-life and/or activity can be assessed using methods known in the art, including without limitation coagulation assays. In other embodiments, administration of rVWF increases the half-life of FVIII by an amount selected from variations 1300 to 1643 found in **Table 9**, as compared to administration of plasma-derived VWF.

[00209] As discussed herein, the stabilization of FVIII activity by rVWF as compared to pdVWF can be measured by metrics in addition to FVIII half-life, including mean residence time (MRT) and area under curve (AUC). In exemplary embodiments, rVWF is administered at a dose and/or frequency such that it increases MRT by about 1-15 hours as compared to pdVWF. In further embodiments, rVWF increases MRT by about 1-25, 2-20, 3-15, 4-10, 5-9, 6-8 hours as compared to pdVWF. In still further embodiments, rVWF increases FVIII MRT by about 10-80%, 15-65%, 20-60%, 25-55%, 30-50%, 35-45% as compared to pdVWF. In yet further embodiments, the average or percentage increase in FVIII half-life is maintained at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 hours after administration of rVWF. In yet further embodiments, the increase in MRT is maintained at least 5-125, 10-115, 15-105, 20-95, 25-85, 30-75, 35-65, 40-55 hours after administration of rVWF. In other embodiments, administration of rVWF increases the MRT of FVIII by an amount selected from variations 1300 to 1643 found in **Table 9**, as compared to administration of plasma-derived VWF.

[00210] In further aspects, the doses of rVWF administered to patients are comparable to doses used in administration of pdVWF/pdFVIII.

[00211] Compositions of rVWF with or without FVIII can be contained in pharmaceutical formulations, as described herein. Such formulations can be administered orally, topically, transdermally, parenterally, by inhalation spray, vaginally, rectally, or by intracranial injection. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intracisternal injection, or infusion techniques. Administration by intravenous, intradermal, intramusclar, intramammary, intraperitoneal, intrathecal, retrobulbar, intrapulmonary injection and or surgical implantation at a particular site is contemplated as well. Generally, compositions are essentially free of pyrogens, as well as other impurities that could be harmful to the recipient.

[00212] In one aspect, formulations of the invention are administered by an initial bolus followed by a continuous infusion to maintain therapeutic circulating levels of drug product.

As another example, the inventive compound is administered as a one-time dose. Those of ordinary skill in the art will readily optimize effective dosages and administration regimens as determined by good medical practice and the clinical condition of the individual patient. The route of administration can be, but is not limited to, by intravenous, intraperitoneal, subcutaneous, or intramuscular administration. The frequency of dosing depends on the pharmacokinetic parameters of the agents and the route of administration. The optimal pharmaceutical formulation is determined by one skilled in the art depending upon the route of administration and desired dosage. See for example, Remington's Pharmaceutical Sciences, 18th Ed., 1990, Mack Publishing Co., Easton, Pa. 18042 pages 1435-1712, the disclosure of which is hereby incorporated by reference in its entirety for all purposes and in particular for all teachings related to formulations, routes of administration and dosages for pharmaceutical products. Such formulations influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the administered agents. Depending on the route of administration, a suitable dose is calculated according to body weight, body surface area or organ size. Appropriate dosages may be ascertained through use of established assays for determining blood level dosages in conjunction with appropriate dose-response data. The final dosage regimen is determined by the attending physician, considering various factors which modify the action of drugs, e.g. the drug's specific activity, the severity of the damage and the responsiveness of the patient, the age, condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors. By way of example, a typical dose of a recombinant VWF of the present invention is approximately 50 U/kg, equal to 500 μg/kg. As studies are conducted, further information will emerge regarding the appropriate dosage levels and duration of treatment for various diseases and conditions.

[00213] In some embodiments, rVWF is administered to a subject alone. In some embodiments, rVWF is administered to a subject in combination with one or more coagulation factors. In further embodiments, the coagulation factor administered with rVWF is FVIII. In still further embodiments rVWF is administered prior to, subsequent to, or simultaneously with a coagulation factor such as FVIII. In certain embodiments, rVWF and FVIII are administered together in a single composition. As will be appreciated, the FVIII that is co-administered with rVWF can be either recombinant FVIII or plasma derived.

[00214] In further embodiments, rVWF (with or without FVIII) is administered to a subject no more than once daily. In further embodiments, rVWF (with or without FVIII) is administered to a subject: no more than once every other day, no more than once every third day, no more than once every fourth day, no more than once every fifth day, no more than

once a week, no more than once every two weeks, no more than once a month. In still further embodiments, rVWF (with or without FVIII) is administered to a subject no more than twice a day.

[00215] In further embodiments, rVWF and FVIII are administered together to a subject in an initial dose, and then subsequent re-dosing is conducted with rVWF alone. In other embodiments, re-dosing is conducted with both rVWF and FVIII.

[00216] In still further embodiments, rVWF (with or without rFVIII) is administered at a dose such that plasma FVIII activity is stabilized for about 10 to about 90 hours. In further embodiments, plasma FVIII activity is stabilized for at least 12, 24, 36, 48 or 72 hours. As will be appreciated, the stabilized plasma FVIII activity may be that of endogenous FVIII, co-administered FVIII (plasma-derived or recombinant) or a combination of both endogenous and co-administered FVIII.

[00217] In some embodiments, rVWF and FVIII are administered together at a dose such that extension of *in vivo* half-life of plasma FVIII activity is stabilized for at least 12, 24, 36, 48 or 72 hours. In further embodiments, the plasma FVIII activity is stabilized for about 10 to about 90 hours. In still further embodiments, the increase in half-life of plasma FVIII is maintained for at least 24, 36, 48, 72, 90, 120, or 168 hours in a patient. The co-administered FVIII can be rFVIII or pdFVIII. In some embodiments, plasma FVIII activity is stabilized for a time selected from variations 1090 to 1299 found in **Table 8**, after co-administration of rVWF and FVIII.

[00218] In preferred aspects, the present invention provides methods for treating coagulation disease, including hemophilia and von Willebrand Disease (VWD).

[00219] As used herein, the terms "hemophilia" or "haemophilia" refer to a group of disease states broadly characterized by reduced blood clotting or coagulation. Hemophilia may refer to Type A, Type B, or Type C hemophilia, or to the composite of all three diseases types. Type A hemophilia (hemophilia A) is caused by a reduction or loss of factor VIII (FVIII) activity and is the most prominent of the hemophilia subtypes. Type B hemophilia (hemophilia B) results from the loss or reduction of factor IX (FIX) clotting function. Type C hemophilia (hemophilia C) is a consequence of the loss or reduction in factor XI (FXI) clotting activity. Hemophilia A and B are X-linked diseases, while hemophilia C is autosomal. Common treatments for hemophilia include both prophylactic and on-demand administration of clotting factors, such as FVIII, FIX, including Bebulin®–VH, and FXI, as well as FEIBA-VH, desmopressin, and plasma infusions.

[00220] As used herein “von Willebrand Disease” refers to the group of diseases caused by a deficiency of von Willebrand factor. Von Willebrand factor helps blood platelets clump

together and stick to the blood vessel wall, which is necessary for normal blood clotting. There are several types of Von Willebrand disease. The following table summarizes the characteristics of different types of VWD:

Type	Characteristics
	Quantitative forms of VWD
Type 1	• Partial quantitative deficiencies of VWF • VWF plasma levels that are 5% to 30% of normal • approximately 60% to 80% of patients
Type 3	• Virtually complete deficiency of VWF • Approximately 1% to 5% of patients
	Qualitative forms of VWD
Type 2	Approximately 10% to 30% of patients
Type 2A	• Decreased VWF-dependent platelet adhesion • Selective deficiency of HMW-VMF multimers • Platelet binding functions of VWF are impaired
Type 2B	• Gain of function mutation with increased VWF binding to platelets • Loss of HMW-VWF multimers from plasma, but not from platelets • Loss of both VWF and platelets through a clearance mechanism
Type 2M	• Decreased VWF-dependent platelet adhesion without selective deficiency of HMW-VWF multimers
Type 2N	• Markedly decreased binding affinity for factor VIII

Adopted from Sadler, J Thromb Haemost 2006; 4, 2103

[00221] Methods for treating coagulation disease include administering rVWF or a combination of rVWF rFVIII to subjects in need thereof in accordance with any of the methods of administration described herein and known in the art. Such subjects may be suffering from any coagulation disease, including without limitation von Willebrand Disease or hemophilia. As will be appreciated, any type of von Willebrand Disease, including any of the types listed in the above table, can be treated in accordance with any of the methods and compositions described herein.

[00222] In some embodiments, rVWF (with or without rFVIII) is administered to a subject such that the level of Factor VIII procoagulant activity (FVIII:C) in the plasma of the subject 24, 36, 48 or more hours post-administration is at least 90% of the level of FVIII:C activity present in the plasma 1 hour post-administration. In further embodiments , the level of the FVIII:C in the plasma of the subject 24, 36, 48 or more hours post-administration is at least between 50% and 100% of the level of FVIII:C activity present in the plasma 1 hour post-

administration. In still further embodiments, the level of the FVIII:C in the plasma of the subject 24, 36, 48 or more hours post-administration is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 100% of the level of FVIII:C activity present in the plasma 1 hour post-administration.

Administration of rVWF

[00223] In one aspect, the present disclosure provides method for treating Von Willebrand Disease (VWD) or Hemophilia A in a subject in need thereof, which includes administering a composition of recombinant Von Willebrand Factor (rVWF) such that Factor VIII (FVIII) stability is increased, as compared to FVIII half-life in a subject administered a composition of plasma derived Von Willebrand Factor (pdVWF). In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In yet another embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers with a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00224] In one embodiment, the method comprises administering a composition of rVWF such that FVIII stability is extended by at least 10%, 20%, 30%, 2 hr, 4 hr, 6 hr, or by an amount selected from variations 1300 to 1643 found in **Table 9**, as compared to FVIII stability in a subject administered a composition of pdVWF. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In yet another embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers with a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00225] In one embodiment, the method comprises administering a composition of rVWF such that FVIII stability is extended by at least 10% as compared to FVIII stability in a

subject administered a composition of pdVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in **Table 3** to **Table 5**. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00226] In one embodiment, the method comprises administering a composition of rVWF such that FVIII stability is extended by at least 20% as compared to FVIII stability in a subject administered a composition of pdVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in **Table 3** to **Table 5**. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00227] In one embodiment, the method comprises administering a composition of rVWF such that FVIII stability is extended by at least 30% as compared to FVIII stability in a subject administered a composition of pdVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in **Table 3** to **Table 5**. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00228] In one embodiment, the method comprises administering a composition of rVWF, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

Table 13. Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.

		Increased Stability (Hours)							
		at least 1 hr	**at least 2 hr**	**at least 3 hr**	**at least 4 hr**	**at least 5 hr**	**at least 6 hr**	**at least 7 hr**	**at least 8 hr**
(mU/µg)	**at least 20**	Var. 2339	Var. 2385	Var. 2431	Var. 2477	Var. 2523	Var. 2569	Var. 2615	Var. 2661
	at least 30	Var. 2340	Var. 2386	Var. 2432	Var. 2478	Var. 2524	Var. 2570	Var. 2616	Var. 2662
	at least 40	Var. 2341	Var. 2387	Var. 2433	Var. 2479	Var. 2525	Var. 2571	Var. 2617	Var. 2663
	at least 50	Var. 2342	Var. 2388	Var. 2434	Var. 2480	Var. 2526	Var. 2572	Var. 2618	Var. 2664
	at least 60	Var. 2343	Var. 2389	Var. 2435	Var. 2481	Var. 2527	Var. 2573	Var. 2619	Var. 2665
	at least 70	Var. 2344	Var. 2390	Var. 2436	Var. 2482	Var. 2528	Var. 2574	Var. 2620	Var. 2666
	at least 80	Var. 2345	Var. 2391	Var. 2437	Var. 2483	Var. 2529	Var. 2575	Var. 2621	Var. 2667
	at least 90	Var. 2346	Var. 2392	Var. 2438	Var. 2484	Var. 2530	Var. 2576	Var. 2622	Var. 2668
	at least 100	Var. 2347	Var. 2393	Var. 2439	Var. 2485	Var. 2531	Var. 2577	Var. 2623	Var. 2669
	at least 125	Var. 2348	Var. 2394	Var. 2440	Var. 2486	Var. 2532	Var. 2578	Var. 2624	Var. 2670
	at least 150	Var. 2349	Var. 2395	Var. 2441	Var. 2487	Var. 2533	Var. 2579	Var. 2625	Var. 2671
	20-150	Var. 2350	Var. 2396	Var. 2442	Var. 2488	Var. 2534	Var. 2580	Var. 2626	Var. 2672
	20-125	Var. 2351	Var. 2397	Var. 2443	Var. 2489	Var. 2535	Var. 2581	Var. 2627	Var. 2673
	20-100	Var. 2352	Var. 2398	Var. 2444	Var. 2490	Var. 2536	Var. 2582	Var. 2628	Var. 2674
	20-90	Var. 2353	Var. 2399	Var. 2445	Var. 2491	Var. 2537	Var. 2583	Var. 2629	Var. 2675
	20-80	Var. 2354	Var. 2400	Var. 2446	Var. 2492	Var. 2538	Var. 2584	Var. 2630	Var. 2676
	20-70	Var. 2355	Var. 2401	Var. 2447	Var. 2493	Var. 2539	Var. 2585	Var. 2631	Var. 2677
	20-60	Var. 2356	Var. 2402	Var. 2448	Var. 2494	Var. 2540	Var. 2586	Var. 2632	Var. 2678

	20-50	Var. 2357	Var. 2403	Var. 2449	Var. 2495	Var. 2541	Var. 2587	Var. 2633	Var. 2679
	20-40	Var. 2358	Var. 2404	Var. 2450	Var. 2496	Var. 2542	Var. 2588	Var. 2634	Var. 2680
	40-150	Var. 2359	Var. 2405	Var. 2451	Var. 2497	Var. 2543	Var. 2589	Var. 2635	Var. 2681
	40-125	Var. 2360	Var. 2406	Var. 2452	Var. 2498	Var. 2544	Var. 2590	Var. 2636	Var. 2682
	40-100	Var. 2361	Var. 2407	Var. 2453	Var. 2499	Var. 2545	Var. 2591	Var. 2637	Var. 2683
	40-90	Var. 2362	Var. 2408	Var. 2454	Var. 2500	Var. 2546	Var. 2592	Var. 2638	Var. 2684
	40-80	Var. 2363	Var. 2409	Var. 2455	Var. 2501	Var. 2547	Var. 2593	Var. 2639	Var. 2685
	40-70	Var. 2364	Var. 2410	Var. 2456	Var. 2502	Var. 2548	Var. 2594	Var. 2640	Var. 2686
	40-60	Var. 2365	Var. 2411	Var. 2457	Var. 2503	Var. 2549	Var. 2595	Var. 2641	Var. 2687
	40-50	Var. 2366	Var. 2412	Var. 2458	Var. 2504	Var. 2550	Var. 2596	Var. 2642	Var. 2688
	60-150	Var. 2367	Var. 2413	Var. 2459	Var. 2505	Var. 2551	Var. 2597	Var. 2643	Var. 2689
	60-125	Var. 2368	Var. 2414	Var. 2460	Var. 2506	Var. 2552	Var. 2598	Var. 2644	Var. 2690
	60-100	Var. 2369	Var. 2415	Var. 2461	Var. 2507	Var. 2553	Var. 2599	Var. 2645	Var. 2691
	60-90	Var. 2370	Var. 2416	Var. 2462	Var. 2508	Var. 2554	Var. 2600	Var. 2646	Var. 2692
	60-80	Var. 2371	Var. 2417	Var. 2463	Var. 2509	Var. 2555	Var. 2601	Var. 2647	Var. 2693
	60-70	Var. 2372	Var. 2418	Var. 2464	Var. 2510	Var. 2556	Var. 2602	Var. 2648	Var. 2694
	70-150	Var. 2373	Var. 2419	Var. 2465	Var. 2511	Var. 2557	Var. 2603	Var. 2649	Var. 2695
	70-125	Var. 2374	Var. 2420	Var. 2466	Var. 2512	Var. 2558	Var. 2604	Var. 2650	Var. 2696
	70-100	Var. 2375	Var. 2421	Var. 2467	Var. 2513	Var. 2559	Var. 2605	Var. 2651	Var. 2697
	70-90	Var. 2376	Var. 2422	Var. 2468	Var. 2514	Var. 2560	Var. 2606	Var. 2652	Var. 2698
	70-80	Var. 2377	Var. 2423	Var. 2469	Var. 2515	Var. 2561	Var. 2607	Var. 2653	Var. 2699
	80-150	Var. 2378	Var. 2424	Var. 2470	Var. 2516	Var. 2562	Var. 2608	Var. 2654	Var. 2700
	80-125	Var. 2379	Var. 2425	Var. 2471	Var. 2517	Var. 2563	Var. 2609	Var. 2655	Var. 2701
	80-100	Var. 2380	Var. 2426	Var. 2472	Var. 2518	Var. 2564	Var. 2610	Var. 2656	Var. 2702
	80-90	Var. 2381	Var. 2427	Var. 2473	Var. 2519	Var. 2565	Var. 2611	Var. 2657	Var. 2703
	90-150	Var. 2382	Var. 2428	Var. 2474	Var. 2520	Var. 2566	Var. 2612	Var. 2658	Var. 2704
	90-125	Var. 2383	Var. 2429	Var. 2475	Var. 2521	Var. 2567	Var. 2613	Var. 2659	Var. 2705
	90-100	Var. 2384	Var. 2430	Var. 2476	Var. 2522	Var. 2568	Var. 2614	Var. 2660	Var. 2706

Var. = Variation

Table 14. Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.

		Increased Stability (Hours)							
		1-8 hr	**1-7 hr**	**1-6 hr**	**1-5 hr**	**1-4 hr**	**1-3 hr**	**1-2 hr**	**2-8 hr**
(mU/μg)	**at least 20**	Var. 2707	Var. 2753	Var. 2799	Var. 2845	Var. 2891	Var. 2937	Var. 2983	Var. 3029
	at least 30	Var. 2708	Var. 2754	Var. 2800	Var. 2846	Var. 2892	Var. 2938	Var. 2984	Var. 3030
	at least 40	Var. 2709	Var. 2755	Var. 2801	Var. 2847	Var. 2893	Var. 2939	Var. 2985	Var. 3031
	at least 50	Var. 2710	Var. 2756	Var. 2802	Var. 2848	Var. 2894	Var. 2940	Var. 2986	Var. 3032
	at least 60	Var. 2711	Var. 2757	Var. 2803	Var. 2849	Var. 2895	Var. 2941	Var. 2987	Var. 3033
	at least 70	Var. 2712	Var. 2758	Var. 2804	Var. 2850	Var. 2896	Var. 2942	Var. 2988	Var. 3034
	at least 80	Var. 2713	Var. 2759	Var. 2805	Var. 2851	Var. 2897	Var. 2943	Var. 2989	Var. 3035
	at least 90	Var. 2714	Var. 2760	Var. 2806	Var. 2852	Var. 2898	Var. 2944	Var. 2990	Var. 3036
	at least 100	Var. 2715	Var. 2761	Var. 2807	Var. 2853	Var. 2899	Var. 2945	Var. 2991	Var. 3037
	at least 125	Var. 2716	Var. 2762	Var. 2808	Var. 2854	Var. 2900	Var. 2946	Var. 2992	Var. 3038
	at least 150	Var. 2717	Var. 2763	Var. 2809	Var. 2855	Var. 2901	Var. 2947	Var. 2993	Var. 3039
	20-150	Var. 2718	Var. 2764	Var. 2810	Var. 2856	Var. 2902	Var. 2948	Var. 2994	Var. 3040
	20-125	Var. 2719	Var. 2765	Var. 2811	Var. 2857	Var. 2903	Var. 2949	Var. 2995	Var. 3041
	20-100	Var. 2720	Var. 2766	Var. 2812	Var. 2858	Var. 2904	Var. 2950	Var. 2996	Var. 3042
	20-90	Var. 2721	Var. 2767	Var. 2813	Var. 2859	Var. 2905	Var. 2951	Var. 2997	Var. 3043
	20-80	Var. 2722	Var. 2768	Var. 2814	Var. 2860	Var. 2906	Var. 2952	Var. 2998	Var. 3044
	20-70	Var. 2723	Var. 2769	Var. 2815	Var. 2861	Var. 2907	Var. 2953	Var. 2999	Var. 3045
	20-60	Var. 2724	Var. 2770	Var. 2816	Var. 2862	Var. 2908	Var. 2954	Var. 3000	Var. 3046
	20-50	Var. 2725	Var. 2771	Var. 2817	Var. 2863	Var. 2909	Var. 2955	Var. 3001	Var. 3047
	20-40	Var. 2726	Var. 2772	Var. 2818	Var. 2864	Var. 2910	Var. 2956	Var. 3002	Var. 3048
	40-150	Var. 2727	Var. 2773	Var. 2819	Var. 2865	Var. 2911	Var. 2957	Var. 3003	Var. 3049
	40-125	Var. 2728	Var. 2774	Var. 2820	Var. 2866	Var. 2912	Var. 2958	Var. 3004	Var. 3050
	40-100	Var. 2729	Var. 2775	Var. 2821	Var. 2867	Var. 2913	Var. 2959	Var. 3005	Var. 3051
	40-90	Var. 2730	Var. 2776	Var. 2822	Var. 2868	Var. 2914	Var. 2960	Var. 3006	Var. 3052
	40-80	Var. 2731	Var. 2777	Var. 2823	Var. 2869	Var. 2915	Var. 2961	Var. 3007	Var. 3053
	40-70	Var. 2732	Var. 2778	Var. 2824	Var. 2870	Var. 2916	Var. 2962	Var. 3008	Var. 3054
	40-60	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.

		2733	2779	2825	2871	2917	2963	3009	3055
	40-50	Var. 2734	Var. 2780	Var. 2826	Var. 2872	Var. 2918	Var. 2964	Var. 3010	Var. 3056
	60-150	Var. 2735	Var. 2781	Var. 2827	Var. 2873	Var. 2919	Var. 2965	Var. 3011	Var. 3057
	60-125	Var. 2736	Var. 2782	Var. 2828	Var. 2874	Var. 2920	Var. 2966	Var. 3012	Var. 3058
	60-100	Var. 2737	Var. 2783	Var. 2829	Var. 2875	Var. 2921	Var. 2967	Var. 3013	Var. 3059
	60-90	Var. 2738	Var. 2784	Var. 2830	Var. 2876	Var. 2922	Var. 2968	Var. 3014	Var. 3060
	60-80	Var. 2739	Var. 2785	Var. 2831	Var. 2877	Var. 2923	Var. 2969	Var. 3015	Var. 3061
	60-70	Var. 2740	Var. 2786	Var. 2832	Var. 2878	Var. 2924	Var. 2970	Var. 3016	Var. 3062
	70-150	Var. 2741	Var. 2787	Var. 2833	Var. 2879	Var. 2925	Var. 2971	Var. 3017	Var. 3063
	70-125	Var. 2742	Var. 2788	Var. 2834	Var. 2880	Var. 2926	Var. 2972	Var. 3018	Var. 3064
	70-100	Var. 2743	Var. 2789	Var. 2835	Var. 2881	Var. 2927	Var. 2973	Var. 3019	Var. 3065
	70-90	Var. 2744	Var. 2790	Var. 2836	Var. 2882	Var. 2928	Var. 2974	Var. 3020	Var. 3066
	70-80	Var. 2745	Var. 2791	Var. 2837	Var. 2883	Var. 2929	Var. 2975	Var. 3021	Var. 3067
	80-150	Var. 2746	Var. 2792	Var. 2838	Var. 2884	Var. 2930	Var. 2976	Var. 3022	Var. 3068
	80-125	Var. 2747	Var. 2793	Var. 2839	Var. 2885	Var. 2931	Var. 2977	Var. 3023	Var. 3069
	80-100	Var. 2748	Var. 2794	Var. 2840	Var. 2886	Var. 2932	Var. 2978	Var. 3024	Var. 3070
	80-90	Var. 2749	Var. 2795	Var. 2841	Var. 2887	Var. 2933	Var. 2979	Var. 3025	Var. 3071
	90-150	Var. 2750	Var. 2796	Var. 2842	Var. 2888	Var. 2934	Var. 2980	Var. 3026	Var. 3072
	90-125	Var. 2751	Var. 2797	Var. 2843	Var. 2889	Var. 2935	Var. 2981	Var. 3027	Var. 3073
	90-100	Var. 2752	Var. 2798	Var. 2844	Var. 2890	Var. 2936	Var. 2982	Var. 3028	Var. 3074

Var. = Variation

Table 15. Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.

		Increased Stability (Hours)							
		2-7 hr	**2-6 hr**	**2-5 hr**	**2-4 hr**	**2-3 hr**	**3-8 hr**	**3-7 hr**	**3-6 hr**
(mU/µg)	**at least 20**	Var. 3075	Var. 3121	Var. 3167	Var. 3213	Var. 3259	Var. 3305	Var. 3351	Var. 3397
	at least 30	Var. 3076	Var. 3122	Var. 3168	Var. 3214	Var. 3260	Var. 3306	Var. 3352	Var. 3398
	at least 40	Var. 3077	Var. 3123	Var. 3169	Var. 3215	Var. 3261	Var. 3307	Var. 3353	Var. 3399
	at least 50	Var. 3078	Var. 3124	Var. 3170	Var. 3216	Var. 3262	Var. 3308	Var. 3354	Var. 3400
	at least 60	Var. 3079	Var. 3125	Var. 3171	Var. 3217	Var. 3263	Var. 3309	Var. 3355	Var. 3401
	at least 70	Var. 3080	Var. 3126	Var. 3172	Var. 3218	Var. 3264	Var. 3310	Var. 3356	Var. 3402

	at least 80	Var. 3081	Var. 3127	Var. 3173	Var. 3219	Var. 3265	Var. 3311	Var. 3357	Var. 3403
	at least 90	Var. 3082	Var. 3128	Var. 3174	Var. 3220	Var. 3266	Var. 3312	Var. 3358	Var. 3404
	at least 100	Var. 3083	Var. 3129	Var. 3175	Var. 3221	Var. 3267	Var. 3313	Var. 3359	Var. 3405
	at least 125	Var. 3084	Var. 3130	Var. 3176	Var. 3222	Var. 3268	Var. 3314	Var. 3360	Var. 3406
	at least 150	Var. 3085	Var. 3131	Var. 3177	Var. 3223	Var. 3269	Var. 3315	Var. 3361	Var. 3407
	20-150	Var. 3086	Var. 3132	Var. 3178	Var. 3224	Var. 3270	Var. 3316	Var. 3362	Var. 3408
	20-125	Var. 3087	Var. 3133	Var. 3179	Var. 3225	Var. 3271	Var. 3317	Var. 3363	Var. 3409
	20-100	Var. 3088	Var. 3134	Var. 3180	Var. 3226	Var. 3272	Var. 3318	Var. 3364	Var. 3410
	20-90	Var. 3089	Var. 3135	Var. 3181	Var. 3227	Var. 3273	Var. 3319	Var. 3365	Var. 3411
	20-80	Var. 3090	Var. 3136	Var. 3182	Var. 3228	Var. 3274	Var. 3320	Var. 3366	Var. 3412
	20-70	Var. 3091	Var. 3137	Var. 3183	Var. 3229	Var. 3275	Var. 3321	Var. 3367	Var. 3413
	20-60	Var. 3092	Var. 3138	Var. 3184	Var. 3230	Var. 3276	Var. 3322	Var. 3368	Var. 3414
	20-50	Var. 3093	Var. 3139	Var. 3185	Var. 3231	Var. 3277	Var. 3323	Var. 3369	Var. 3415
	20-40	Var. 3094	Var. 3140	Var. 3186	Var. 3232	Var. 3278	Var. 3324	Var. 3370	Var. 3416
	40-150	Var. 3095	Var. 3141	Var. 3187	Var. 3233	Var. 3279	Var. 3325	Var. 3371	Var. 3417
	40-125	Var. 3096	Var. 3142	Var. 3188	Var. 3234	Var. 3280	Var. 3326	Var. 3372	Var. 3418
	40-100	Var. 3097	Var. 3143	Var. 3189	Var. 3235	Var. 3281	Var. 3327	Var. 3373	Var. 3419
	40-90	Var. 3098	Var. 3144	Var. 3190	Var. 3236	Var. 3282	Var. 3328	Var. 3374	Var. 3420
	40-80	Var. 3099	Var. 3145	Var. 3191	Var. 3237	Var. 3283	Var. 3329	Var. 3375	Var. 3421
	40-70	Var. 3100	Var. 3146	Var. 3192	Var. 3238	Var. 3284	Var. 3330	Var. 3376	Var. 3422
	40-60	Var. 3101	Var. 3147	Var. 3193	Var. 3239	Var. 3285	Var. 3331	Var. 3377	Var. 3423
	40-50	Var. 3102	Var. 3148	Var. 3194	Var. 3240	Var. 3286	Var. 3332	Var. 3378	Var. 3424
	60-150	Var. 3103	Var. 3149	Var. 3195	Var. 3241	Var. 3287	Var. 3333	Var. 3379	Var. 3425
	60-125	Var. 3104	Var. 3150	Var. 3196	Var. 3242	Var. 3288	Var. 3334	Var. 3380	Var. 3426
	60-100	Var. 3105	Var. 3151	Var. 3197	Var. 3243	Var. 3289	Var. 3335	Var. 3381	Var. 3427
	60-90	Var. 3106	Var. 3152	Var. 3198	Var. 3244	Var. 3290	Var. 3336	Var. 3382	Var. 3428
	60-80	Var. 3107	Var. 3153	Var. 3199	Var. 3245	Var. 3291	Var. 3337	Var. 3383	Var. 3429
	60-70	Var. 3108	Var. 3154	Var. 3200	Var. 3246	Var. 3292	Var. 3338	Var. 3384	Var. 3430
	70-150	Var. 3109	Var. 3155	Var. 3201	Var. 3247	Var. 3293	Var. 3339	Var. 3385	Var. 3431
	70-125	Var. 3110	Var. 3156	Var. 3202	Var. 3248	Var. 3294	Var. 3340	Var. 3386	Var. 3432
	70-100	Var.	Var.	Var.	Var.	Var.	Var.	Var.	Var.

		3111	3157	3203	3249	3295	3341	3387	3433
	70-90	Var. 3112	Var. 3158	Var. 3204	Var. 3250	Var. 3296	Var. 3342	Var. 3388	Var. 3434
	70-80	Var. 3113	Var. 3159	Var. 3205	Var. 3251	Var. 3297	Var. 3343	Var. 3389	Var. 3435
	80-150	Var. 3114	Var. 3160	Var. 3206	Var. 3252	Var. 3298	Var. 3344	Var. 3390	Var. 3436
	80-125	Var. 3115	Var. 3161	Var. 3207	Var. 3253	Var. 3299	Var. 3345	Var. 3391	Var. 3437
	80-100	Var. 3116	Var. 3162	Var. 3208	Var. 3254	Var. 3300	Var. 3346	Var. 3392	Var. 3438
	80-90	Var. 3117	Var. 3163	Var. 3209	Var. 3255	Var. 3301	Var. 3347	Var. 3393	Var. 3439
	90-150	Var. 3118	Var. 3164	Var. 3210	Var. 3256	Var. 3302	Var. 3348	Var. 3394	Var. 3440
	90-125	Var. 3119	Var. 3165	Var. 3211	Var. 3257	Var. 3303	Var. 3349	Var. 3395	Var. 3441
	90-100	Var. 3120	Var. 3166	Var. 3212	Var. 3258	Var. 3304	Var. 3350	Var. 3396	Var. 3442

Var. = Variation

Table 16. Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.

		Increased Stability (Hours)							
		3-5 hr	**3-4 hr**	**4-8 hr**	**4-7 hr**	**4-6 hr**	**4-5 hr**	**5-8 hr**	**5-7 hr**
(mU/µg)	**at least 20**	Var. 3443	Var. 3489	Var. 3535	Var. 3581	Var. 3627	Var. 3673	Var. 3719	Var. 3765
	at least 30	Var. 3444	Var. 3490	Var. 3536	Var. 3582	Var. 3628	Var. 3674	Var. 3720	Var. 3766
	at least 40	Var. 3445	Var. 3491	Var. 3537	Var. 3583	Var. 3629	Var. 3675	Var. 3721	Var. 3767
	at least 50	Var. 3446	Var. 3492	Var. 3538	Var. 3584	Var. 3630	Var. 3676	Var. 3722	Var. 3768
	at least 60	Var. 3447	Var. 3493	Var. 3539	Var. 3585	Var. 3631	Var. 3677	Var. 3723	Var. 3769
	at least 70	Var. 3448	Var. 3494	Var. 3540	Var. 3586	Var. 3632	Var. 3678	Var. 3724	Var. 3770
	at least 80	Var. 3449	Var. 3495	Var. 3541	Var. 3587	Var. 3633	Var. 3679	Var. 3725	Var. 3771
	at least 90	Var. 3450	Var. 3496	Var. 3542	Var. 3588	Var. 3634	Var. 3680	Var. 3726	Var. 3772
	at least 100	Var. 3451	Var. 3497	Var. 3543	Var. 3589	Var. 3635	Var. 3681	Var. 3727	Var. 3773
	at least 125	Var. 3452	Var. 3498	Var. 3544	Var. 3590	Var. 3636	Var. 3682	Var. 3728	Var. 3774
	at least 150	Var. 3453	Var. 3499	Var. 3545	Var. 3591	Var. 3637	Var. 3683	Var. 3729	Var. 3775
	20-150	Var. 3454	Var. 3500	Var. 3546	Var. 3592	Var. 3638	Var. 3684	Var. 3730	Var. 3776
	20-125	Var. 3455	Var. 3501	Var. 3547	Var. 3593	Var. 3639	Var. 3685	Var. 3731	Var. 3777
	20-100	Var. 3456	Var. 3502	Var. 3548	Var. 3594	Var. 3640	Var. 3686	Var. 3732	Var. 3778
	20-90	Var. 3457	Var. 3503	Var. 3549	Var. 3595	Var. 3641	Var. 3687	Var. 3733	Var. 3779
	20-80	Var. 3458	Var. 3504	Var. 3550	Var. 3596	Var. 3642	Var. 3688	Var. 3734	Var. 3780

	20-70	Var. 3459	Var. 3505	Var. 3551	Var. 3597	Var. 3643	Var. 3689	Var. 3735	Var. 3781
	20-60	Var. 3460	Var. 3506	Var. 3552	Var. 3598	Var. 3644	Var. 3690	Var. 3736	Var. 3782
	20-50	Var. 3461	Var. 3507	Var. 3553	Var. 3599	Var. 3645	Var. 3691	Var. 3737	Var. 3783
	20-40	Var. 3462	Var. 3508	Var. 3554	Var. 3600	Var. 3646	Var. 3692	Var. 3738	Var. 3784
	40-150	Var. 3463	Var. 3509	Var. 3555	Var. 3601	Var. 3647	Var. 3693	Var. 3739	Var. 3785
	40-125	Var. 3464	Var. 3510	Var. 3556	Var. 3602	Var. 3648	Var. 3694	Var. 3740	Var. 3786
	40-100	Var. 3465	Var. 3511	Var. 3557	Var. 3603	Var. 3649	Var. 3695	Var. 3741	Var. 3787
	40-90	Var. 3466	Var. 3512	Var. 3558	Var. 3604	Var. 3650	Var. 3696	Var. 3742	Var. 3788
	40-80	Var. 3467	Var. 3513	Var. 3559	Var. 3605	Var. 3651	Var. 3697	Var. 3743	Var. 3789
	40-70	Var. 3468	Var. 3514	Var. 3560	Var. 3606	Var. 3652	Var. 3698	Var. 3744	Var. 3790
	40-60	Var. 3469	Var. 3515	Var. 3561	Var. 3607	Var. 3653	Var. 3699	Var. 3745	Var. 3791
	40-50	Var. 3470	Var. 3516	Var. 3562	Var. 3608	Var. 3654	Var. 3700	Var. 3746	Var. 3792
	60-150	Var. 3471	Var. 3517	Var. 3563	Var. 3609	Var. 3655	Var. 3701	Var. 3747	Var. 3793
	60-125	Var. 3472	Var. 3518	Var. 3564	Var. 3610	Var. 3656	Var. 3702	Var. 3748	Var. 3794
	60-100	Var. 3473	Var. 3519	Var. 3565	Var. 3611	Var. 3657	Var. 3703	Var. 3749	Var. 3795
	60-90	Var. 3474	Var. 3520	Var. 3566	Var. 3612	Var. 3658	Var. 3704	Var. 3750	Var. 3796
	60-80	Var. 3475	Var. 3521	Var. 3567	Var. 3613	Var. 3659	Var. 3705	Var. 3751	Var. 3797
	60-70	Var. 3476	Var. 3522	Var. 3568	Var. 3614	Var. 3660	Var. 3706	Var. 3752	Var. 3798
	70-150	Var. 3477	Var. 3523	Var. 3569	Var. 3615	Var. 3661	Var. 3707	Var. 3753	Var. 3799
	70-125	Var. 3478	Var. 3524	Var. 3570	Var. 3616	Var. 3662	Var. 3708	Var. 3754	Var. 3800
	70-100	Var. 3479	Var. 3525	Var. 3571	Var. 3617	Var. 3663	Var. 3709	Var. 3755	Var. 3801
	70-90	Var. 3480	Var. 3526	Var. 3572	Var. 3618	Var. 3664	Var. 3710	Var. 3756	Var. 3802
	70-80	Var. 3481	Var. 3527	Var. 3573	Var. 3619	Var. 3665	Var. 3711	Var. 3757	Var. 3803
	80-150	Var. 3482	Var. 3528	Var. 3574	Var. 3620	Var. 3666	Var. 3712	Var. 3758	Var. 3804
	80-125	Var. 3483	Var. 3529	Var. 3575	Var. 3621	Var. 3667	Var. 3713	Var. 3759	Var. 3805
	80-100	Var. 3484	Var. 3530	Var. 3576	Var. 3622	Var. 3668	Var. 3714	Var. 3760	Var. 3806
	80-90	Var. 3485	Var. 3531	Var. 3577	Var. 3623	Var. 3669	Var. 3715	Var. 3761	Var. 3807
	90-150	Var. 3486	Var. 3532	Var. 3578	Var. 3624	Var. 3670	Var. 3716	Var. 3762	Var. 3808
	90-125	Var. 3487	Var. 3533	Var. 3579	Var. 3625	Var. 3671	Var. 3717	Var. 3763	Var. 3809
	90-100	Var. 3488	Var. 3534	Var. 3580	Var. 3626	Var. 3672	Var. 3718	Var. 3764	Var. 3810

Var. = Variation

Table 17. Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.

		Increased Stability (Hours)				**Increased Stability (Percent)**			
		5-6 hr	**6-8 hr**	**6-7 hr**	**7-8 hr**	**at least 10%**	**at least 20%**	**at least 30%**	**at least 40%**
(mU/µg)	**at least 20**	Var. 3811	Var. 3857	Var. 3903	Var. 3949	Var. 3995	Var. 4041	Var. 4087	Var. 4133
	at least 30	Var. 3812	Var. 3858	Var. 3904	Var. 3950	Var. 3996	Var. 4042	Var. 4088	Var. 4134
	at least 40	Var. 3813	Var. 3859	Var. 3905	Var. 3951	Var. 3997	Var. 4043	Var. 4089	Var. 4135
	at least 50	Var. 3814	Var. 3860	Var. 3906	Var. 3952	Var. 3998	Var. 4044	Var. 4090	Var. 4136
	at least 60	Var. 3815	Var. 3861	Var. 3907	Var. 3953	Var. 3999	Var. 4045	Var. 4091	Var. 4137
	at least 70	Var. 3816	Var. 3862	Var. 3908	Var. 3954	Var. 4000	Var. 4046	Var. 4092	Var. 4138
	at least 80	Var. 3817	Var. 3863	Var. 3909	Var. 3955	Var. 4001	Var. 4047	Var. 4093	Var. 4139
	at least 90	Var. 3818	Var. 3864	Var. 3910	Var. 3956	Var. 4002	Var. 4048	Var. 4094	Var. 4140
	at least 100	Var. 3819	Var. 3865	Var. 3911	Var. 3957	Var. 4003	Var. 4049	Var. 4095	Var. 4141
	at least 125	Var. 3820	Var. 3866	Var. 3912	Var. 3958	Var. 4004	Var. 4050	Var. 4096	Var. 4142
	at least 150	Var. 3821	Var. 3867	Var. 3913	Var. 3959	Var. 4005	Var. 4051	Var. 4097	Var. 4143
	20-150	Var. 3822	Var. 3868	Var. 3914	Var. 3960	Var. 4006	Var. 4052	Var. 4098	Var. 4144
	20-125	Var. 3823	Var. 3869	Var. 3915	Var. 3961	Var. 4007	Var. 4053	Var. 4099	Var. 4145
	20-100	Var. 3824	Var. 3870	Var. 3916	Var. 3962	Var. 4008	Var. 4054	Var. 4100	Var. 4146
	20-90	Var. 3825	Var. 3871	Var. 3917	Var. 3963	Var. 4009	Var. 4055	Var. 4101	Var. 4147
	20-80	Var. 3826	Var. 3872	Var. 3918	Var. 3964	Var. 4010	Var. 4056	Var. 4102	Var. 4148
	20-70	Var. 3827	Var. 3873	Var. 3919	Var. 3965	Var. 4011	Var. 4057	Var. 4103	Var. 4149
	20-60	Var. 3828	Var. 3874	Var. 3920	Var. 3966	Var. 4012	Var. 4058	Var. 4104	Var. 4150
	20-50	Var. 3829	Var. 3875	Var. 3921	Var. 3967	Var. 4013	Var. 4059	Var. 4105	Var. 4151
	20-40	Var. 3830	Var. 3876	Var. 3922	Var. 3968	Var. 4014	Var. 4060	Var. 4106	Var. 4152
	40-150	Var. 3831	Var. 3877	Var. 3923	Var. 3969	Var. 4015	Var. 4061	Var. 4107	Var. 4153
	40-125	Var. 3832	Var. 3878	Var. 3924	Var. 3970	Var. 4016	Var. 4062	Var. 4108	Var. 4154
	40-100	Var. 3833	Var. 3879	Var. 3925	Var. 3971	Var. 4017	Var. 4063	Var. 4109	Var. 4155
	40-90	Var. 3834	Var. 3880	Var. 3926	Var. 3972	Var. 4018	Var. 4064	Var. 4110	Var. 4156
	40-80	Var. 3835	Var. 3881	Var. 3927	Var. 3973	Var. 4019	Var. 4065	Var. 4111	Var. 4157
	40-70	Var. 3836	Var. 3882	Var. 3928	Var. 3974	Var. 4020	Var. 4066	Var. 4112	Var. 4158

	40-60	Var. 3837	Var. 3883	Var. 3929	Var. 3975	Var. 4021	Var. 4067	Var. 4113	Var. 4159
	40-50	Var. 3838	Var. 3884	Var. 3930	Var. 3976	Var. 4022	Var. 4068	Var. 4114	Var. 4160
	60-150	Var. 3839	Var. 3885	Var. 3931	Var. 3977	Var. 4023	Var. 4069	Var. 4115	Var. 4161
	60-125	Var. 3840	Var. 3886	Var. 3932	Var. 3978	Var. 4024	Var. 4070	Var. 4116	Var. 4162
	60-100	Var. 3841	Var. 3887	Var. 3933	Var. 3979	Var. 4025	Var. 4071	Var. 4117	Var. 4163
	60-90	Var. 3842	Var. 3888	Var. 3934	Var. 3980	Var. 4026	Var. 4072	Var. 4118	Var. 4164
	60-80	Var. 3843	Var. 3889	Var. 3935	Var. 3981	Var. 4027	Var. 4073	Var. 4119	Var. 4165
	60-70	Var. 3844	Var. 3890	Var. 3936	Var. 3982	Var. 4028	Var. 4074	Var. 4120	Var. 4166
	70-150	Var. 3845	Var. 3891	Var. 3937	Var. 3983	Var. 4029	Var. 4075	Var. 4121	Var. 4167
	70-125	Var. 3846	Var. 3892	Var. 3938	Var. 3984	Var. 4030	Var. 4076	Var. 4122	Var. 4168
	70-100	Var. 3847	Var. 3893	Var. 3939	Var. 3985	Var. 4031	Var. 4077	Var. 4123	Var. 4169
	70-90	Var. 3848	Var. 3894	Var. 3940	Var. 3986	Var. 4032	Var. 4078	Var. 4124	Var. 4170
	70-80	Var. 3849	Var. 3895	Var. 3941	Var. 3987	Var. 4033	Var. 4079	Var. 4125	Var. 4171
	80-150	Var. 3850	Var. 3896	Var. 3942	Var. 3988	Var. 4034	Var. 4080	Var. 4126	Var. 4172
	80-125	Var. 3851	Var. 3897	Var. 3943	Var. 3989	Var. 4035	Var. 4081	Var. 4127	Var. 4173
	80-100	Var. 3852	Var. 3898	Var. 3944	Var. 3990	Var. 4036	Var. 4082	Var. 4128	Var. 4174
	80-90	Var. 3853	Var. 3899	Var. 3945	Var. 3991	Var. 4037	Var. 4083	Var. 4129	Var. 4175
	90-150	Var. 3854	Var. 3900	Var. 3946	Var. 3992	Var. 4038	Var. 4084	Var. 4130	Var. 4176
	90-125	Var. 3855	Var. 3901	Var. 3947	Var. 3993	Var. 4039	Var. 4085	Var. 4131	Var. 4177
	90-100	Var. 3856	Var. 3902	Var. 3948	Var. 3994	Var. 4040	Var. 4086	Var. 4132	Var. 4178

Var. = Variation

Table 18. Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.

		Increased Stability (Percent)							
		at least 50%	**10-50%**	**10-40%**	**10-30%**	**10-20%**	**15-50%**	**15-40%**	**15-30%**
(mU/µg)	**at least 20**	Var. 4179	Var. 4225	Var. 4271	Var. 4317	Var. 4363	Var. 4409	Var. 4455	Var. 4501
	at least 30	Var. 4180	Var. 4226	Var. 4272	Var. 4318	Var. 4364	Var. 4410	Var. 4456	Var. 4502
	at least 40	Var. 4181	Var. 4227	Var. 4273	Var. 4319	Var. 4365	Var. 4411	Var. 4457	Var. 4503
	at least 50	Var. 4182	Var. 4228	Var. 4274	Var. 4320	Var. 4366	Var. 4412	Var. 4458	Var. 4504
	at least 60	Var. 4183	Var. 4229	Var. 4275	Var. 4321	Var. 4367	Var. 4413	Var. 4459	Var. 4505

	at least 70	Var. 4184	Var. 4230	Var. 4276	Var. 4322	Var. 4368	Var. 4414	Var. 4460	Var. 4506
	at least 80	Var. 4185	Var. 4231	Var. 4277	Var. 4323	Var. 4369	Var. 4415	Var. 4461	Var. 4507
	at least 90	Var. 4186	Var. 4232	Var. 4278	Var. 4324	Var. 4370	Var. 4416	Var. 4462	Var. 4508
	at least 100	Var. 4187	Var. 4233	Var. 4279	Var. 4325	Var. 4371	Var. 4417	Var. 4463	Var. 4509
	at least 125	Var. 4188	Var. 4234	Var. 4280	Var. 4326	Var. 4372	Var. 4418	Var. 4464	Var. 4510
	at least 150	Var. 4189	Var. 4235	Var. 4281	Var. 4327	Var. 4373	Var. 4419	Var. 4465	Var. 4511
	20-150	Var. 4190	Var. 4236	Var. 4282	Var. 4328	Var. 4374	Var. 4420	Var. 4466	Var. 4512
	20-125	Var. 4191	Var. 4237	Var. 4283	Var. 4329	Var. 4375	Var. 4421	Var. 4467	Var. 4513
	20-100	Var. 4192	Var. 4238	Var. 4284	Var. 4330	Var. 4376	Var. 4422	Var. 4468	Var. 4514
	20-90	Var. 4193	Var. 4239	Var. 4285	Var. 4331	Var. 4377	Var. 4423	Var. 4469	Var. 4515
	20-80	Var. 4194	Var. 4240	Var. 4286	Var. 4332	Var. 4378	Var. 4424	Var. 4470	Var. 4516
	20-70	Var. 4195	Var. 4241	Var. 4287	Var. 4333	Var. 4379	Var. 4425	Var. 4471	Var. 4517
	20-60	Var. 4196	Var. 4242	Var. 4288	Var. 4334	Var. 4380	Var. 4426	Var. 4472	Var. 4518
	20-50	Var. 4197	Var. 4243	Var. 4289	Var. 4335	Var. 4381	Var. 4427	Var. 4473	Var. 4519
	20-40	Var. 4198	Var. 4244	Var. 4290	Var. 4336	Var. 4382	Var. 4428	Var. 4474	Var. 4520
	40-150	Var. 4199	Var. 4245	Var. 4291	Var. 4337	Var. 4383	Var. 4429	Var. 4475	Var. 4521
	40-125	Var. 4200	Var. 4246	Var. 4292	Var. 4338	Var. 4384	Var. 4430	Var. 4476	Var. 4522
	40-100	Var. 4201	Var. 4247	Var. 4293	Var. 4339	Var. 4385	Var. 4431	Var. 4477	Var. 4523
	40-90	Var. 4202	Var. 4248	Var. 4294	Var. 4340	Var. 4386	Var. 4432	Var. 4478	Var. 4524
	40-80	Var. 4203	Var. 4249	Var. 4295	Var. 4341	Var. 4387	Var. 4433	Var. 4479	Var. 4525
	40-70	Var. 4204	Var. 4250	Var. 4296	Var. 4342	Var. 4388	Var. 4434	Var. 4480	Var. 4526
	40-60	Var. 4205	Var. 4251	Var. 4297	Var. 4343	Var. 4389	Var. 4435	Var. 4481	Var. 4527
	40-50	Var. 4206	Var. 4252	Var. 4298	Var. 4344	Var. 4390	Var. 4436	Var. 4482	Var. 4528
	60-150	Var. 4207	Var. 4253	Var. 4299	Var. 4345	Var. 4391	Var. 4437	Var. 4483	Var. 4529
	60-125	Var. 4208	Var. 4254	Var. 4300	Var. 4346	Var. 4392	Var. 4438	Var. 4484	Var. 4530
	60-100	Var. 4209	Var. 4255	Var. 4301	Var. 4347	Var. 4393	Var. 4439	Var. 4485	Var. 4531
	60-90	Var. 4210	Var. 4256	Var. 4302	Var. 4348	Var. 4394	Var. 4440	Var. 4486	Var. 4532
	60-80	Var. 4211	Var. 4257	Var. 4303	Var. 4349	Var. 4395	Var. 4441	Var. 4487	Var. 4533
	60-70	Var. 4212	Var. 4258	Var. 4304	Var. 4350	Var. 4396	Var. 4442	Var. 4488	Var. 4534
	70-150	Var. 4213	Var. 4259	Var. 4305	Var. 4351	Var. 4397	Var. 4443	Var. 4489	Var. 4535
	70-125	Var. 4214	Var.	Var.	Var.	Var.	Var.	Var.	Var.

			4260	4306	4352	4398	4444	4490	4536
	70-100	Var. 4215	Var. 4261	Var. 4307	Var. 4353	Var. 4399	Var. 4445	Var. 4491	Var. 4537
	70-90	Var. 4216	Var. 4262	Var. 4308	Var. 4354	Var. 4400	Var. 4446	Var. 4492	Var. 4538
	70-80	Var. 4217	Var. 4263	Var. 4309	Var. 4355	Var. 4401	Var. 4447	Var. 4493	Var. 4539
	80-150	Var. 4218	Var. 4264	Var. 4310	Var. 4356	Var. 4402	Var. 4448	Var. 4494	Var. 4540
	80-125	Var. 4219	Var. 4265	Var. 4311	Var. 4357	Var. 4403	Var. 4449	Var. 4495	Var. 4541
	80-100	Var. 4220	Var. 4266	Var. 4312	Var. 4358	Var. 4404	Var. 4450	Var. 4496	Var. 4542
	80-90	Var. 4221	Var. 4267	Var. 4313	Var. 4359	Var. 4405	Var. 4451	Var. 4497	Var. 4543
	90-150	Var. 4222	Var. 4268	Var. 4314	Var. 4360	Var. 4406	Var. 4452	Var. 4498	Var. 4544
	90-125	Var. 4223	Var. 4269	Var. 4315	Var. 4361	Var. 4407	Var. 4453	Var. 4499	Var. 4545
	90-100	Var. 4224	Var. 4270	Var. 4316	Var. 4362	Var. 4408	Var. 4454	Var. 4500	Var. 4546

Var. = Variation

Table 19. Exemplary embodiments for the combination of rVWF specific activity in a composition used herein and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.

		Increased Stability (Percent)							
		15-20%	**20-50%**	**20-40%**	**20-30%**	**30-50%**	**30-40%**	**40-50%**	
(mU/µg)	**at least 20**	Var. 4547	Var. 4593	Var. 4639	Var. 4685	Var. 4731	Var. 4777	Var. 4823	
	at least 30	Var. 4548	Var. 4594	Var. 4640	Var. 4686	Var. 4732	Var. 4778	Var. 4824	
	at least 40	Var. 4549	Var. 4595	Var. 4641	Var. 4687	Var. 4733	Var. 4779	Var. 4825	
	at least 50	Var. 4550	Var. 4596	Var. 4642	Var. 4688	Var. 4734	Var. 4780	Var. 4826	
	at least 60	Var. 4551	Var. 4597	Var. 4643	Var. 4689	Var. 4735	Var. 4781	Var. 4827	
	at least 70	Var. 4552	Var. 4598	Var. 4644	Var. 4690	Var. 4736	Var. 4782	Var. 4828	
	at least 80	Var. 4553	Var. 4599	Var. 4645	Var. 4691	Var. 4737	Var. 4783	Var. 4829	
	at least 90	Var. 4554	Var. 4600	Var. 4646	Var. 4692	Var. 4738	Var. 4784	Var. 4830	
	at least 100	Var. 4555	Var. 4601	Var. 4647	Var. 4693	Var. 4739	Var. 4785	Var. 4831	
	at least 125	Var. 4556	Var. 4602	Var. 4648	Var. 4694	Var. 4740	Var. 4786	Var. 4832	
	at least 150	Var. 4557	Var. 4603	Var. 4649	Var. 4695	Var. 4741	Var. 4787	Var. 4833	
	20-150	Var. 4558	Var. 4604	Var. 4650	Var. 4696	Var. 4742	Var. 4788	Var. 4834	
	20-125	Var. 4559	Var. 4605	Var. 4651	Var. 4697	Var. 4743	Var. 4789	Var. 4835	
	20-100	Var. 4560	Var. 4606	Var. 4652	Var. 4698	Var. 4744	Var. 4790	Var. 4836	
	20-90	Var. 4561	Var. 4607	Var. 4653	Var. 4699	Var. 4745	Var. 4791	Var. 4837	
	20-80	Var. 4562	Var. 4608	Var. 4654	Var. 4700	Var. 4746	Var. 4792	Var. 4838	
	20-70	Var. 4563	Var. 4609	Var. 4655	Var. 4701	Var. 4747	Var. 4793	Var. 4839	
	20-60	Var. 4564	Var. 4610	Var. 4656	Var. 4702	Var. 4748	Var. 4794	Var. 4840	
	20-50	Var. 4565	Var. 4611	Var. 4657	Var. 4703	Var. 4749	Var. 4795	Var. 4841	
	20-40	Var. 4566	Var. 4612	Var. 4658	Var. 4704	Var. 4750	Var. 4796	Var. 4842	
	40-150	Var. 4567	Var. 4613	Var. 4659	Var. 4705	Var. 4751	Var. 4797	Var. 4843	
	40-125	Var. 4568	Var. 4614	Var. 4660	Var. 4706	Var. 4752	Var. 4798	Var. 4844	
	40-100	Var. 4569	Var. 4615	Var. 4661	Var. 4707	Var. 4753	Var. 4799	Var. 4845	
	40-90	Var. 4570	Var. 4616	Var. 4662	Var. 4708	Var. 4754	Var. 4800	Var. 4846	

	40-80	Var. 4571	Var. 4617	Var. 4663	Var. 4709	Var. 4755	Var. 4801	Var. 4847	
	40-70	Var. 4572	Var. 4618	Var. 4664	Var. 4710	Var. 4756	Var. 4802	Var. 4848	
	40-60	Var. 4573	Var. 4619	Var. 4665	Var. 4711	Var. 4757	Var. 4803	Var. 4849	
	40-50	Var. 4574	Var. 4620	Var. 4666	Var. 4712	Var. 4758	Var. 4804	Var. 4850	
	60-150	Var. 4575	Var. 4621	Var. 4667	Var. 4713	Var. 4759	Var. 4805	Var. 4851	
	60-125	Var. 4576	Var. 4622	Var. 4668	Var. 4714	Var. 4760	Var. 4806	Var. 4852	
	60-100	Var. 4577	Var. 4623	Var. 4669	Var. 4715	Var. 4761	Var. 4807	Var. 4853	
	60-90	Var. 4578	Var. 4624	Var. 4670	Var. 4716	Var. 4762	Var. 4808	Var. 4854	
	60-80	Var. 4579	Var. 4625	Var. 4671	Var. 4717	Var. 4763	Var. 4809	Var. 4855	
	60-70	Var. 4580	Var. 4626	Var. 4672	Var. 4718	Var. 4764	Var. 4810	Var. 4856	
	70-150	Var. 4581	Var. 4627	Var. 4673	Var. 4719	Var. 4765	Var. 4811	Var. 4857	
	70-125	Var. 4582	Var. 4628	Var. 4674	Var. 4720	Var. 4766	Var. 4812	Var. 4858	
	70-100	Var. 4583	Var. 4629	Var. 4675	Var. 4721	Var. 4767	Var. 4813	Var. 4859	
	70-90	Var. 4584	Var. 4630	Var. 4676	Var. 4722	Var. 4768	Var. 4814	Var. 4860	
	70-80	Var. 4585	Var. 4631	Var. 4677	Var. 4723	Var. 4769	Var. 4815	Var. 4861	
	80-150	Var. 4586	Var. 4632	Var. 4678	Var. 4724	Var. 4770	Var. 4816	Var. 4862	
	80-125	Var. 4587	Var. 4633	Var. 4679	Var. 4725	Var. 4771	Var. 4817	Var. 4863	
	80-100	Var. 4588	Var. 4634	Var. 4680	Var. 4726	Var. 4772	Var. 4818	Var. 4864	
	80-90	Var. 4589	Var. 4635	Var. 4681	Var. 4727	Var. 4773	Var. 4819	Var. 4865	
	90-150	Var. 4590	Var. 4636	Var. 4682	Var. 4728	Var. 4774	Var. 4820	Var. 4866	
	90-125	Var. 4591	Var. 4637	Var. 4683	Var. 4729	Var. 4775	Var. 4821	Var. 4867	
	90-100	Var. 4592	Var. 4638	Var. 4684	Var. 4730	Var. 4776	Var. 4822	Var. 4868	

Var. = Variation

[00229] In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 30% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00230] In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 50% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations

2339 to 4868 in **Table 13** to **Table 19**. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00231] In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 70% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00232] In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in **Table 3** to **Table 5**, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00233] In one embodiment, the method comprises administering a dosage of a rVWF composition containing from 10 IU/kg to 40 IU/kg rVWF:RCo activity, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected

from variations 2339 to 4868 in **Table 13** to **Table 19**. In a specific embodiment, the composition contains from 20 IU/kg to 30 IU/kg rVWF:RCo activity. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00234] In one embodiment, the method comprises administering a dosage of a rVWF composition containing from 25 IU/kg to 75 IU/kg rVWF:RCo activity, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In a specific embodiment, the composition contains from 40 IU/kg to 60 IU/kg rVWF:RCo activity. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00235] In one embodiment, the method comprises administering a dosage of a rVWF composition containing from 75 IU/kg to 125 IU/kg rVWF:RCo activity, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In a specific embodiment, the composition contains from 75 IU/kg to 100 IU/kg rVWF:RCo activity. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00236] In one embodiment, the method comprises administering a composition of rVWF, wherein the subject is administered a dose of rVWF selected from variations 2141 to 2338 in **Table 12**, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In one embodiment, the composition of rVWF administered to the subject is a composition of

high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00237] In one embodiment, the method comprises administering a composition of rVWF, wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In yet another embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers with a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

Table 20. Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.

		Increased Stability (Hours)						
		at least 1 hr	**at least 2 hr**	**at least 3 hr**	**at least 4 hr**	**at least 5 hr**	**at least 6 hr**	**at least 7 hr**
Dosage (IU/kg rVWF:RCo activity)	**0.5-200**	Var. 4869	Var. 4926	Var. 4983	Var. 5040	Var. 5097	Var. 5154	Var. 5211
	0.5-150	Var. 4870	Var. 4927	Var. 4984	Var. 5041	Var. 5098	Var. 5155	Var. 5212
	0.5-100	Var. 4871	Var. 4928	Var. 4985	Var. 5042	Var. 5099	Var. 5156	Var. 5213
	0.5-75	Var. 4872	Var. 4929	Var. 4986	Var. 5043	Var. 5100	Var. 5157	Var. 5214
	0.5-50	Var. 4873	Var. 4930	Var. 4987	Var. 5044	Var. 5101	Var. 5158	Var. 5215
	0.5-25	Var. 4874	Var. 4931	Var. 4988	Var. 5045	Var. 5102	Var. 5159	Var. 5216
	0.5-10	Var. 4875	Var. 4932	Var. 4989	Var. 5046	Var. 5103	Var. 5160	Var. 5217
	0.5-5	Var. 4876	Var. 4933	Var. 4990	Var. 5047	Var. 5104	Var. 5161	Var. 5218
	0.5-2.5	Var. 4877	Var. 4934	Var. 4991	Var. 5048	Var. 5105	Var. 5162	Var. 5219
	0.5-1	Var. 4878	Var. 4935	Var. 4992	Var. 5049	Var. 5106	Var. 5163	Var. 5220
	2.5-200	Var. 4879	Var. 4936	Var. 4993	Var. 5050	Var. 5107	Var. 5164	Var. 5221
	2.5-150	Var. 4880	Var. 4937	Var. 4994	Var. 5051	Var. 5108	Var. 5165	Var. 5222
	2.5-100	Var. 4881	Var. 4938	Var. 4995	Var. 5052	Var. 5109	Var. 5166	Var. 5223
	2.5-75	Var. 4882	Var. 4939	Var. 4996	Var. 5053	Var. 5110	Var. 5167	Var. 5224
	2.5-50	Var. 4883	Var. 4940	Var. 4997	Var. 5054	Var. 5111	Var. 5168	Var. 5225
	2.5-25	Var. 4884	Var. 4941	Var. 4998	Var. 5055	Var. 5112	Var. 5169	Var. 5226
	2.5-10	Var. 4885	Var. 4942	Var. 4999	Var. 5056	Var. 5113	Var. 5170	Var. 5227
	2.5-5	Var. 4886	Var. 4943	Var. 5000	Var. 5057	Var. 5114	Var. 5171	Var. 5228

	5-200	Var. 4887	Var. 4944	Var. 5001	Var. 5058	Var. 5115	Var. 5172	Var. 5229
	5-175	Var. 4888	Var. 4945	Var. 5002	Var. 5059	Var. 5116	Var. 5173	Var. 5230
	5-150	Var. 4889	Var. 4946	Var. 5003	Var. 5060	Var. 5117	Var. 5174	Var. 5231
	5-125	Var. 4890	Var. 4947	Var. 5004	Var. 5061	Var. 5118	Var. 5175	Var. 5232
	5-100	Var. 4891	Var. 4948	Var. 5005	Var. 5062	Var. 5119	Var. 5176	Var. 5233
	5-75	Var. 4892	Var. 4949	Var. 5006	Var. 5063	Var. 5120	Var. 5177	Var. 5234
	5-50	Var. 4893	Var. 4950	Var. 5007	Var. 5064	Var. 5121	Var. 5178	Var. 5235
	5-25	Var. 4894	Var. 4951	Var. 5008	Var. 5065	Var. 5122	Var. 5179	Var. 5236
	5-10	Var. 4895	Var. 4952	Var. 5009	Var. 5066	Var. 5123	Var. 5180	Var. 5237
	10-200	Var. 4896	Var. 4953	Var. 5010	Var. 5067	Var. 5124	Var. 5181	Var. 5238
	10-150	Var. 4897	Var. 4954	Var. 5011	Var. 5068	Var. 5125	Var. 5182	Var. 5239
	10-100	Var. 4898	Var. 4955	Var. 5012	Var. 5069	Var. 5126	Var. 5183	Var. 5240
	10-75	Var. 4899	Var. 4956	Var. 5013	Var. 5070	Var. 5127	Var. 5184	Var. 5241
	10-50	Var. 4900	Var. 4957	Var. 5014	Var. 5071	Var. 5128	Var. 5185	Var. 5242
	10-25	Var. 4901	Var. 4958	Var. 5015	Var. 5072	Var. 5129	Var. 5186	Var. 5243
	25-200	Var. 4902	Var. 4959	Var. 5016	Var. 5073	Var. 5130	Var. 5187	Var. 5244
	25-150	Var. 4903	Var. 4960	Var. 5017	Var. 5074	Var. 5131	Var. 5188	Var. 5245
	25-100	Var. 4904	Var. 4961	Var. 5018	Var. 5075	Var. 5132	Var. 5189	Var. 5246
	25-75	Var. 4905	Var. 4962	Var. 5019	Var. 5076	Var. 5133	Var. 5190	Var. 5247
	25-50	Var. 4906	Var. 4963	Var. 5020	Var. 5077	Var. 5134	Var. 5191	Var. 5248
	50-200	Var. 4907	Var. 4964	Var. 5021	Var. 5078	Var. 5135	Var. 5192	Var. 5249
	50-150	Var. 4908	Var. 4965	Var. 5022	Var. 5079	Var. 5136	Var. 5193	Var. 5250
	50-100	Var. 4909	Var. 4966	Var. 5023	Var. 5080	Var. 5137	Var. 5194	Var. 5251
	50-75	Var. 4910	Var. 4967	Var. 5024	Var. 5081	Var. 5138	Var. 5195	Var. 5252
	75-200	Var. 4911	Var. 4968	Var. 5025	Var. 5082	Var. 5139	Var. 5196	Var. 5253
	75-175	Var. 4912	Var. 4969	Var. 5026	Var. 5083	Var. 5140	Var. 5197	Var. 5254
	75-150	Var. 4913	Var. 4970	Var. 5027	Var. 5084	Var. 5141	Var. 5198	Var. 5255
	75-125	Var. 4914	Var. 4971	Var. 5028	Var. 5085	Var. 5142	Var. 5199	Var. 5256
	75-100	Var. 4915	Var. 4972	Var. 5029	Var. 5086	Var. 5143	Var. 5200	Var. 5257
	100-200	Var. 4916	Var. 4973	Var. 5030	Var. 5087	Var. 5144	Var. 5201	Var. 5258
	100-175	Var. 4917	Var. 4974	Var. 5031	Var. 5088	Var. 5145	Var. 5202	Var. 5259
	100-150	Var. 4918	Var. 4975	Var. 5032	Var. 5089	Var. 5146	Var. 5203	Var. 5260
	100-125	Var. 4919	Var. 4976	Var. 5033	Var. 5090	Var. 5147	Var. 5204	Var. 5261
	125-200	Var. 4920	Var. 4977	Var. 5034	Var. 5091	Var. 5148	Var. 5205	Var. 5262
	125-175	Var. 4921	Var. 4978	Var. 5035	Var. 5092	Var. 5149	Var. 5206	Var. 5263
	125-150	Var. 4922	Var. 4979	Var. 5036	Var. 5093	Var. 5150	Var. 5207	Var. 5264
	150-200	Var. 4923	Var. 4980	Var. 5037	Var. 5094	Var. 5151	Var. 5208	Var. 5265
	150-200	Var. 4924	Var. 4981	Var. 5038	Var. 5095	Var. 5152	Var. 5209	Var. 5266
	175-200	Var. 4925	Var. 4982	Var. 5039	Var. 5096	Var. 5153	Var. 5210	Var. 5267

Var. = Variation

Table 21. Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.

		Increased Stability (Hours)						
		at least 8 hr	**1-8 hr**	**1-7 hr**	**1-6 hr**	**1-5 hr**	**1-4 hr**	**1-3 hr**
Dosage (IU/kg)	**0.5-200**	Var. 5268	Var. 5325	Var. 5382	Var. 5439	Var. 5496	Var. 5553	Var. 5610
	0.5-150	Var. 5269	Var. 5326	Var. 5383	Var. 5440	Var. 5497	Var. 5554	Var. 5611

	0.5-100	Var. 5270	Var. 5327	Var. 5384	Var. 5441	Var. 5498	Var. 5555	Var. 5612
	0.5-75	Var. 5271	Var. 5328	Var. 5385	Var. 5442	Var. 5499	Var. 5556	Var. 5613
	0.5-50	Var. 5272	Var. 5329	Var. 5386	Var. 5443	Var. 5500	Var. 5557	Var. 5614
	0.5-25	Var. 5273	Var. 5330	Var. 5387	Var. 5444	Var. 5501	Var. 5558	Var. 5615
	0.5-10	Var. 5274	Var. 5331	Var. 5388	Var. 5445	Var. 5502	Var. 5559	Var. 5616
	0.5-5	Var. 5275	Var. 5332	Var. 5389	Var. 5446	Var. 5503	Var. 5560	Var. 5617
	0.5-2.5	Var. 5276	Var. 5333	Var. 5390	Var. 5447	Var. 5504	Var. 5561	Var. 5618
	0.5-1	Var. 5277	Var. 5334	Var. 5391	Var. 5448	Var. 5505	Var. 5562	Var. 5619
	2.5-200	Var. 5278	Var. 5335	Var. 5392	Var. 5449	Var. 5506	Var. 5563	Var. 5620
	2.5-150	Var. 5279	Var. 5336	Var. 5393	Var. 5450	Var. 5507	Var. 5564	Var. 5621
	2.5-100	Var. 5280	Var. 5337	Var. 5394	Var. 5451	Var. 5508	Var. 5565	Var. 5622
	2.5-75	Var. 5281	Var. 5338	Var. 5395	Var. 5452	Var. 5509	Var. 5566	Var. 5623
	2.5-50	Var. 5282	Var. 5339	Var. 5396	Var. 5453	Var. 5510	Var. 5567	Var. 5624
	2.5-25	Var. 5283	Var. 5340	Var. 5397	Var. 5454	Var. 5511	Var. 5568	Var. 5625
	2.5-10	Var. 5284	Var. 5341	Var. 5398	Var. 5455	Var. 5512	Var. 5569	Var. 5626
	2.5-5	Var. 5285	Var. 5342	Var. 5399	Var. 5456	Var. 5513	Var. 5570	Var. 5627
	5-200	Var. 5286	Var. 5343	Var. 5400	Var. 5457	Var. 5514	Var. 5571	Var. 5628
	5-175	Var. 5287	Var. 5344	Var. 5401	Var. 5458	Var. 5515	Var. 5572	Var. 5629
	5-150	Var. 5288	Var. 5345	Var. 5402	Var. 5459	Var. 5516	Var. 5573	Var. 5630
	5-125	Var. 5289	Var. 5346	Var. 5403	Var. 5460	Var. 5517	Var. 5574	Var. 5631
	5-100	Var. 5290	Var. 5347	Var. 5404	Var. 5461	Var. 5518	Var. 5575	Var. 5632
	5-75	Var. 5291	Var. 5348	Var. 5405	Var. 5462	Var. 5519	Var. 5576	Var. 5633
	5-50	Var. 5292	Var. 5349	Var. 5406	Var. 5463	Var. 5520	Var. 5577	Var. 5634
	5-25	Var. 5293	Var. 5350	Var. 5407	Var. 5464	Var. 5521	Var. 5578	Var. 5635
	5-10	Var. 5294	Var. 5351	Var. 5408	Var. 5465	Var. 5522	Var. 5579	Var. 5636
	10-200	Var. 5295	Var. 5352	Var. 5409	Var. 5466	Var. 5523	Var. 5580	Var. 5637
	10-150	Var. 5296	Var. 5353	Var. 5410	Var. 5467	Var. 5524	Var. 5581	Var. 5638
	10-100	Var. 5297	Var. 5354	Var. 5411	Var. 5468	Var. 5525	Var. 5582	Var. 5639
	10-75	Var. 5298	Var. 5355	Var. 5412	Var. 5469	Var. 5526	Var. 5583	Var. 5640
	10-50	Var. 5299	Var. 5356	Var. 5413	Var. 5470	Var. 5527	Var. 5584	Var. 5641
	10-25	Var. 5300	Var. 5357	Var. 5414	Var. 5471	Var. 5528	Var. 5585	Var. 5642
	25-200	Var. 5301	Var. 5358	Var. 5415	Var. 5472	Var. 5529	Var. 5586	Var. 5643
	25-150	Var. 5302	Var. 5359	Var. 5416	Var. 5473	Var. 5530	Var. 5587	Var. 5644
	25-100	Var. 5303	Var. 5360	Var. 5417	Var. 5474	Var. 5531	Var. 5588	Var. 5645
	25-75	Var. 5304	Var. 5361	Var. 5418	Var. 5475	Var. 5532	Var. 5589	Var. 5646
	25-50	Var. 5305	Var. 5362	Var. 5419	Var. 5476	Var. 5533	Var. 5590	Var. 5647
	50-200	Var. 5306	Var. 5363	Var. 5420	Var. 5477	Var. 5534	Var. 5591	Var. 5648
	50-150	Var. 5307	Var. 5364	Var. 5421	Var. 5478	Var. 5535	Var. 5592	Var. 5649
	50-100	Var. 5308	Var. 5365	Var. 5422	Var. 5479	Var. 5536	Var. 5593	Var. 5650
	50-75	Var. 5309	Var. 5366	Var. 5423	Var. 5480	Var. 5537	Var. 5594	Var. 5651
	75-200	Var. 5310	Var. 5367	Var. 5424	Var. 5481	Var. 5538	Var. 5595	Var. 5652
	75-175	Var. 5311	Var. 5368	Var. 5425	Var. 5482	Var. 5539	Var. 5596	Var. 5653
	75-150	Var. 5312	Var. 5369	Var. 5426	Var. 5483	Var. 5540	Var. 5597	Var. 5654
	75-125	Var. 5313	Var. 5370	Var. 5427	Var. 5484	Var. 5541	Var. 5598	Var. 5655
	75-100	Var. 5314	Var. 5371	Var. 5428	Var. 5485	Var. 5542	Var. 5599	Var. 5656
	100-200	Var. 5315	Var. 5372	Var. 5429	Var. 5486	Var. 5543	Var. 5600	Var. 5657
	100-175	Var. 5316	Var. 5373	Var. 5430	Var. 5487	Var. 5544	Var. 5601	Var. 5658
	100-150	Var. 5317	Var. 5374	Var. 5431	Var. 5488	Var. 5545	Var. 5602	Var. 5659
	100-125	Var. 5318	Var. 5375	Var. 5432	Var. 5489	Var. 5546	Var. 5603	Var. 5660

	125-200	Var. 5319	Var. 5376	Var. 5433	Var. 5490	Var. 5547	Var. 5604	Var. 5661
	125-175	Var. 5320	Var. 5377	Var. 5434	Var. 5491	Var. 5548	Var. 5605	Var. 5662
	125-150	Var. 5321	Var. 5378	Var. 5435	Var. 5492	Var. 5549	Var. 5606	Var. 5663
	150-200	Var. 5322	Var. 5379	Var. 5436	Var. 5493	Var. 5550	Var. 5607	Var. 5664
	150-200	Var. 5323	Var. 5380	Var. 5437	Var. 5494	Var. 5551	Var. 5608	Var. 5665
	175-200	Var. 5324	Var. 5381	Var. 5438	Var. 5495	Var. 5552	Var. 5609	Var. 5666

Var. = Variation

Table 22. Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.

		Increased Stability (Hours)						
		1-2 hr	**2-8 hr**	**2-7 hr**	**2-6 hr**	**2-5 hr**	**2-4 hr**	**2-3 hr**
Dosage (IU/kg rVWF:RCo activity)	**0.5-200**	Var. 5667	Var. 5724	Var. 5781	Var. 5838	Var. 5895	Var. 5952	Var. 6009
	0.5-150	Var. 5668	Var. 5725	Var. 5782	Var. 5839	Var. 5896	Var. 5953	Var. 6010
	0.5-100	Var. 5669	Var. 5726	Var. 5783	Var. 5840	Var. 5897	Var. 5954	Var. 6011
	0.5-75	Var. 5670	Var. 5727	Var. 5784	Var. 5841	Var. 5898	Var. 5955	Var. 6012
	0.5-50	Var. 5671	Var. 5728	Var. 5785	Var. 5842	Var. 5899	Var. 5956	Var. 6013
	0.5-25	Var. 5672	Var. 5729	Var. 5786	Var. 5843	Var. 5900	Var. 5957	Var. 6014
	0.5-10	Var. 5673	Var. 5730	Var. 5787	Var. 5844	Var. 5901	Var. 5958	Var. 6015
	0.5-5	Var. 5674	Var. 5731	Var. 5788	Var. 5845	Var. 5902	Var. 5959	Var. 6016
	0.5-2.5	Var. 5675	Var. 5732	Var. 5789	Var. 5846	Var. 5903	Var. 5960	Var. 6017
	0.5-1	Var. 5676	Var. 5733	Var. 5790	Var. 5847	Var. 5904	Var. 5961	Var. 6018
	2.5-200	Var. 5677	Var. 5734	Var. 5791	Var. 5848	Var. 5905	Var. 5962	Var. 6019
	2.5-150	Var. 5678	Var. 5735	Var. 5792	Var. 5849	Var. 5906	Var. 5963	Var. 6020
	2.5-100	Var. 5679	Var. 5736	Var. 5793	Var. 5850	Var. 5907	Var. 5964	Var. 6021
	2.5-75	Var. 5680	Var. 5737	Var. 5794	Var. 5851	Var. 5908	Var. 5965	Var. 6022
	2.5-50	Var. 5681	Var. 5738	Var. 5795	Var. 5852	Var. 5909	Var. 5966	Var. 6023
	2.5-25	Var. 5682	Var. 5739	Var. 5796	Var. 5853	Var. 5910	Var. 5967	Var. 6024
	2.5-10	Var. 5683	Var. 5740	Var. 5797	Var. 5854	Var. 5911	Var. 5968	Var. 6025
	2.5-5	Var. 5684	Var. 5741	Var. 5798	Var. 5855	Var. 5912	Var. 5969	Var. 6026
	5-200	Var. 5685	Var. 5742	Var. 5799	Var. 5856	Var. 5913	Var. 5970	Var. 6027
	5-175	Var. 5686	Var. 5743	Var. 5800	Var. 5857	Var. 5914	Var. 5971	Var. 6028
	5-150	Var. 5687	Var. 5744	Var. 5801	Var. 5858	Var. 5915	Var. 5972	Var. 6029
	5-125	Var. 5688	Var. 5745	Var. 5802	Var. 5859	Var. 5916	Var. 5973	Var. 6030
	5-100	Var. 5689	Var. 5746	Var. 5803	Var. 5860	Var. 5917	Var. 5974	Var. 6031
	5-75	Var. 5690	Var. 5747	Var. 5804	Var. 5861	Var. 5918	Var. 5975	Var. 6032
	5-50	Var. 5691	Var. 5748	Var. 5805	Var. 5862	Var. 5919	Var. 5976	Var. 6033
	5-25	Var. 5692	Var. 5749	Var. 5806	Var. 5863	Var. 5920	Var. 5977	Var. 6034
	5-10	Var. 5693	Var. 5750	Var. 5807	Var. 5864	Var. 5921	Var. 5978	Var. 6035
	10-200	Var. 5694	Var. 5751	Var. 5808	Var. 5865	Var. 5922	Var. 5979	Var. 6036
	10-150	Var. 5695	Var. 5752	Var. 5809	Var. 5866	Var. 5923	Var. 5980	Var. 6037
	10-100	Var. 5696	Var. 5753	Var. 5810	Var. 5867	Var. 5924	Var. 5981	Var. 6038
	10-75	Var. 5697	Var. 5754	Var. 5811	Var. 5868	Var. 5925	Var. 5982	Var. 6039
	10-50	Var. 5698	Var. 5755	Var. 5812	Var. 5869	Var. 5926	Var. 5983	Var. 6040
	10-25	Var. 5699	Var. 5756	Var. 5813	Var. 5870	Var. 5927	Var. 5984	Var. 6041
	25-200	Var. 5700	Var. 5757	Var. 5814	Var. 5871	Var. 5928	Var. 5985	Var. 6042
	25-150	Var. 5701	Var. 5758	Var. 5815	Var. 5872	Var. 5929	Var. 5986	Var. 6043

	25-100	Var. 5702	Var. 5759	Var. 5816	Var. 5873	Var. 5930	Var. 5987	Var. 6044
	25-75	Var. 5703	Var. 5760	Var. 5817	Var. 5874	Var. 5931	Var. 5988	Var. 6045
	25-50	Var. 5704	Var. 5761	Var. 5818	Var. 5875	Var. 5932	Var. 5989	Var. 6046
	50-200	Var. 5705	Var. 5762	Var. 5819	Var. 5876	Var. 5933	Var. 5990	Var. 6047
	50-150	Var. 5706	Var. 5763	Var. 5820	Var. 5877	Var. 5934	Var. 5991	Var. 6048
	50-100	Var. 5707	Var. 5764	Var. 5821	Var. 5878	Var. 5935	Var. 5992	Var. 6049
	50-75	Var. 5708	Var. 5765	Var. 5822	Var. 5879	Var. 5936	Var. 5993	Var. 6050
	75-200	Var. 5709	Var. 5766	Var. 5823	Var. 5880	Var. 5937	Var. 5994	Var. 6051
	75-175	Var. 5710	Var. 5767	Var. 5824	Var. 5881	Var. 5938	Var. 5995	Var. 6052
	75-150	Var. 5711	Var. 5768	Var. 5825	Var. 5882	Var. 5939	Var. 5996	Var. 6053
	75-125	Var. 5712	Var. 5769	Var. 5826	Var. 5883	Var. 5940	Var. 5997	Var. 6054
	75-100	Var. 5713	Var. 5770	Var. 5827	Var. 5884	Var. 5941	Var. 5998	Var. 6055
	100-200	Var. 5714	Var. 5771	Var. 5828	Var. 5885	Var. 5942	Var. 5999	Var. 6056
	100-175	Var. 5715	Var. 5772	Var. 5829	Var. 5886	Var. 5943	Var. 6000	Var. 6057
	100-150	Var. 5716	Var. 5773	Var. 5830	Var. 5887	Var. 5944	Var. 6001	Var. 6058
	100-125	Var. 5717	Var. 5774	Var. 5831	Var. 5888	Var. 5945	Var. 6002	Var. 6059
	125-200	Var. 5718	Var. 5775	Var. 5832	Var. 5889	Var. 5946	Var. 6003	Var. 6060
	125-175	Var. 5719	Var. 5776	Var. 5833	Var. 5890	Var. 5947	Var. 6004	Var. 6061
	125-150	Var. 5720	Var. 5777	Var. 5834	Var. 5891	Var. 5948	Var. 6005	Var. 6062
	150-200	Var. 5721	Var. 5778	Var. 5835	Var. 5892	Var. 5949	Var. 6006	Var. 6063
	150-200	Var. 5722	Var. 5779	Var. 5836	Var. 5893	Var. 5950	Var. 6007	Var. 6064
	175-200	Var. 5723	Var. 5780	Var. 5837	Var. 5894	Var. 5951	Var. 6008	Var. 6065

Var. = Variation

Table 23. Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.

		Increased Stability (Hours)						
		3-8 hr	**3-7 hr**	**3-6 hr**	**3-5 hr**	**3-4 hr**	**4-8 hr**	**4-7 hr**
Dosage (IU/kg rVWF:RCo activity)	**0.5-200**	Var. 6066	Var. 6123	Var. 6180	Var. 6237	Var. 6294	Var. 6351	Var. 6408
	0.5-150	Var. 6067	Var. 6124	Var. 6181	Var. 6238	Var. 6295	Var. 6352	Var. 6409
	0.5-100	Var. 6068	Var. 6125	Var. 6182	Var. 6239	Var. 6296	Var. 6353	Var. 6410
	0.5-75	Var. 6069	Var. 6126	Var. 6183	Var. 6240	Var. 6297	Var. 6354	Var. 6411
	0.5-50	Var. 6070	Var. 6127	Var. 6184	Var. 6241	Var. 6298	Var. 6355	Var. 6412
	0.5-25	Var. 6071	Var. 6128	Var. 6185	Var. 6242	Var. 6299	Var. 6356	Var. 6413
	0.5-10	Var. 6072	Var. 6129	Var. 6186	Var. 6243	Var. 6300	Var. 6357	Var. 6414
	0.5-5	Var. 6073	Var. 6130	Var. 6187	Var. 6244	Var. 6301	Var. 6358	Var. 6415
	0.5-2.5	Var. 6074	Var. 6131	Var. 6188	Var. 6245	Var. 6302	Var. 6359	Var. 6416
	0.5-1	Var. 6075	Var. 6132	Var. 6189	Var. 6246	Var. 6303	Var. 6360	Var. 6417
	2.5-200	Var. 6076	Var. 6133	Var. 6190	Var. 6247	Var. 6304	Var. 6361	Var. 6418
	2.5-150	Var. 6077	Var. 6134	Var. 6191	Var. 6248	Var. 6305	Var. 6362	Var. 6419
	2.5-100	Var. 6078	Var. 6135	Var. 6192	Var. 6249	Var. 6306	Var. 6363	Var. 6420
	2.5-75	Var. 6079	Var. 6136	Var. 6193	Var. 6250	Var. 6307	Var. 6364	Var. 6421
	2.5-50	Var. 6080	Var. 6137	Var. 6194	Var. 6251	Var. 6308	Var. 6365	Var. 6422
	2.5-25	Var. 6081	Var. 6138	Var. 6195	Var. 6252	Var. 6309	Var. 6366	Var. 6423
	2.5-10	Var. 6082	Var. 6139	Var. 6196	Var. 6253	Var. 6310	Var. 6367	Var. 6424
	2.5-5	Var. 6083	Var. 6140	Var. 6197	Var. 6254	Var. 6311	Var. 6368	Var. 6425
	5-200	Var. 6084	Var. 6141	Var. 6198	Var. 6255	Var. 6312	Var. 6369	Var. 6426

	5-175	Var. 6085	Var. 6142	Var. 6199	Var. 6256	Var. 6313	Var. 6370	Var. 6427
	5-150	Var. 6086	Var. 6143	Var. 6200	Var. 6257	Var. 6314	Var. 6371	Var. 6428
	5-125	Var. 6087	Var. 6144	Var. 6201	Var. 6258	Var. 6315	Var. 6372	Var. 6429
	5-100	Var. 6088	Var. 6145	Var. 6202	Var. 6259	Var. 6316	Var. 6373	Var. 6430
	5-75	Var. 6089	Var. 6146	Var. 6203	Var. 6260	Var. 6317	Var. 6374	Var. 6431
	5-50	Var. 6090	Var. 6147	Var. 6204	Var. 6261	Var. 6318	Var. 6375	Var. 6432
	5-25	Var. 6091	Var. 6148	Var. 6205	Var. 6262	Var. 6319	Var. 6376	Var. 6433
	5-10	Var. 6092	Var. 6149	Var. 6206	Var. 6263	Var. 6320	Var. 6377	Var. 6434
	10-200	Var. 6093	Var. 6150	Var. 6207	Var. 6264	Var. 6321	Var. 6378	Var. 6435
	10-150	Var. 6094	Var. 6151	Var. 6208	Var. 6265	Var. 6322	Var. 6379	Var. 6436
	10-100	Var. 6095	Var. 6152	Var. 6209	Var. 6266	Var. 6323	Var. 6380	Var. 6437
	10-75	Var. 6096	Var. 6153	Var. 6210	Var. 6267	Var. 6324	Var. 6381	Var. 6438
	10-50	Var. 6097	Var. 6154	Var. 6211	Var. 6268	Var. 6325	Var. 6382	Var. 6439
	10-25	Var. 6098	Var. 6155	Var. 6212	Var. 6269	Var. 6326	Var. 6383	Var. 6440
	25-200	Var. 6099	Var. 6156	Var. 6213	Var. 6270	Var. 6327	Var. 6384	Var. 6441
	25-150	Var. 6100	Var. 6157	Var. 6214	Var. 6271	Var. 6328	Var. 6385	Var. 6442
	25-100	Var. 6101	Var. 6158	Var. 6215	Var. 6272	Var. 6329	Var. 6386	Var. 6443
	25-75	Var. 6102	Var. 6159	Var. 6216	Var. 6273	Var. 6330	Var. 6387	Var. 6444
	25-50	Var. 6103	Var. 6160	Var. 6217	Var. 6274	Var. 6331	Var. 6388	Var. 6445
	50-200	Var. 6104	Var. 6161	Var. 6218	Var. 6275	Var. 6332	Var. 6389	Var. 6446
	50-150	Var. 6105	Var. 6162	Var. 6219	Var. 6276	Var. 6333	Var. 6390	Var. 6447
	50-100	Var. 6106	Var. 6163	Var. 6220	Var. 6277	Var. 6334	Var. 6391	Var. 6448
	50-75	Var. 6107	Var. 6164	Var. 6221	Var. 6278	Var. 6335	Var. 6392	Var. 6449
	75-200	Var. 6108	Var. 6165	Var. 6222	Var. 6279	Var. 6336	Var. 6393	Var. 6450
	75-175	Var. 6109	Var. 6166	Var. 6223	Var. 6280	Var. 6337	Var. 6394	Var. 6451
	75-150	Var. 6110	Var. 6167	Var. 6224	Var. 6281	Var. 6338	Var. 6395	Var. 6452
	75-125	Var. 6111	Var. 6168	Var. 6225	Var. 6282	Var. 6339	Var. 6396	Var. 6453
	75-100	Var. 6112	Var. 6169	Var. 6226	Var. 6283	Var. 6340	Var. 6397	Var. 6454
	100-200	Var. 6113	Var. 6170	Var. 6227	Var. 6284	Var. 6341	Var. 6398	Var. 6455
	100-175	Var. 6114	Var. 6171	Var. 6228	Var. 6285	Var. 6342	Var. 6399	Var. 6456
	100-150	Var. 6115	Var. 6172	Var. 6229	Var. 6286	Var. 6343	Var. 6400	Var. 6457
	100-125	Var. 6116	Var. 6173	Var. 6230	Var. 6287	Var. 6344	Var. 6401	Var. 6458
	125-200	Var. 6117	Var. 6174	Var. 6231	Var. 6288	Var. 6345	Var. 6402	Var. 6459
	125-175	Var. 6118	Var. 6175	Var. 6232	Var. 6289	Var. 6346	Var. 6403	Var. 6460
	125-150	Var. 6119	Var. 6176	Var. 6233	Var. 6290	Var. 6347	Var. 6404	Var. 6461
	150-200	Var. 6120	Var. 6177	Var. 6234	Var. 6291	Var. 6348	Var. 6405	Var. 6462
	150-200	Var. 6121	Var. 6178	Var. 6235	Var. 6292	Var. 6349	Var. 6406	Var. 6463
	175-200	Var. 6122	Var. 6179	Var. 6236	Var. 6293	Var. 6350	Var. 6407	Var. 6464

Var. = Variation

Table 24. Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.

		Increased Stability (Hours)						
		4-6 hr	**4-5 hr**	**5-8 hr**	**5-7 hr**	**5-6 hr**	**6-8 hr**	**6-7 hr**
Dosage (IU/kg rVWF:	**0.5-200**	Var. 6465	Var. 6522	Var. 6579	Var. 6636	Var. 6693	Var. 6750	Var. 6807
	0.5-150	Var. 6466	Var. 6523	Var. 6580	Var. 6637	Var. 6694	Var. 6751	Var. 6808
	0.5-100	Var. 6467	Var. 6524	Var. 6581	Var. 6638	Var. 6695	Var. 6752	Var. 6809

	0.5-75	Var. 6468	Var. 6525	Var. 6582	Var. 6639	Var. 6696	Var. 6753	Var. 6810
	0.5-50	Var. 6469	Var. 6526	Var. 6583	Var. 6640	Var. 6697	Var. 6754	Var. 6811
	0.5-25	Var. 6470	Var. 6527	Var. 6584	Var. 6641	Var. 6698	Var. 6755	Var. 6812
	0.5-10	Var. 6471	Var. 6528	Var. 6585	Var. 6642	Var. 6699	Var. 6756	Var. 6813
	0.5-5	Var. 6472	Var. 6529	Var. 6586	Var. 6643	Var. 6700	Var. 6757	Var. 6814
	0.5-2.5	Var. 6473	Var. 6530	Var. 6587	Var. 6644	Var. 6701	Var. 6758	Var. 6815
	0.5-1	Var. 6474	Var. 6531	Var. 6588	Var. 6645	Var. 6702	Var. 6759	Var. 6816
	2.5-200	Var. 6475	Var. 6532	Var. 6589	Var. 6646	Var. 6703	Var. 6760	Var. 6817
	2.5-150	Var. 6476	Var. 6533	Var. 6590	Var. 6647	Var. 6704	Var. 6761	Var. 6818
	2.5-100	Var. 6477	Var. 6534	Var. 6591	Var. 6648	Var. 6705	Var. 6762	Var. 6819
	2.5-75	Var. 6478	Var. 6535	Var. 6592	Var. 6649	Var. 6706	Var. 6763	Var. 6820
	2.5-50	Var. 6479	Var. 6536	Var. 6593	Var. 6650	Var. 6707	Var. 6764	Var. 6821
	2.5-25	Var. 6480	Var. 6537	Var. 6594	Var. 6651	Var. 6708	Var. 6765	Var. 6822
	2.5-10	Var. 6481	Var. 6538	Var. 6595	Var. 6652	Var. 6709	Var. 6766	Var. 6823
	2.5-5	Var. 6482	Var. 6539	Var. 6596	Var. 6653	Var. 6710	Var. 6767	Var. 6824
	5-200	Var. 6483	Var. 6540	Var. 6597	Var. 6654	Var. 6711	Var. 6768	Var. 6825
	5-175	Var. 6484	Var. 6541	Var. 6598	Var. 6655	Var. 6712	Var. 6769	Var. 6826
	5-150	Var. 6485	Var. 6542	Var. 6599	Var. 6656	Var. 6713	Var. 6770	Var. 6827
	5-125	Var. 6486	Var. 6543	Var. 6600	Var. 6657	Var. 6714	Var. 6771	Var. 6828
	5-100	Var. 6487	Var. 6544	Var. 6601	Var. 6658	Var. 6715	Var. 6772	Var. 6829
	5-75	Var. 6488	Var. 6545	Var. 6602	Var. 6659	Var. 6716	Var. 6773	Var. 6830
	5-50	Var. 6489	Var. 6546	Var. 6603	Var. 6660	Var. 6717	Var. 6774	Var. 6831
	5-25	Var. 6490	Var. 6547	Var. 6604	Var. 6661	Var. 6718	Var. 6775	Var. 6832
	5-10	Var. 6491	Var. 6548	Var. 6605	Var. 6662	Var. 6719	Var. 6776	Var. 6833
	10-200	Var. 6492	Var. 6549	Var. 6606	Var. 6663	Var. 6720	Var. 6777	Var. 6834
	10-150	Var. 6493	Var. 6550	Var. 6607	Var. 6664	Var. 6721	Var. 6778	Var. 6835
	10-100	Var. 6494	Var. 6551	Var. 6608	Var. 6665	Var. 6722	Var. 6779	Var. 6836
	10-75	Var. 6495	Var. 6552	Var. 6609	Var. 6666	Var. 6723	Var. 6780	Var. 6837
	10-50	Var. 6496	Var. 6553	Var. 6610	Var. 6667	Var. 6724	Var. 6781	Var. 6838
	10-25	Var. 6497	Var. 6554	Var. 6611	Var. 6668	Var. 6725	Var. 6782	Var. 6839
	25-200	Var. 6498	Var. 6555	Var. 6612	Var. 6669	Var. 6726	Var. 6783	Var. 6840
	25-150	Var. 6499	Var. 6556	Var. 6613	Var. 6670	Var. 6727	Var. 6784	Var. 6841
	25-100	Var. 6500	Var. 6557	Var. 6614	Var. 6671	Var. 6728	Var. 6785	Var. 6842
	25-75	Var. 6501	Var. 6558	Var. 6615	Var. 6672	Var. 6729	Var. 6786	Var. 6843
	25-50	Var. 6502	Var. 6559	Var. 6616	Var. 6673	Var. 6730	Var. 6787	Var. 6844
	50-200	Var. 6503	Var. 6560	Var. 6617	Var. 6674	Var. 6731	Var. 6788	Var. 6845
	50-150	Var. 6504	Var. 6561	Var. 6618	Var. 6675	Var. 6732	Var. 6789	Var. 6846
	50-100	Var. 6505	Var. 6562	Var. 6619	Var. 6676	Var. 6733	Var. 6790	Var. 6847
	50-75	Var. 6506	Var. 6563	Var. 6620	Var. 6677	Var. 6734	Var. 6791	Var. 6848
	75-200	Var. 6507	Var. 6564	Var. 6621	Var. 6678	Var. 6735	Var. 6792	Var. 6849
	75-175	Var. 6508	Var. 6565	Var. 6622	Var. 6679	Var. 6736	Var. 6793	Var. 6850
	75-150	Var. 6509	Var. 6566	Var. 6623	Var. 6680	Var. 6737	Var. 6794	Var. 6851
	75-125	Var. 6510	Var. 6567	Var. 6624	Var. 6681	Var. 6738	Var. 6795	Var. 6852
	75-100	Var. 6511	Var. 6568	Var. 6625	Var. 6682	Var. 6739	Var. 6796	Var. 6853
	100-200	Var. 6512	Var. 6569	Var. 6626	Var. 6683	Var. 6740	Var. 6797	Var. 6854
	100-175	Var. 6513	Var. 6570	Var. 6627	Var. 6684	Var. 6741	Var. 6798	Var. 6855
	100-150	Var. 6514	Var. 6571	Var. 6628	Var. 6685	Var. 6742	Var. 6799	Var. 6856
	100-125	Var. 6515	Var. 6572	Var. 6629	Var. 6686	Var. 6743	Var. 6800	Var. 6857
	125-200	Var. 6516	Var. 6573	Var. 6630	Var. 6687	Var. 6744	Var. 6801	Var. 6858

	125-175	Var. 6517	Var. 6574	Var. 6631	Var. 6688	Var. 6745	Var. 6802	Var. 6859
	125-150	Var. 6518	Var. 6575	Var. 6632	Var. 6689	Var. 6746	Var. 6803	Var. 6860
	150-200	Var. 6519	Var. 6576	Var. 6633	Var. 6690	Var. 6747	Var. 6804	Var. 6861
	150-200	Var. 6520	Var. 6577	Var. 6634	Var. 6691	Var. 6748	Var. 6805	Var. 6862
	175-200	Var. 6521	Var. 6578	Var. 6635	Var. 6692	Var. 6749	Var. 6806	Var. 6863

Var. = Variation

Table 25. Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.

		Increased Stability (Hours / Percent)						
		7-8 hr	**at least 10%**	**at least 20%**	**at least 30%**	**at least 40%**	**at least 50%**	**10-50%**
Dosage (IU/kg rVWF:RCo activity)	**0.5-200**	Var. 6864	Var. 6921	Var. 6978	Var. 7035	Var. 7092	Var. 7149	Var. 7206
	0.5-150	Var. 6865	Var. 6922	Var. 6979	Var. 7036	Var. 7093	Var. 7150	Var. 7207
	0.5-100	Var. 6866	Var. 6923	Var. 6980	Var. 7037	Var. 7094	Var. 7151	Var. 7208
	0.5-75	Var. 6867	Var. 6924	Var. 6981	Var. 7038	Var. 7095	Var. 7152	Var. 7209
	0.5-50	Var. 6868	Var. 6925	Var. 6982	Var. 7039	Var. 7096	Var. 7153	Var. 7210
	0.5-25	Var. 6869	Var. 6926	Var. 6983	Var. 7040	Var. 7097	Var. 7154	Var. 7211
	0.5-10	Var. 6870	Var. 6927	Var. 6984	Var. 7041	Var. 7098	Var. 7155	Var. 7212
	0.5-5	Var. 6871	Var. 6928	Var. 6985	Var. 7042	Var. 7099	Var. 7156	Var. 7213
	0.5-2.5	Var. 6872	Var. 6929	Var. 6986	Var. 7043	Var. 7100	Var. 7157	Var. 7214
	0.5-1	Var. 6873	Var. 6930	Var. 6987	Var. 7044	Var. 7101	Var. 7158	Var. 7215
	2.5-200	Var. 6874	Var. 6931	Var. 6988	Var. 7045	Var. 7102	Var. 7159	Var. 7216
	2.5-150	Var. 6875	Var. 6932	Var. 6989	Var. 7046	Var. 7103	Var. 7160	Var. 7217
	2.5-100	Var. 6876	Var. 6933	Var. 6990	Var. 7047	Var. 7104	Var. 7161	Var. 7218
	2.5-75	Var. 6877	Var. 6934	Var. 6991	Var. 7048	Var. 7105	Var. 7162	Var. 7219
	2.5-50	Var. 6878	Var. 6935	Var. 6992	Var. 7049	Var. 7106	Var. 7163	Var. 7220
	2.5-25	Var. 6879	Var. 6936	Var. 6993	Var. 7050	Var. 7107	Var. 7164	Var. 7221
	2.5-10	Var. 6880	Var. 6937	Var. 6994	Var. 7051	Var. 7108	Var. 7165	Var. 7222
	2.5-5	Var. 6881	Var. 6938	Var. 6995	Var. 7052	Var. 7109	Var. 7166	Var. 7223
	5-200	Var. 6882	Var. 6939	Var. 6996	Var. 7053	Var. 7110	Var. 7167	Var. 7224
	5-175	Var. 6883	Var. 6940	Var. 6997	Var. 7054	Var. 7111	Var. 7168	Var. 7225
	5-150	Var. 6884	Var. 6941	Var. 6998	Var. 7055	Var. 7112	Var. 7169	Var. 7226
	5-125	Var. 6885	Var. 6942	Var. 6999	Var. 7056	Var. 7113	Var. 7170	Var. 7227
	5-100	Var. 6886	Var. 6943	Var. 7000	Var. 7057	Var. 7114	Var. 7171	Var. 7228
	5-75	Var. 6887	Var. 6944	Var. 7001	Var. 7058	Var. 7115	Var. 7172	Var. 7229
	5-50	Var. 6888	Var. 6945	Var. 7002	Var. 7059	Var. 7116	Var. 7173	Var. 7230
	5-25	Var. 6889	Var. 6946	Var. 7003	Var. 7060	Var. 7117	Var. 7174	Var. 7231
	5-10	Var. 6890	Var. 6947	Var. 7004	Var. 7061	Var. 7118	Var. 7175	Var. 7232
	10-200	Var. 6891	Var. 6948	Var. 7005	Var. 7062	Var. 7119	Var. 7176	Var. 7233
	10-150	Var. 6892	Var. 6949	Var. 7006	Var. 7063	Var. 7120	Var. 7177	Var. 7234
	10-100	Var. 6893	Var. 6950	Var. 7007	Var. 7064	Var. 7121	Var. 7178	Var. 7235
	10-75	Var. 6894	Var. 6951	Var. 7008	Var. 7065	Var. 7122	Var. 7179	Var. 7236
	10-50	Var. 6895	Var. 6952	Var. 7009	Var. 7066	Var. 7123	Var. 7180	Var. 7237
	10-25	Var. 6896	Var. 6953	Var. 7010	Var. 7067	Var. 7124	Var. 7181	Var. 7238
	25-200	Var. 6897	Var. 6954	Var. 7011	Var. 7068	Var. 7125	Var. 7182	Var. 7239
	25-150	Var. 6898	Var. 6955	Var. 7012	Var. 7069	Var. 7126	Var. 7183	Var. 7240

	25-100	Var. 6899	Var. 6956	Var. 7013	Var. 7070	Var. 7127	Var. 7184	Var. 7241
	25-75	Var. 6900	Var. 6957	Var. 7014	Var. 7071	Var. 7128	Var. 7185	Var. 7242
	25-50	Var. 6901	Var. 6958	Var. 7015	Var. 7072	Var. 7129	Var. 7186	Var. 7243
	50-200	Var. 6902	Var. 6959	Var. 7016	Var. 7073	Var. 7130	Var. 7187	Var. 7244
	50-150	Var. 6903	Var. 6960	Var. 7017	Var. 7074	Var. 7131	Var. 7188	Var. 7245
	50-100	Var. 6904	Var. 6961	Var. 7018	Var. 7075	Var. 7132	Var. 7189	Var. 7246
	50-75	Var. 6905	Var. 6962	Var. 7019	Var. 7076	Var. 7133	Var. 7190	Var. 7247
	75-200	Var. 6906	Var. 6963	Var. 7020	Var. 7077	Var. 7134	Var. 7191	Var. 7248
	75-175	Var. 6907	Var. 6964	Var. 7021	Var. 7078	Var. 7135	Var. 7192	Var. 7249
	75-150	Var. 6908	Var. 6965	Var. 7022	Var. 7079	Var. 7136	Var. 7193	Var. 7250
	75-125	Var. 6909	Var. 6966	Var. 7023	Var. 7080	Var. 7137	Var. 7194	Var. 7251
	75-100	Var. 6910	Var. 6967	Var. 7024	Var. 7081	Var. 7138	Var. 7195	Var. 7252
	100-200	Var. 6911	Var. 6968	Var. 7025	Var. 7082	Var. 7139	Var. 7196	Var. 7253
	100-175	Var. 6912	Var. 6969	Var. 7026	Var. 7083	Var. 7140	Var. 7197	Var. 7254
	100-150	Var. 6913	Var. 6970	Var. 7027	Var. 7084	Var. 7141	Var. 7198	Var. 7255
	100-125	Var. 6914	Var. 6971	Var. 7028	Var. 7085	Var. 7142	Var. 7199	Var. 7256
	125-200	Var. 6915	Var. 6972	Var. 7029	Var. 7086	Var. 7143	Var. 7200	Var. 7257
	125-175	Var. 6916	Var. 6973	Var. 7030	Var. 7087	Var. 7144	Var. 7201	Var. 7258
	125-150	Var. 6917	Var. 6974	Var. 7031	Var. 7088	Var. 7145	Var. 7202	Var. 7259
	150-200	Var. 6918	Var. 6975	Var. 7032	Var. 7089	Var. 7146	Var. 7203	Var. 7260
	150-200	Var. 6919	Var. 6976	Var. 7033	Var. 7090	Var. 7147	Var. 7204	Var. 7261
	175-200	Var. 6920	Var. 6977	Var. 7034	Var. 7091	Var. 7148	Var. 7205	Var. 7262

Var. = Variation

Table 26. Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.

		Increased Stability (Percent)						
		10-40%	**10-30%**	**10-20%**	**15-50%**	**15-40%**	**15-30%**	**15-20%**
Dosage (IU/kg rVWF:RCo activity)	**0.5-200**	Var. 7263	Var. 7320	Var. 7377	Var. 7434	Var. 7491	Var. 7548	Var. 7605
	0.5-150	Var. 7264	Var. 7321	Var. 7378	Var. 7435	Var. 7492	Var. 7549	Var. 7606
	0.5-100	Var. 7265	Var. 7322	Var. 7379	Var. 7436	Var. 7493	Var. 7550	Var. 7607
	0.5-75	Var. 7266	Var. 7323	Var. 7380	Var. 7437	Var. 7494	Var. 7551	Var. 7608
	0.5-50	Var. 7267	Var. 7324	Var. 7381	Var. 7438	Var. 7495	Var. 7552	Var. 7609
	0.5-25	Var. 7268	Var. 7325	Var. 7382	Var. 7439	Var. 7496	Var. 7553	Var. 7610
	0.5-10	Var. 7269	Var. 7326	Var. 7383	Var. 7440	Var. 7497	Var. 7554	Var. 7611
	0.5-5	Var. 7270	Var. 7327	Var. 7384	Var. 7441	Var. 7498	Var. 7555	Var. 7612
	0.5-2.5	Var. 7271	Var. 7328	Var. 7385	Var. 7442	Var. 7499	Var. 7556	Var. 7613
	0.5-1	Var. 7272	Var. 7329	Var. 7386	Var. 7443	Var. 7500	Var. 7557	Var. 7614
	2.5-200	Var. 7273	Var. 7330	Var. 7387	Var. 7444	Var. 7501	Var. 7558	Var. 7615
	2.5-150	Var. 7274	Var. 7331	Var. 7388	Var. 7445	Var. 7502	Var. 7559	Var. 7616
	2.5-100	Var. 7275	Var. 7332	Var. 7389	Var. 7446	Var. 7503	Var. 7560	Var. 7617
	2.5-75	Var. 7276	Var. 7333	Var. 7390	Var. 7447	Var. 7504	Var. 7561	Var. 7618
	2.5-50	Var. 7277	Var. 7334	Var. 7391	Var. 7448	Var. 7505	Var. 7562	Var. 7619
	2.5-25	Var. 7278	Var. 7335	Var. 7392	Var. 7449	Var. 7506	Var. 7563	Var. 7620
	2.5-10	Var. 7279	Var. 7336	Var. 7393	Var. 7450	Var. 7507	Var. 7564	Var. 7621
	2.5-5	Var. 7280	Var. 7337	Var. 7394	Var. 7451	Var. 7508	Var. 7565	Var. 7622
	5-200	Var. 7281	Var. 7338	Var. 7395	Var. 7452	Var. 7509	Var. 7566	Var. 7623

	5-175	Var. 7282	Var. 7339	Var. 7396	Var. 7453	Var. 7510	Var. 7567	Var. 7624
	5-150	Var. 7283	Var. 7340	Var. 7397	Var. 7454	Var. 7511	Var. 7568	Var. 7625
	5-125	Var. 7284	Var. 7341	Var. 7398	Var. 7455	Var. 7512	Var. 7569	Var. 7626
	5-100	Var. 7285	Var. 7342	Var. 7399	Var. 7456	Var. 7513	Var. 7570	Var. 7627
	5-75	Var. 7286	Var. 7343	Var. 7400	Var. 7457	Var. 7514	Var. 7571	Var. 7628
	5-50	Var. 7287	Var. 7344	Var. 7401	Var. 7458	Var. 7515	Var. 7572	Var. 7629
	5-25	Var. 7288	Var. 7345	Var. 7402	Var. 7459	Var. 7516	Var. 7573	Var. 7630
	5-10	Var. 7289	Var. 7346	Var. 7403	Var. 7460	Var. 7517	Var. 7574	Var. 7631
	10-200	Var. 7290	Var. 7347	Var. 7404	Var. 7461	Var. 7518	Var. 7575	Var. 7632
	10-150	Var. 7291	Var. 7348	Var. 7405	Var. 7462	Var. 7519	Var. 7576	Var. 7633
	10-100	Var. 7292	Var. 7349	Var. 7406	Var. 7463	Var. 7520	Var. 7577	Var. 7634
	10-75	Var. 7293	Var. 7350	Var. 7407	Var. 7464	Var. 7521	Var. 7578	Var. 7635
	10-50	Var. 7294	Var. 7351	Var. 7408	Var. 7465	Var. 7522	Var. 7579	Var. 7636
	10-25	Var. 7295	Var. 7352	Var. 7409	Var. 7466	Var. 7523	Var. 7580	Var. 7637
	25-200	Var. 7296	Var. 7353	Var. 7410	Var. 7467	Var. 7524	Var. 7581	Var. 7638
	25-150	Var. 7297	Var. 7354	Var. 7411	Var. 7468	Var. 7525	Var. 7582	Var. 7639
	25-100	Var. 7298	Var. 7355	Var. 7412	Var. 7469	Var. 7526	Var. 7583	Var. 7640
	25-75	Var. 7299	Var. 7356	Var. 7413	Var. 7470	Var. 7527	Var. 7584	Var. 7641
	25-50	Var. 7300	Var. 7357	Var. 7414	Var. 7471	Var. 7528	Var. 7585	Var. 7642
	50-200	Var. 7301	Var. 7358	Var. 7415	Var. 7472	Var. 7529	Var. 7586	Var. 7643
	50-150	Var. 7302	Var. 7359	Var. 7416	Var. 7473	Var. 7530	Var. 7587	Var. 7644
	50-100	Var. 7303	Var. 7360	Var. 7417	Var. 7474	Var. 7531	Var. 7588	Var. 7645
	50-75	Var. 7304	Var. 7361	Var. 7418	Var. 7475	Var. 7532	Var. 7589	Var. 7646
	75-200	Var. 7305	Var. 7362	Var. 7419	Var. 7476	Var. 7533	Var. 7590	Var. 7647
	75-175	Var. 7306	Var. 7363	Var. 7420	Var. 7477	Var. 7534	Var. 7591	Var. 7648
	75-150	Var. 7307	Var. 7364	Var. 7421	Var. 7478	Var. 7535	Var. 7592	Var. 7649
	75-125	Var. 7308	Var. 7365	Var. 7422	Var. 7479	Var. 7536	Var. 7593	Var. 7650
	75-100	Var. 7309	Var. 7366	Var. 7423	Var. 7480	Var. 7537	Var. 7594	Var. 7651
	100-200	Var. 7310	Var. 7367	Var. 7424	Var. 7481	Var. 7538	Var. 7595	Var. 7652
	100-175	Var. 7311	Var. 7368	Var. 7425	Var. 7482	Var. 7539	Var. 7596	Var. 7653
	100-150	Var. 7312	Var. 7369	Var. 7426	Var. 7483	Var. 7540	Var. 7597	Var. 7654
	100-125	Var. 7313	Var. 7370	Var. 7427	Var. 7484	Var. 7541	Var. 7598	Var. 7655
	125-200	Var. 7314	Var. 7371	Var. 7428	Var. 7485	Var. 7542	Var. 7599	Var. 7656
	125-175	Var. 7315	Var. 7372	Var. 7429	Var. 7486	Var. 7543	Var. 7600	Var. 7657
	125-150	Var. 7316	Var. 7373	Var. 7430	Var. 7487	Var. 7544	Var. 7601	Var. 7658
	150-200	Var. 7317	Var. 7374	Var. 7431	Var. 7488	Var. 7545	Var. 7602	Var. 7659
	150-200	Var. 7318	Var. 7375	Var. 7432	Var. 7489	Var. 7546	Var. 7603	Var. 7660
	175-200	Var. 7319	Var. 7376	Var. 7433	Var. 7490	Var. 7547	Var. 7604	Var. 7661

Var. = Variation

Table 27. Exemplary embodiments for the combination of rVWF dosage and increase in FVIII stability achieved, as compared to FVIII stability in a subject administered a composition of pdVWF.

		Increased Stability (Percent)						
		20-50%	**20-40%**	**20-30%**	**30-50%**	**30-40%**	**40-50%**	
Dosage (IU/kg rVWF)	**0.5-200**	Var. 7662	Var. 7719	Var. 7776	Var. 7833	Var. 7890	Var. 7947	
	0.5-150	Var. 7663	Var. 7720	Var. 7777	Var. 7834	Var. 7891	Var. 7948	
	0.5-100	Var. 7664	Var. 7721	Var. 7778	Var. 7835	Var. 7892	Var. 7949	

	0.5-75	Var. 7665	Var. 7722	Var. 7779	Var. 7836	Var. 7893	Var. 7950	
	0.5-50	Var. 7666	Var. 7723	Var. 7780	Var. 7837	Var. 7894	Var. 7951	
	0.5-25	Var. 7667	Var. 7724	Var. 7781	Var. 7838	Var. 7895	Var. 7952	
	0.5-10	Var. 7668	Var. 7725	Var. 7782	Var. 7839	Var. 7896	Var. 7953	
	0.5-5	Var. 7669	Var. 7726	Var. 7783	Var. 7840	Var. 7897	Var. 7954	
	0.5-2.5	Var. 7670	Var. 7727	Var. 7784	Var. 7841	Var. 7898	Var. 7955	
	0.5-1	Var. 7671	Var. 7728	Var. 7785	Var. 7842	Var. 7899	Var. 7956	
	2.5-200	Var. 7672	Var. 7729	Var. 7786	Var. 7843	Var. 7900	Var. 7957	
	2.5-150	Var. 7673	Var. 7730	Var. 7787	Var. 7844	Var. 7901	Var. 7958	
	2.5-100	Var. 7674	Var. 7731	Var. 7788	Var. 7845	Var. 7902	Var. 7959	
	2.5-75	Var. 7675	Var. 7732	Var. 7789	Var. 7846	Var. 7903	Var. 7960	
	2.5-50	Var. 7676	Var. 7733	Var. 7790	Var. 7847	Var. 7904	Var. 7961	
	2.5-25	Var. 7677	Var. 7734	Var. 7791	Var. 7848	Var. 7905	Var. 7962	
	2.5-10	Var. 7678	Var. 7735	Var. 7792	Var. 7849	Var. 7906	Var. 7963	
	2.5-5	Var. 7679	Var. 7736	Var. 7793	Var. 7850	Var. 7907	Var. 7964	
	5-200	Var. 7680	Var. 7737	Var. 7794	Var. 7851	Var. 7908	Var. 7965	
	5-175	Var. 7681	Var. 7738	Var. 7795	Var. 7852	Var. 7909	Var. 7966	
	5-150	Var. 7682	Var. 7739	Var. 7796	Var. 7853	Var. 7910	Var. 7967	
	5-125	Var. 7683	Var. 7740	Var. 7797	Var. 7854	Var. 7911	Var. 7968	
	5-100	Var. 7684	Var. 7741	Var. 7798	Var. 7855	Var. 7912	Var. 7969	
	5-75	Var. 7685	Var. 7742	Var. 7799	Var. 7856	Var. 7913	Var. 7970	
	5-50	Var. 7686	Var. 7743	Var. 7800	Var. 7857	Var. 7914	Var. 7971	
	5-25	Var. 7687	Var. 7744	Var. 7801	Var. 7858	Var. 7915	Var. 7972	
	5-10	Var. 7688	Var. 7745	Var. 7802	Var. 7859	Var. 7916	Var. 7973	
	10-200	Var. 7689	Var. 7746	Var. 7803	Var. 7860	Var. 7917	Var. 7974	
	10-150	Var. 7690	Var. 7747	Var. 7804	Var. 7861	Var. 7918	Var. 7975	
	10-100	Var. 7691	Var. 7748	Var. 7805	Var. 7862	Var. 7919	Var. 7976	
	10-75	Var. 7692	Var. 7749	Var. 7806	Var. 7863	Var. 7920	Var. 7977	
	10-50	Var. 7693	Var. 7750	Var. 7807	Var. 7864	Var. 7921	Var. 7978	
	10-25	Var. 7694	Var. 7751	Var. 7808	Var. 7865	Var. 7922	Var. 7979	
	25-200	Var. 7695	Var. 7752	Var. 7809	Var. 7866	Var. 7923	Var. 7980	
	25-150	Var. 7696	Var. 7753	Var. 7810	Var. 7867	Var. 7924	Var. 7981	
	25-100	Var. 7697	Var. 7754	Var. 7811	Var. 7868	Var. 7925	Var. 7982	
	25-75	Var. 7698	Var. 7755	Var. 7812	Var. 7869	Var. 7926	Var. 7983	
	25-50	Var. 7699	Var. 7756	Var. 7813	Var. 7870	Var. 7927	Var. 7984	
	50-200	Var. 7700	Var. 7757	Var. 7814	Var. 7871	Var. 7928	Var. 7985	
	50-150	Var. 7701	Var. 7758	Var. 7815	Var. 7872	Var. 7929	Var. 7986	
	50-100	Var. 7702	Var. 7759	Var. 7816	Var. 7873	Var. 7930	Var. 7987	
	50-75	Var. 7703	Var. 7760	Var. 7817	Var. 7874	Var. 7931	Var. 7988	
	75-200	Var. 7704	Var. 7761	Var. 7818	Var. 7875	Var. 7932	Var. 7989	
	75-175	Var. 7705	Var. 7762	Var. 7819	Var. 7876	Var. 7933	Var. 7990	
	75-150	Var. 7706	Var. 7763	Var. 7820	Var. 7877	Var. 7934	Var. 7991	
	75-125	Var. 7707	Var. 7764	Var. 7821	Var. 7878	Var. 7935	Var. 7992	
	75-100	Var. 7708	Var. 7765	Var. 7822	Var. 7879	Var. 7936	Var. 7993	
	100-200	Var. 7709	Var. 7766	Var. 7823	Var. 7880	Var. 7937	Var. 7994	
	100-175	Var. 7710	Var. 7767	Var. 7824	Var. 7881	Var. 7938	Var. 7995	
	100-150	Var. 7711	Var. 7768	Var. 7825	Var. 7882	Var. 7939	Var. 7996	
	100-125	Var. 7712	Var. 7769	Var. 7826	Var. 7883	Var. 7940	Var. 7997	
	125-200	Var. 7713	Var. 7770	Var. 7827	Var. 7884	Var. 7941	Var. 7998	

	125-175	Var. 7714	Var. 7771	Var. 7828	Var. 7885	Var. 7942	Var. 7999	
	125-150	Var. 7715	Var. 7772	Var. 7829	Var. 7886	Var. 7943	Var. 8000	
	150-200	Var. 7716	Var. 7773	Var. 7830	Var. 7887	Var. 7944	Var. 8001	
	150-200	Var. 7717	Var. 7774	Var. 7831	Var. 7888	Var. 7945	Var. 8002	
	175-200	Var. 7718	Var. 7775	Var. 7832	Var. 7889	Var. 7946	Var. 8003	

Var. = Variation

[00238] In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 30% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00239] In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 50% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00240] In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 70% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized

by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00241] In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in **Table 3** to **Table 5**, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00242] In one embodiment, the method comprises administering a composition of rVWF, wherein the rVWF in the composition has a specific activity of from 40 mU/μg to 60 mU/μg, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00243] In one embodiment, the method comprises administering a composition of rVWF, wherein the rVWF in the composition has a specific activity of at least 60 mU/μg, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00244] In one embodiment, the method comprises administering a composition of rVWF, wherein the rVWF in the composition has a specific activity of at least 80 mU/μg, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00245] In one embodiment, the method comprises administering a composition of rVWF, wherein the rVWF in the composition has a specific activity selected from variations 1 to 133 found in **Table 1**, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00246] In one embodiment, the method comprises administering a composition of rVWF, wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In yet another embodiment, the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers with a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

Table 28. Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.

		Specific Activity (mU/μg)

		at least 20	at least 30	at least 40	at least 50	at least 60	at least 70	at least 80
Dosage (IU/kg rVWF:RCo activity)	**0.5-200**	Var. 8004	Var. 8061	Var. 8118	Var. 8175	Var. 8232	Var. 8289	Var. 8346
	0.5-150	Var. 8005	Var. 8062	Var. 8119	Var. 8176	Var. 8233	Var. 8290	Var. 8347
	0.5-100	Var. 8006	Var. 8063	Var. 8120	Var. 8177	Var. 8234	Var. 8291	Var. 8348
	0.5-75	Var. 8007	Var. 8064	Var. 8121	Var. 8178	Var. 8235	Var. 8292	Var. 8349
	0.5-50	Var. 8008	Var. 8065	Var. 8122	Var. 8179	Var. 8236	Var. 8293	Var. 8350
	0.5-25	Var. 8009	Var. 8066	Var. 8123	Var. 8180	Var. 8237	Var. 8294	Var. 8351
	0.5-10	Var. 8010	Var. 8067	Var. 8124	Var. 8181	Var. 8238	Var. 8295	Var. 8352
	0.5-5	Var. 8011	Var. 8068	Var. 8125	Var. 8182	Var. 8239	Var. 8296	Var. 8353
	0.5-2.5	Var. 8012	Var. 8069	Var. 8126	Var. 8183	Var. 8240	Var. 8297	Var. 8354
	0.5-1	Var. 8013	Var. 8070	Var. 8127	Var. 8184	Var. 8241	Var. 8298	Var. 8355
	2.5-200	Var. 8014	Var. 8071	Var. 8128	Var. 8185	Var. 8242	Var. 8299	Var. 8356
	2.5-150	Var. 8015	Var. 8072	Var. 8129	Var. 8186	Var. 8243	Var. 8300	Var. 8357
	2.5-100	Var. 8016	Var. 8073	Var. 8130	Var. 8187	Var. 8244	Var. 8301	Var. 8358
	2.5-75	Var. 8017	Var. 8074	Var. 8131	Var. 8188	Var. 8245	Var. 8302	Var. 8359
	2.5-50	Var. 8018	Var. 8075	Var. 8132	Var. 8189	Var. 8246	Var. 8303	Var. 8360
	2.5-25	Var. 8019	Var. 8076	Var. 8133	Var. 8190	Var. 8247	Var. 8304	Var. 8361
	2.5-10	Var. 8020	Var. 8077	Var. 8134	Var. 8191	Var. 8248	Var. 8305	Var. 8362
	2.5-5	Var. 8021	Var. 8078	Var. 8135	Var. 8192	Var. 8249	Var. 8306	Var. 8363
	5-200	Var. 8022	Var. 8079	Var. 8136	Var. 8193	Var. 8250	Var. 8307	Var. 8364
	5-175	Var. 8023	Var. 8080	Var. 8137	Var. 8194	Var. 8251	Var. 8308	Var. 8365
	5-150	Var. 8024	Var. 8081	Var. 8138	Var. 8195	Var. 8252	Var. 8309	Var. 8366
	5-125	Var. 8025	Var. 8082	Var. 8139	Var. 8196	Var. 8253	Var. 8310	Var. 8367
	5-100	Var. 8026	Var. 8083	Var. 8140	Var. 8197	Var. 8254	Var. 8311	Var. 8368
	5-75	Var. 8027	Var. 8084	Var. 8141	Var. 8198	Var. 8255	Var. 8312	Var. 8369
	5-50	Var. 8028	Var. 8085	Var. 8142	Var. 8199	Var. 8256	Var. 8313	Var. 8370
	5-25	Var. 8029	Var. 8086	Var. 8143	Var. 8200	Var. 8257	Var. 8314	Var. 8371
	5-10	Var. 8030	Var. 8087	Var. 8144	Var. 8201	Var. 8258	Var. 8315	Var. 8372
	10-200	Var. 8031	Var. 8088	Var. 8145	Var. 8202	Var. 8259	Var. 8316	Var. 8373
	10-150	Var. 8032	Var. 8089	Var. 8146	Var. 8203	Var. 8260	Var. 8317	Var. 8374
	10-100	Var. 8033	Var. 8090	Var. 8147	Var. 8204	Var. 8261	Var. 8318	Var. 8375
	10-75	Var. 8034	Var. 8091	Var. 8148	Var. 8205	Var. 8262	Var. 8319	Var. 8376
	10-50	Var. 8035	Var. 8092	Var. 8149	Var. 8206	Var. 8263	Var. 8320	Var. 8377
	10-25	Var. 8036	Var. 8093	Var. 8150	Var. 8207	Var. 8264	Var. 8321	Var. 8378
	25-200	Var. 8037	Var. 8094	Var. 8151	Var. 8208	Var. 8265	Var. 8322	Var. 8379
	25-150	Var. 8038	Var. 8095	Var. 8152	Var. 8209	Var. 8266	Var. 8323	Var. 8380
	25-100	Var. 8039	Var. 8096	Var. 8153	Var. 8210	Var. 8267	Var. 8324	Var. 8381
	25-75	Var. 8040	Var. 8097	Var. 8154	Var. 8211	Var. 8268	Var. 8325	Var. 8382
	25-50	Var. 8041	Var. 8098	Var. 8155	Var. 8212	Var. 8269	Var. 8326	Var. 8383
	50-200	Var. 8042	Var. 8099	Var. 8156	Var. 8213	Var. 8270	Var. 8327	Var. 8384
	50-150	Var. 8043	Var. 8100	Var. 8157	Var. 8214	Var. 8271	Var. 8328	Var. 8385
	50-100	Var. 8044	Var. 8101	Var. 8158	Var. 8215	Var. 8272	Var. 8329	Var. 8386
	50-75	Var. 8045	Var. 8102	Var. 8159	Var. 8216	Var. 8273	Var. 8330	Var. 8387
	75-200	Var. 8046	Var. 8103	Var. 8160	Var. 8217	Var. 8274	Var. 8331	Var. 8388
	75-175	Var. 8047	Var. 8104	Var. 8161	Var. 8218	Var. 8275	Var. 8332	Var. 8389
	75-150	Var. 8048	Var. 8105	Var. 8162	Var. 8219	Var. 8276	Var. 8333	Var. 8390
	75-125	Var. 8049	Var. 8106	Var. 8163	Var. 8220	Var. 8277	Var. 8334	Var. 8391
	75-100	Var. 8050	Var. 8107	Var. 8164	Var. 8221	Var. 8278	Var. 8335	Var. 8392
	100-200	Var. 8051	Var. 8108	Var. 8165	Var. 8222	Var. 8279	Var. 8336	Var. 8393
	100-175	Var. 8052	Var. 8109	Var. 8166	Var. 8223	Var. 8280	Var. 8337	Var. 8394
	100-150	Var. 8053	Var. 8110	Var. 8167	Var. 8224	Var. 8281	Var. 8338	Var. 8395
	100-125	Var. 8054	Var. 8111	Var. 8168	Var. 8225	Var. 8282	Var. 8339	Var. 8396
	125-200	Var. 8055	Var. 8112	Var. 8169	Var. 8226	Var. 8283	Var. 8340	Var. 8397
	125-175	Var. 8056	Var. 8113	Var. 8170	Var. 8227	Var. 8284	Var. 8341	Var. 8398

	125-150	Var. 8057	Var. 8114	Var. 8171	Var. 8228	Var. 8285	Var. 8342	Var. 8399
	150-200	Var. 8058	Var. 8115	Var. 8172	Var. 8229	Var. 8286	Var. 8343	Var. 8400
	150-200	Var. 8059	Var. 8116	Var. 8173	Var. 8230	Var. 8287	Var. 8344	Var. 8401
	175-200	Var. 8060	Var. 8117	Var. 8174	Var. 8231	Var. 8288	Var. 8345	Var. 8402

Var. = Variation

Table 29. Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.

		Specific Activity (mU/µg)						
		at least 90	**at least 100**	**at least 125**	**at least 150**	**20-150**	**20-125**	**20-100**
Dosage (IU/kg rVWF:RCo activity)	**0.5-200**	Var. 8403	Var. 8460	Var. 8517	Var. 8574	Var. 8631	Var. 8688	Var. 8745
	0.5-150	Var. 8404	Var. 8461	Var. 8518	Var. 8575	Var. 8632	Var. 8689	Var. 8746
	0.5-100	Var. 8405	Var. 8462	Var. 8519	Var. 8576	Var. 8633	Var. 8690	Var. 8747
	0.5-75	Var. 8406	Var. 8463	Var. 8520	Var. 8577	Var. 8634	Var. 8691	Var. 8748
	0.5-50	Var. 8407	Var. 8464	Var. 8521	Var. 8578	Var. 8635	Var. 8692	Var. 8749
	0.5-25	Var. 8408	Var. 8465	Var. 8522	Var. 8579	Var. 8636	Var. 8693	Var. 8750
	0.5-10	Var. 8409	Var. 8466	Var. 8523	Var. 8580	Var. 8637	Var. 8694	Var. 8751
	0.5-5	Var. 8410	Var. 8467	Var. 8524	Var. 8581	Var. 8638	Var. 8695	Var. 8752
	0.5-2.5	Var. 8411	Var. 8468	Var. 8525	Var. 8582	Var. 8639	Var. 8696	Var. 8753
	0.5-1	Var. 8412	Var. 8469	Var. 8526	Var. 8583	Var. 8640	Var. 8697	Var. 8754
	2.5-200	Var. 8413	Var. 8470	Var. 8527	Var. 8584	Var. 8641	Var. 8698	Var. 8755
	2.5-150	Var. 8414	Var. 8471	Var. 8528	Var. 8585	Var. 8642	Var. 8699	Var. 8756
	2.5-100	Var. 8415	Var. 8472	Var. 8529	Var. 8586	Var. 8643	Var. 8700	Var. 8757
	2.5-75	Var. 8416	Var. 8473	Var. 8530	Var. 8587	Var. 8644	Var. 8701	Var. 8758
	2.5-50	Var. 8417	Var. 8474	Var. 8531	Var. 8588	Var. 8645	Var. 8702	Var. 8759
	2.5-25	Var. 8418	Var. 8475	Var. 8532	Var. 8589	Var. 8646	Var. 8703	Var. 8760
	2.5-10	Var. 8419	Var. 8476	Var. 8533	Var. 8590	Var. 8647	Var. 8704	Var. 8761
	2.5-5	Var. 8420	Var. 8477	Var. 8534	Var. 8591	Var. 8648	Var. 8705	Var. 8762
	5-200	Var. 8421	Var. 8478	Var. 8535	Var. 8592	Var. 8649	Var. 8706	Var. 8763
	5-175	Var. 8422	Var. 8479	Var. 8536	Var. 8593	Var. 8650	Var. 8707	Var. 8764
	5-150	Var. 8423	Var. 8480	Var. 8537	Var. 8594	Var. 8651	Var. 8708	Var. 8765
	5-125	Var. 8424	Var. 8481	Var. 8538	Var. 8595	Var. 8652	Var. 8709	Var. 8766
	5-100	Var. 8425	Var. 8482	Var. 8539	Var. 8596	Var. 8653	Var. 8710	Var. 8767
	5-75	Var. 8426	Var. 8483	Var. 8540	Var. 8597	Var. 8654	Var. 8711	Var. 8768
	5-50	Var. 8427	Var. 8484	Var. 8541	Var. 8598	Var. 8655	Var. 8712	Var. 8769
	5-25	Var. 8428	Var. 8485	Var. 8542	Var. 8599	Var. 8656	Var. 8713	Var. 8770
	5-10	Var. 8429	Var. 8486	Var. 8543	Var. 8600	Var. 8657	Var. 8714	Var. 8771
	10-200	Var. 8430	Var. 8487	Var. 8544	Var. 8601	Var. 8658	Var. 8715	Var. 8772
	10-150	Var. 8431	Var. 8488	Var. 8545	Var. 8602	Var. 8659	Var. 8716	Var. 8773
	10-100	Var. 8432	Var. 8489	Var. 8546	Var. 8603	Var. 8660	Var. 8717	Var. 8774
	10-75	Var. 8433	Var. 8490	Var. 8547	Var. 8604	Var. 8661	Var. 8718	Var. 8775
	10-50	Var. 8434	Var. 8491	Var. 8548	Var. 8605	Var. 8662	Var. 8719	Var. 8776
	10-25	Var. 8435	Var. 8492	Var. 8549	Var. 8606	Var. 8663	Var. 8720	Var. 8777
	25-200	Var. 8436	Var. 8493	Var. 8550	Var. 8607	Var. 8664	Var. 8721	Var. 8778
	25-150	Var. 8437	Var. 8494	Var. 8551	Var. 8608	Var. 8665	Var. 8722	Var. 8779
	25-100	Var. 8438	Var. 8495	Var. 8552	Var. 8609	Var. 8666	Var. 8723	Var. 8780
	25-75	Var. 8439	Var. 8496	Var. 8553	Var. 8610	Var. 8667	Var. 8724	Var. 8781
	25-50	Var. 8440	Var. 8497	Var. 8554	Var. 8611	Var. 8668	Var. 8725	Var. 8782
	50-200	Var. 8441	Var. 8498	Var. 8555	Var. 8612	Var. 8669	Var. 8726	Var. 8783
	50-150	Var. 8442	Var. 8499	Var. 8556	Var. 8613	Var. 8670	Var. 8727	Var. 8784
	50-100	Var. 8443	Var. 8500	Var. 8557	Var. 8614	Var. 8671	Var. 8728	Var. 8785
	50-75	Var. 8444	Var. 8501	Var. 8558	Var. 8615	Var. 8672	Var. 8729	Var. 8786

	75-200	Var. 8445	Var. 8502	Var. 8559	Var. 8616	Var. 8673	Var. 8730	Var. 8787
	75-175	Var. 8446	Var. 8503	Var. 8560	Var. 8617	Var. 8674	Var. 8731	Var. 8788
	75-150	Var. 8447	Var. 8504	Var. 8561	Var. 8618	Var. 8675	Var. 8732	Var. 8789
	75-125	Var. 8448	Var. 8505	Var. 8562	Var. 8619	Var. 8676	Var. 8733	Var. 8790
	75-100	Var. 8449	Var. 8506	Var. 8563	Var. 8620	Var. 8677	Var. 8734	Var. 8791
	100-200	Var. 8450	Var. 8507	Var. 8564	Var. 8621	Var. 8678	Var. 8735	Var. 8792
	100-175	Var. 8451	Var. 8508	Var. 8565	Var. 8622	Var. 8679	Var. 8736	Var. 8793
	100-150	Var. 8452	Var. 8509	Var. 8566	Var. 8623	Var. 8680	Var. 8737	Var. 8794
	100-125	Var. 8453	Var. 8510	Var. 8567	Var. 8624	Var. 8681	Var. 8738	Var. 8795
	125-200	Var. 8454	Var. 8511	Var. 8568	Var. 8625	Var. 8682	Var. 8739	Var. 8796
	125-175	Var. 8455	Var. 8512	Var. 8569	Var. 8626	Var. 8683	Var. 8740	Var. 8797
	125-150	Var. 8456	Var. 8513	Var. 8570	Var. 8627	Var. 8684	Var. 8741	Var. 8798
	150-200	Var. 8457	Var. 8514	Var. 8571	Var. 8628	Var. 8685	Var. 8742	Var. 8799
	150-200	Var. 8458	Var. 8515	Var. 8572	Var. 8629	Var. 8686	Var. 8743	Var. 8800
	175-200	Var. 8459	Var. 8516	Var. 8573	Var. 8630	Var. 8687	Var. 8744	Var. 8801

Var. = Variation

Table 30. Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.

		Specific Activity (mU/µg)						
		20-90	**20-80**	**20-70**	**20-60**	**20-50**	**20-40**	**40-150**
Dosage (IU/kg rVWF:RCo activity)	**0.5-200**	Var. 8802	Var. 8859	Var. 8916	Var. 8973	Var. 9030	Var. 9087	Var. 9144
	0.5-150	Var. 8803	Var. 8860	Var. 8917	Var. 8974	Var. 9031	Var. 9088	Var. 9145
	0.5-100	Var. 8804	Var. 8861	Var. 8918	Var. 8975	Var. 9032	Var. 9089	Var. 9146
	0.5-75	Var. 8805	Var. 8862	Var. 8919	Var. 8976	Var. 9033	Var. 9090	Var. 9147
	0.5-50	Var. 8806	Var. 8863	Var. 8920	Var. 8977	Var. 9034	Var. 9091	Var. 9148
	0.5-25	Var. 8807	Var. 8864	Var. 8921	Var. 8978	Var. 9035	Var. 9092	Var. 9149
	0.5-10	Var. 8808	Var. 8865	Var. 8922	Var. 8979	Var. 9036	Var. 9093	Var. 9150
	0.5-5	Var. 8809	Var. 8866	Var. 8923	Var. 8980	Var. 9037	Var. 9094	Var. 9151
	0.5-2.5	Var. 8810	Var. 8867	Var. 8924	Var. 8981	Var. 9038	Var. 9095	Var. 9152
	0.5-1	Var. 8811	Var. 8868	Var. 8925	Var. 8982	Var. 9039	Var. 9096	Var. 9153
	2.5-200	Var. 8812	Var. 8869	Var. 8926	Var. 8983	Var. 9040	Var. 9097	Var. 9154
	2.5-150	Var. 8813	Var. 8870	Var. 8927	Var. 8984	Var. 9041	Var. 9098	Var. 9155
	2.5-100	Var. 8814	Var. 8871	Var. 8928	Var. 8985	Var. 9042	Var. 9099	Var. 9156
	2.5-75	Var. 8815	Var. 8872	Var. 8929	Var. 8986	Var. 9043	Var. 9100	Var. 9157
	2.5-50	Var. 8816	Var. 8873	Var. 8930	Var. 8987	Var. 9044	Var. 9101	Var. 9158
	2.5-25	Var. 8817	Var. 8874	Var. 8931	Var. 8988	Var. 9045	Var. 9102	Var. 9159
	2.5-10	Var. 8818	Var. 8875	Var. 8932	Var. 8989	Var. 9046	Var. 9103	Var. 9160
	2.5-5	Var. 8819	Var. 8876	Var. 8933	Var. 8990	Var. 9047	Var. 9104	Var. 9161
	5-200	Var. 8820	Var. 8877	Var. 8934	Var. 8991	Var. 9048	Var. 9105	Var. 9162
	5-175	Var. 8821	Var. 8878	Var. 8935	Var. 8992	Var. 9049	Var. 9106	Var. 9163
	5-150	Var. 8822	Var. 8879	Var. 8936	Var. 8993	Var. 9050	Var. 9107	Var. 9164
	5-125	Var. 8823	Var. 8880	Var. 8937	Var. 8994	Var. 9051	Var. 9108	Var. 9165
	5-100	Var. 8824	Var. 8881	Var. 8938	Var. 8995	Var. 9052	Var. 9109	Var. 9166
	5-75	Var. 8825	Var. 8882	Var. 8939	Var. 8996	Var. 9053	Var. 9110	Var. 9167
	5-50	Var. 8826	Var. 8883	Var. 8940	Var. 8997	Var. 9054	Var. 9111	Var. 9168
	5-25	Var. 8827	Var. 8884	Var. 8941	Var. 8998	Var. 9055	Var. 9112	Var. 9169
	5-10	Var. 8828	Var. 8885	Var. 8942	Var. 8999	Var. 9056	Var. 9113	Var. 9170
	10-200	Var. 8829	Var. 8886	Var. 8943	Var. 9000	Var. 9057	Var. 9114	Var. 9171
	10-150	Var. 8830	Var. 8887	Var. 8944	Var. 9001	Var. 9058	Var. 9115	Var. 9172
	10-100	Var. 8831	Var. 8888	Var. 8945	Var. 9002	Var. 9059	Var. 9116	Var. 9173
	10-75	Var. 8832	Var. 8889	Var. 8946	Var. 9003	Var. 9060	Var. 9117	Var. 9174
	10-50	Var. 8833	Var. 8890	Var. 8947	Var. 9004	Var. 9061	Var. 9118	Var. 9175

	10-25	Var. 8834	Var. 8891	Var. 8948	Var. 9005	Var. 9062	Var. 9119	Var. 9176
	25-200	Var. 8835	Var. 8892	Var. 8949	Var. 9006	Var. 9063	Var. 9120	Var. 9177
	25-150	Var. 8836	Var. 8893	Var. 8950	Var. 9007	Var. 9064	Var. 9121	Var. 9178
	25-100	Var. 8837	Var. 8894	Var. 8951	Var. 9008	Var. 9065	Var. 9122	Var. 9179
	25-75	Var. 8838	Var. 8895	Var. 8952	Var. 9009	Var. 9066	Var. 9123	Var. 9180
	25-50	Var. 8839	Var. 8896	Var. 8953	Var. 9010	Var. 9067	Var. 9124	Var. 9181
	50-200	Var. 8840	Var. 8897	Var. 8954	Var. 9011	Var. 9068	Var. 9125	Var. 9182
	50-150	Var. 8841	Var. 8898	Var. 8955	Var. 9012	Var. 9069	Var. 9126	Var. 9183
	50-100	Var. 8842	Var. 8899	Var. 8956	Var. 9013	Var. 9070	Var. 9127	Var. 9184
	50-75	Var. 8843	Var. 8900	Var. 8957	Var. 9014	Var. 9071	Var. 9128	Var. 9185
	75-200	Var. 8844	Var. 8901	Var. 8958	Var. 9015	Var. 9072	Var. 9129	Var. 9186
	75-175	Var. 8845	Var. 8902	Var. 8959	Var. 9016	Var. 9073	Var. 9130	Var. 9187
	75-150	Var. 8846	Var. 8903	Var. 8960	Var. 9017	Var. 9074	Var. 9131	Var. 9188
	75-125	Var. 8847	Var. 8904	Var. 8961	Var. 9018	Var. 9075	Var. 9132	Var. 9189
	75-100	Var. 8848	Var. 8905	Var. 8962	Var. 9019	Var. 9076	Var. 9133	Var. 9190
	100-200	Var. 8849	Var. 8906	Var. 8963	Var. 9020	Var. 9077	Var. 9134	Var. 9191
	100-175	Var. 8850	Var. 8907	Var. 8964	Var. 9021	Var. 9078	Var. 9135	Var. 9192
	100-150	Var. 8851	Var. 8908	Var. 8965	Var. 9022	Var. 9079	Var. 9136	Var. 9193
	100-125	Var. 8852	Var. 8909	Var. 8966	Var. 9023	Var. 9080	Var. 9137	Var. 9194
	125-200	Var. 8853	Var. 8910	Var. 8967	Var. 9024	Var. 9081	Var. 9138	Var. 9195
	125-175	Var. 8854	Var. 8911	Var. 8968	Var. 9025	Var. 9082	Var. 9139	Var. 9196
	125-150	Var. 8855	Var. 8912	Var. 8969	Var. 9026	Var. 9083	Var. 9140	Var. 9197
	150-200	Var. 8856	Var. 8913	Var. 8970	Var. 9027	Var. 9084	Var. 9141	Var. 9198
	150-200	Var. 8857	Var. 8914	Var. 8971	Var. 9028	Var. 9085	Var. 9142	Var. 9199
	175-200	Var. 8858	Var. 8915	Var. 8972	Var. 9029	Var. 9086	Var. 9143	Var. 9200

Var. = Variation

Table 31. Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.

		Specific Activity (mU/µg)						
		40-125	**40-100**	**40-90**	**40-80**	**40-70**	**40-60**	**40-50**
Dosage (IU/kg rVWF:RCo activity)	**0.5-200**	Var. 9201	Var. 9258	Var. 9315	Var. 9372	Var. 9429	Var. 9486	Var. 9543
	0.5-150	Var. 9202	Var. 9259	Var. 9316	Var. 9373	Var. 9430	Var. 9487	Var. 9544
	0.5-100	Var. 9203	Var. 9260	Var. 9317	Var. 9374	Var. 9431	Var. 9488	Var. 9545
	0.5-75	Var. 9204	Var. 9261	Var. 9318	Var. 9375	Var. 9432	Var. 9489	Var. 9546
	0.5-50	Var. 9205	Var. 9262	Var. 9319	Var. 9376	Var. 9433	Var. 9490	Var. 9547
	0.5-25	Var. 9206	Var. 9263	Var. 9320	Var. 9377	Var. 9434	Var. 9491	Var. 9548
	0.5-10	Var. 9207	Var. 9264	Var. 9321	Var. 9378	Var. 9435	Var. 9492	Var. 9549
	0.5-5	Var. 9208	Var. 9265	Var. 9322	Var. 9379	Var. 9436	Var. 9493	Var. 9550
	0.5-2.5	Var. 9209	Var. 9266	Var. 9323	Var. 9380	Var. 9437	Var. 9494	Var. 9551
	0.5-1	Var. 9210	Var. 9267	Var. 9324	Var. 9381	Var. 9438	Var. 9495	Var. 9552
	2.5-200	Var. 9211	Var. 9268	Var. 9325	Var. 9382	Var. 9439	Var. 9496	Var. 9553
	2.5-150	Var. 9212	Var. 9269	Var. 9326	Var. 9383	Var. 9440	Var. 9497	Var. 9554
	2.5-100	Var. 9213	Var. 9270	Var. 9327	Var. 9384	Var. 9441	Var. 9498	Var. 9555
	2.5-75	Var. 9214	Var. 9271	Var. 9328	Var. 9385	Var. 9442	Var. 9499	Var. 9556
	2.5-50	Var. 9215	Var. 9272	Var. 9329	Var. 9386	Var. 9443	Var. 9500	Var. 9557
	2.5-25	Var. 9216	Var. 9273	Var. 9330	Var. 9387	Var. 9444	Var. 9501	Var. 9558
	2.5-10	Var. 9217	Var. 9274	Var. 9331	Var. 9388	Var. 9445	Var. 9502	Var. 9559
	2.5-5	Var. 9218	Var. 9275	Var. 9332	Var. 9389	Var. 9446	Var. 9503	Var. 9560
	5-200	Var. 9219	Var. 9276	Var. 9333	Var. 9390	Var. 9447	Var. 9504	Var. 9561
	5-175	Var. 9220	Var. 9277	Var. 9334	Var. 9391	Var. 9448	Var. 9505	Var. 9562
	5-150	Var. 9221	Var. 9278	Var. 9335	Var. 9392	Var. 9449	Var. 9506	Var. 9563
	5-125	Var. 9222	Var. 9279	Var. 9336	Var. 9393	Var. 9450	Var. 9507	Var. 9564
	5-100	Var. 9223	Var. 9280	Var. 9337	Var. 9394	Var. 9451	Var. 9508	Var. 9565

	5-75	Var. 9224	Var. 9281	Var. 9338	Var. 9395	Var. 9452	Var. 9509	Var. 9566
	5-50	Var. 9225	Var. 9282	Var. 9339	Var. 9396	Var. 9453	Var. 9510	Var. 9567
	5-25	Var. 9226	Var. 9283	Var. 9340	Var. 9397	Var. 9454	Var. 9511	Var. 9568
	5-10	Var. 9227	Var. 9284	Var. 9341	Var. 9398	Var. 9455	Var. 9512	Var. 9569
	10-200	Var. 9228	Var. 9285	Var. 9342	Var. 9399	Var. 9456	Var. 9513	Var. 9570
	10-150	Var. 9229	Var. 9286	Var. 9343	Var. 9400	Var. 9457	Var. 9514	Var. 9571
	10-100	Var. 9230	Var. 9287	Var. 9344	Var. 9401	Var. 9458	Var. 9515	Var. 9572
	10-75	Var. 9231	Var. 9288	Var. 9345	Var. 9402	Var. 9459	Var. 9516	Var. 9573
	10-50	Var. 9232	Var. 9289	Var. 9346	Var. 9403	Var. 9460	Var. 9517	Var. 9574
	10-25	Var. 9233	Var. 9290	Var. 9347	Var. 9404	Var. 9461	Var. 9518	Var. 9575
	25-200	Var. 9234	Var. 9291	Var. 9348	Var. 9405	Var. 9462	Var. 9519	Var. 9576
	25-150	Var. 9235	Var. 9292	Var. 9349	Var. 9406	Var. 9463	Var. 9520	Var. 9577
	25-100	Var. 9236	Var. 9293	Var. 9350	Var. 9407	Var. 9464	Var. 9521	Var. 9578
	25-75	Var. 9237	Var. 9294	Var. 9351	Var. 9408	Var. 9465	Var. 9522	Var. 9579
	25-50	Var. 9238	Var. 9295	Var. 9352	Var. 9409	Var. 9466	Var. 9523	Var. 9580
	50-200	Var. 9239	Var. 9296	Var. 9353	Var. 9410	Var. 9467	Var. 9524	Var. 9581
	50-150	Var. 9240	Var. 9297	Var. 9354	Var. 9411	Var. 9468	Var. 9525	Var. 9582
	50-100	Var. 9241	Var. 9298	Var. 9355	Var. 9412	Var. 9469	Var. 9526	Var. 9583
	50-75	Var. 9242	Var. 9299	Var. 9356	Var. 9413	Var. 9470	Var. 9527	Var. 9584
	75-200	Var. 9243	Var. 9300	Var. 9357	Var. 9414	Var. 9471	Var. 9528	Var. 9585
	75-175	Var. 9244	Var. 9301	Var. 9358	Var. 9415	Var. 9472	Var. 9529	Var. 9586
	75-150	Var. 9245	Var. 9302	Var. 9359	Var. 9416	Var. 9473	Var. 9530	Var. 9587
	75-125	Var. 9246	Var. 9303	Var. 9360	Var. 9417	Var. 9474	Var. 9531	Var. 9588
	75-100	Var. 9247	Var. 9304	Var. 9361	Var. 9418	Var. 9475	Var. 9532	Var. 9589
	100-200	Var. 9248	Var. 9305	Var. 9362	Var. 9419	Var. 9476	Var. 9533	Var. 9590
	100-175	Var. 9249	Var. 9306	Var. 9363	Var. 9420	Var. 9477	Var. 9534	Var. 9591
	100-150	Var. 9250	Var. 9307	Var. 9364	Var. 9421	Var. 9478	Var. 9535	Var. 9592
	100-125	Var. 9251	Var. 9308	Var. 9365	Var. 9422	Var. 9479	Var. 9536	Var. 9593
	125-200	Var. 9252	Var. 9309	Var. 9366	Var. 9423	Var. 9480	Var. 9537	Var. 9594
	125-175	Var. 9253	Var. 9310	Var. 9367	Var. 9424	Var. 9481	Var. 9538	Var. 9595
	125-150	Var. 9254	Var. 9311	Var. 9368	Var. 9425	Var. 9482	Var. 9539	Var. 9596
	150-200	Var. 9255	Var. 9312	Var. 9369	Var. 9426	Var. 9483	Var. 9540	Var. 9597
	150-200	Var. 9256	Var. 9313	Var. 9370	Var. 9427	Var. 9484	Var. 9541	Var. 9598
	175-200	Var. 9257	Var. 9314	Var. 9371	Var. 9428	Var. 9485	Var. 9542	Var. 9599

Var. = Variation

Table 32. Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.

		Specific Activity (mU/µg)					
		60-150	**60-125**	**60-100**	**60-90**	**60-80**	**60-70**
Dosage (IU/kg rVWF:RCo activity)	**0.5-200**	Var. 9600	Var. 9657	Var. 9714	Var. 9771	Var. 9828	Var. 9885
	0.5-150	Var. 9601	Var. 9658	Var. 9715	Var. 9772	Var. 9829	Var. 9886
	0.5-100	Var. 9602	Var. 9659	Var. 9716	Var. 9773	Var. 9830	Var. 9887
	0.5-75	Var. 9603	Var. 9660	Var. 9717	Var. 9774	Var. 9831	Var. 9888
	0.5-50	Var. 9604	Var. 9661	Var. 9718	Var. 9775	Var. 9832	Var. 9889
	0.5-25	Var. 9605	Var. 9662	Var. 9719	Var. 9776	Var. 9833	Var. 9890
	0.5-10	Var. 9606	Var. 9663	Var. 9720	Var. 9777	Var. 9834	Var. 9891
	0.5-5	Var. 9607	Var. 9664	Var. 9721	Var. 9778	Var. 9835	Var. 9892
	0.5-2.5	Var. 9608	Var. 9665	Var. 9722	Var. 9779	Var. 9836	Var. 9893
	0.5-1	Var. 9609	Var. 9666	Var. 9723	Var. 9780	Var. 9837	Var. 9894
	2.5-200	Var. 9610	Var. 9667	Var. 9724	Var. 9781	Var. 9838	Var. 9895
	2.5-150	Var. 9611	Var. 9668	Var. 9725	Var. 9782	Var. 9839	Var. 9896
	2.5-100	Var. 9612	Var. 9669	Var. 9726	Var. 9783	Var. 9840	Var. 9897
	2.5-75	Var. 9613	Var. 9670	Var. 9727	Var. 9784	Var. 9841	Var. 9898

	2.5-50	Var. 9614	Var. 9671	Var. 9728	Var. 9785	Var. 9842	Var. 9899
	2.5-25	Var. 9615	Var. 9672	Var. 9729	Var. 9786	Var. 9843	Var. 9900
	2.5-10	Var. 9616	Var. 9673	Var. 9730	Var. 9787	Var. 9844	Var. 9901
	2.5-5	Var. 9617	Var. 9674	Var. 9731	Var. 9788	Var. 9845	Var. 9902
	5-200	Var. 9618	Var. 9675	Var. 9732	Var. 9789	Var. 9846	Var. 9903
	5-175	Var. 9619	Var. 9676	Var. 9733	Var. 9790	Var. 9847	Var. 9904
	5-150	Var. 9620	Var. 9677	Var. 9734	Var. 9791	Var. 9848	Var. 9905
	5-125	Var. 9621	Var. 9678	Var. 9735	Var. 9792	Var. 9849	Var. 9906
	5-100	Var. 9622	Var. 9679	Var. 9736	Var. 9793	Var. 9850	Var. 9907
	5-75	Var. 9623	Var. 9680	Var. 9737	Var. 9794	Var. 9851	Var. 9908
	5-50	Var. 9624	Var. 9681	Var. 9738	Var. 9795	Var. 9852	Var. 9909
	5-25	Var. 9625	Var. 9682	Var. 9739	Var. 9796	Var. 9853	Var. 9910
	5-10	Var. 9626	Var. 9683	Var. 9740	Var. 9797	Var. 9854	Var. 9911
	10-200	Var. 9627	Var. 9684	Var. 9741	Var. 9798	Var. 9855	Var. 9912
	10-150	Var. 9628	Var. 9685	Var. 9742	Var. 9799	Var. 9856	Var. 9913
	10-100	Var. 9629	Var. 9686	Var. 9743	Var. 9800	Var. 9857	Var. 9914
	10-75	Var. 9630	Var. 9687	Var. 9744	Var. 9801	Var. 9858	Var. 9915
	10-50	Var. 9631	Var. 9688	Var. 9745	Var. 9802	Var. 9859	Var. 9916
	10-25	Var. 9632	Var. 9689	Var. 9746	Var. 9803	Var. 9860	Var. 9917
	25-200	Var. 9633	Var. 9690	Var. 9747	Var. 9804	Var. 9861	Var. 9918
	25-150	Var. 9634	Var. 9691	Var. 9748	Var. 9805	Var. 9862	Var. 9919
	25-100	Var. 9635	Var. 9692	Var. 9749	Var. 9806	Var. 9863	Var. 9920
	25-75	Var. 9636	Var. 9693	Var. 9750	Var. 9807	Var. 9864	Var. 9921
	25-50	Var. 9637	Var. 9694	Var. 9751	Var. 9808	Var. 9865	Var. 9922
	50-200	Var. 9638	Var. 9695	Var. 9752	Var. 9809	Var. 9866	Var. 9923
	50-150	Var. 9639	Var. 9696	Var. 9753	Var. 9810	Var. 9867	Var. 9924
	50-100	Var. 9640	Var. 9697	Var. 9754	Var. 9811	Var. 9868	Var. 9925
	50-75	Var. 9641	Var. 9698	Var. 9755	Var. 9812	Var. 9869	Var. 9926
	75-200	Var. 9642	Var. 9699	Var. 9756	Var. 9813	Var. 9870	Var. 9927
	75-175	Var. 9643	Var. 9700	Var. 9757	Var. 9814	Var. 9871	Var. 9928
	75-150	Var. 9644	Var. 9701	Var. 9758	Var. 9815	Var. 9872	Var. 9929
	75-125	Var. 9645	Var. 9702	Var. 9759	Var. 9816	Var. 9873	Var. 9930
	75-100	Var. 9646	Var. 9703	Var. 9760	Var. 9817	Var. 9874	Var. 9931
	100-200	Var. 9647	Var. 9704	Var. 9761	Var. 9818	Var. 9875	Var. 9932
	100-175	Var. 9648	Var. 9705	Var. 9762	Var. 9819	Var. 9876	Var. 9933
	100-150	Var. 9649	Var. 9706	Var. 9763	Var. 9820	Var. 9877	Var. 9934
	100-125	Var. 9650	Var. 9707	Var. 9764	Var. 9821	Var. 9878	Var. 9935
	125-200	Var. 9651	Var. 9708	Var. 9765	Var. 9822	Var. 9879	Var. 9936
	125-175	Var. 9652	Var. 9709	Var. 9766	Var. 9823	Var. 9880	Var. 9937
	125-150	Var. 9653	Var. 9710	Var. 9767	Var. 9824	Var. 9881	Var. 9938
	150-200	Var. 9654	Var. 9711	Var. 9768	Var. 9825	Var. 9882	Var. 9939
	150-200	Var. 9655	Var. 9712	Var. 9769	Var. 9826	Var. 9883	Var. 9940
	175-200	Var. 9656	Var. 9713	Var. 9770	Var. 9827	Var. 9884	Var. 9941

Var. = Variation

Table 33. Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.

		Specific Activity (mU/µg)					
		70-150	**70-125**	**70-100**	**70-90**	**70-80**	**80-150**
Dosage (IU/kg	**0.5-200**	Var. 9942	Var. 9999	Var. 10056	Var. 10113	Var. 10170	Var. 10227
	0.5-150	Var. 9943	Var. 10000	Var. 10057	Var. 10114	Var. 10171	Var. 10228
	0.5-100	Var. 9944	Var. 10001	Var. 10058	Var. 10115	Var. 10172	Var. 10229
	0.5-75	Var. 9945	Var. 10002	Var. 10059	Var. 10116	Var. 10173	Var. 10230
	0.5-50	Var. 9946	Var. 10003	Var. 10060	Var. 10117	Var. 10174	Var. 10231

	0.5-25	Var. 9947	Var. 10004	Var. 10061	Var. 10118	Var. 10175	Var. 10232
	0.5-10	Var. 9948	Var. 10005	Var. 10062	Var. 10119	Var. 10176	Var. 10233
	0.5-5	Var. 9949	Var. 10006	Var. 10063	Var. 10120	Var. 10177	Var. 10234
	0.5-2.5	Var. 9950	Var. 10007	Var. 10064	Var. 10121	Var. 10178	Var. 10235
	0.5-1	Var. 9951	Var. 10008	Var. 10065	Var. 10122	Var. 10179	Var. 10236
	2.5-200	Var. 9952	Var. 10009	Var. 10066	Var. 10123	Var. 10180	Var. 10237
	2.5-150	Var. 9953	Var. 10010	Var. 10067	Var. 10124	Var. 10181	Var. 10238
	2.5-100	Var. 9954	Var. 10011	Var. 10068	Var. 10125	Var. 10182	Var. 10239
	2.5-75	Var. 9955	Var. 10012	Var. 10069	Var. 10126	Var. 10183	Var. 10240
	2.5-50	Var. 9956	Var. 10013	Var. 10070	Var. 10127	Var. 10184	Var. 10241
	2.5-25	Var. 9957	Var. 10014	Var. 10071	Var. 10128	Var. 10185	Var. 10242
	2.5-10	Var. 9958	Var. 10015	Var. 10072	Var. 10129	Var. 10186	Var. 10243
	2.5-5	Var. 9959	Var. 10016	Var. 10073	Var. 10130	Var. 10187	Var. 10244
	5-200	Var. 9960	Var. 10017	Var. 10074	Var. 10131	Var. 10188	Var. 10245
	5-175	Var. 9961	Var. 10018	Var. 10075	Var. 10132	Var. 10189	Var. 10246
	5-150	Var. 9962	Var. 10019	Var. 10076	Var. 10133	Var. 10190	Var. 10247
	5-125	Var. 9963	Var. 10020	Var. 10077	Var. 10134	Var. 10191	Var. 10248
	5-100	Var. 9964	Var. 10021	Var. 10078	Var. 10135	Var. 10192	Var. 10249
	5-75	Var. 9965	Var. 10022	Var. 10079	Var. 10136	Var. 10193	Var. 10250
	5-50	Var. 9966	Var. 10023	Var. 10080	Var. 10137	Var. 10194	Var. 10251
	5-25	Var. 9967	Var. 10024	Var. 10081	Var. 10138	Var. 10195	Var. 10252
	5-10	Var. 9968	Var. 10025	Var. 10082	Var. 10139	Var. 10196	Var. 10253
	10-200	Var. 9969	Var. 10026	Var. 10083	Var. 10140	Var. 10197	Var. 10254
	10-150	Var. 9970	Var. 10027	Var. 10084	Var. 10141	Var. 10198	Var. 10255
	10-100	Var. 9971	Var. 10028	Var. 10085	Var. 10142	Var. 10199	Var. 10256
	10-75	Var. 9972	Var. 10029	Var. 10086	Var. 10143	Var. 10200	Var. 10257
	10-50	Var. 9973	Var. 10030	Var. 10087	Var. 10144	Var. 10201	Var. 10258
	10-25	Var. 9974	Var. 10031	Var. 10088	Var. 10145	Var. 10202	Var. 10259
	25-200	Var. 9975	Var. 10032	Var. 10089	Var. 10146	Var. 10203	Var. 10260
	25-150	Var. 9976	Var. 10033	Var. 10090	Var. 10147	Var. 10204	Var. 10261
	25-100	Var. 9977	Var. 10034	Var. 10091	Var. 10148	Var. 10205	Var. 10262
	25-75	Var. 9978	Var. 10035	Var. 10092	Var. 10149	Var. 10206	Var. 10263
	25-50	Var. 9979	Var. 10036	Var. 10093	Var. 10150	Var. 10207	Var. 10264
	50-200	Var. 9980	Var. 10037	Var. 10094	Var. 10151	Var. 10208	Var. 10265
	50-150	Var. 9981	Var. 10038	Var. 10095	Var. 10152	Var. 10209	Var. 10266
	50-100	Var. 9982	Var. 10039	Var. 10096	Var. 10153	Var. 10210	Var. 10267
	50-75	Var. 9983	Var. 10040	Var. 10097	Var. 10154	Var. 10211	Var. 10268
	75-200	Var. 9984	Var. 10041	Var. 10098	Var. 10155	Var. 10212	Var. 10269
	75-175	Var. 9985	Var. 10042	Var. 10099	Var. 10156	Var. 10213	Var. 10270
	75-150	Var. 9986	Var. 10043	Var. 10100	Var. 10157	Var. 10214	Var. 10271
	75-125	Var. 9987	Var. 10044	Var. 10101	Var. 10158	Var. 10215	Var. 10272
	75-100	Var. 9988	Var. 10045	Var. 10102	Var. 10159	Var. 10216	Var. 10273
	100-200	Var. 9989	Var. 10046	Var. 10103	Var. 10160	Var. 10217	Var. 10274
	100-175	Var. 9990	Var. 10047	Var. 10104	Var. 10161	Var. 10218	Var. 10275
	100-150	Var. 9991	Var. 10048	Var. 10105	Var. 10162	Var. 10219	Var. 10276
	100-125	Var. 9992	Var. 10049	Var. 10106	Var. 10163	Var. 10220	Var. 10277
	125-200	Var. 9993	Var. 10050	Var. 10107	Var. 10164	Var. 10221	Var. 10278
	125-175	Var. 9994	Var. 10051	Var. 10108	Var. 10165	Var. 10222	Var. 10279
	125-150	Var. 9995	Var. 10052	Var. 10109	Var. 10166	Var. 10223	Var. 10280
	150-200	Var. 9996	Var. 10053	Var. 10110	Var. 10167	Var. 10224	Var. 10281
	150-200	Var. 9997	Var. 10054	Var. 10111	Var. 10168	Var. 10225	Var. 10282
	175-200	Var. 9998	Var. 10055	Var. 10112	Var. 10169	Var. 10226	Var. 10283

Var. = Variation

Table 34. Exemplary embodiments for the combination of rVWF dosage and rVWF specific activity useful in the methods described herein.

		Specific Activity (mU/µg)					
		80-125	**80-100**	**80-90**	**90-150**	**90-125**	**90-100**
Dosage (IU/kg rVWF:RCo activity)	**0.5-200**	Var. 10284	Var. 10341	Var. 10398	Var. 10455	Var. 10512	Var. 10569
	0.5-150	Var. 10285	Var. 10342	Var. 10399	Var. 10456	Var. 10513	Var. 10570
	0.5-100	Var. 10286	Var. 10343	Var. 10400	Var. 10457	Var. 10514	Var. 10571
	0.5-75	Var. 10287	Var. 10344	Var. 10401	Var. 10458	Var. 10515	Var. 10572
	0.5-50	Var. 10288	Var. 10345	Var. 10402	Var. 10459	Var. 10516	Var. 10573
	0.5-25	Var. 10289	Var. 10346	Var. 10403	Var. 10460	Var. 10517	Var. 10574
	0.5-10	Var. 10290	Var. 10347	Var. 10404	Var. 10461	Var. 10518	Var. 10575
	0.5-5	Var. 10291	Var. 10348	Var. 10405	Var. 10462	Var. 10519	Var. 10576
	0.5-2.5	Var. 10292	Var. 10349	Var. 10406	Var. 10463	Var. 10520	Var. 10577
	0.5-1	Var. 10293	Var. 10350	Var. 10407	Var. 10464	Var. 10521	Var. 10578
	2.5-200	Var. 10294	Var. 10351	Var. 10408	Var. 10465	Var. 10522	Var. 10579
	2.5-150	Var. 10295	Var. 10352	Var. 10409	Var. 10466	Var. 10523	Var. 10580
	2.5-100	Var. 10296	Var. 10353	Var. 10410	Var. 10467	Var. 10524	Var. 10581
	2.5-75	Var. 10297	Var. 10354	Var. 10411	Var. 10468	Var. 10525	Var. 10582
	2.5-50	Var. 10298	Var. 10355	Var. 10412	Var. 10469	Var. 10526	Var. 10583
	2.5-25	Var. 10299	Var. 10356	Var. 10413	Var. 10470	Var. 10527	Var. 10584
	2.5-10	Var. 10300	Var. 10357	Var. 10414	Var. 10471	Var. 10528	Var. 10585
	2.5-5	Var. 10301	Var. 10358	Var. 10415	Var. 10472	Var. 10529	Var. 10586
	5-200	Var. 10302	Var. 10359	Var. 10416	Var. 10473	Var. 10530	Var. 10587
	5-175	Var. 10303	Var. 10360	Var. 10417	Var. 10474	Var. 10531	Var. 10588
	5-150	Var. 10304	Var. 10361	Var. 10418	Var. 10475	Var. 10532	Var. 10589
	5-125	Var. 10305	Var. 10362	Var. 10419	Var. 10476	Var. 10533	Var. 10590
	5-100	Var. 10306	Var. 10363	Var. 10420	Var. 10477	Var. 10534	Var. 10591
	5-75	Var. 10307	Var. 10364	Var. 10421	Var. 10478	Var. 10535	Var. 10592
	5-50	Var. 10308	Var. 10365	Var. 10422	Var. 10479	Var. 10536	Var. 10593
	5-25	Var. 10309	Var. 10366	Var. 10423	Var. 10480	Var. 10537	Var. 10594
	5-10	Var. 10310	Var. 10367	Var. 10424	Var. 10481	Var. 10538	Var. 10595
	10-200	Var. 10311	Var. 10368	Var. 10425	Var. 10482	Var. 10539	Var. 10596
	10-150	Var. 10312	Var. 10369	Var. 10426	Var. 10483	Var. 10540	Var. 10597
	10-100	Var. 10313	Var. 10370	Var. 10427	Var. 10484	Var. 10541	Var. 10598
	10-75	Var. 10314	Var. 10371	Var. 10428	Var. 10485	Var. 10542	Var. 10599
	10-50	Var. 10315	Var. 10372	Var. 10429	Var. 10486	Var. 10543	Var. 10600
	10-25	Var. 10316	Var. 10373	Var. 10430	Var. 10487	Var. 10544	Var. 10601
	25-200	Var. 10317	Var. 10374	Var. 10431	Var. 10488	Var. 10545	Var. 10602
	25-150	Var. 10318	Var. 10375	Var. 10432	Var. 10489	Var. 10546	Var. 10603
	25-100	Var. 10319	Var. 10376	Var. 10433	Var. 10490	Var. 10547	Var. 10604
	25-75	Var. 10320	Var. 10377	Var. 10434	Var. 10491	Var. 10548	Var. 10605
	25-50	Var. 10321	Var. 10378	Var. 10435	Var. 10492	Var. 10549	Var. 10606
	50-200	Var. 10322	Var. 10379	Var. 10436	Var. 10493	Var. 10550	Var. 10607
	50-150	Var. 10323	Var. 10380	Var. 10437	Var. 10494	Var. 10551	Var. 10608
	50-100	Var. 10324	Var. 10381	Var. 10438	Var. 10495	Var. 10552	Var. 10609
	50-75	Var. 10325	Var. 10382	Var. 10439	Var. 10496	Var. 10553	Var. 10610
	75-200	Var. 10326	Var. 10383	Var. 10440	Var. 10497	Var. 10554	Var. 10611
	75-175	Var. 10327	Var. 10384	Var. 10441	Var. 10498	Var. 10555	Var. 10612
	75-150	Var. 10328	Var. 10385	Var. 10442	Var. 10499	Var. 10556	Var. 10613
	75-125	Var. 10329	Var. 10386	Var. 10443	Var. 10500	Var. 10557	Var. 10614
	75-100	Var. 10330	Var. 10387	Var. 10444	Var. 10501	Var. 10558	Var. 10615
	100-200	Var. 10331	Var. 10388	Var. 10445	Var. 10502	Var. 10559	Var. 10616
	100-175	Var. 10332	Var. 10389	Var. 10446	Var. 10503	Var. 10560	Var. 10617

	100-150	Var. 10333	Var. 10390	Var. 10447	Var. 10504	Var. 10561	Var. 10618
	100-125	Var. 10334	Var. 10391	Var. 10448	Var. 10505	Var. 10562	Var. 10619
	125-200	Var. 10335	Var. 10392	Var. 10449	Var. 10506	Var. 10563	Var. 10620
	125-175	Var. 10336	Var. 10393	Var. 10450	Var. 10507	Var. 10564	Var. 10621
	125-150	Var. 10337	Var. 10394	Var. 10451	Var. 10508	Var. 10565	Var. 10622
	150-200	Var. 10338	Var. 10395	Var. 10452	Var. 10509	Var. 10566	Var. 10623
	150-200	Var. 10339	Var. 10396	Var. 10453	Var. 10510	Var. 10567	Var. 10624
	175-200	Var. 10340	Var. 10397	Var. 10454	Var. 10511	Var. 10568	Var. 10625

Var. = Variation

[00247] In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 30% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00248] In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 50% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00249] In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers in which at least 70% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment,

FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00250] In one embodiment, the method comprises administering a composition of rVWF, wherein the composition of rVWF administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in **Table 3** to **Table 5**, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00251] In one embodiment, the method comprises administering a composition of rVWF, wherein FVIII in the subject is stabilized for at least 18 hours post-administration, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00252] In one embodiment, the method comprises administering a composition of rVWF, wherein FVIII in the subject is stabilized for at least 24 hours post-administration, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00253] In one embodiment, the method comprises administering a composition of rVWF, wherein FVIII in the subject is stabilized for at least 30 hours post-administration, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF administered to the subject has a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

Administration of rVWF/rFVIII

[00254] In one aspect, the present disclosure provides method for treating Von Willebrand Disease (VWD) or Hemophilia A in a subject in need thereof, which includes administering a composition of recombinant Von Willebrand Factor (rVWF) and recombinant FVIII (rFVIII) such that Factor VIII (FVIII) stability is increased, as compared to FVIII half-life in a subject administered a composition of plasma derived Von Willebrand Factor (pdVWF). In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF. In yet another embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers with a higher VWF specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00255] In one embodiment, the method comprises administering a composition of rVWF/rFVIII such that FVIII stability is extended by at least 10%, 20%, 30%, 2 hr, 4 hr, 6 hr, or by an amount selected from variations 1300 to 1643 found in **Table 9**, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In yet another embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers with

a higher specific activity than a composition of pdVWF. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00256] In one embodiment, the method comprises administering a composition of rVWF/rFVIII such that FVIII stability is extended by at least 10% as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in **Table 3** to **Table 5**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00257] In one embodiment, the method comprises administering a composition of rVWF/rFVIII such that FVIII stability is extended by at least 20% as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in **Table 3** to **Table 5**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00258] In one embodiment, the method comprises administering a composition of rVWF/rFVIII such that FVIII stability is extended by at least 30% as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found

in **Table 3** to **Table 5**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00259] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00260] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers in which at least 30% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00261] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers in which at least 50% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In one embodiment, the

composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00262] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers in which at least 70% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00263] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in **Table 3** to **Table 5**, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00264] In one embodiment, the method comprises administering a dosage of a rVWF/rFVIII composition containing from 10 IU/kg to 40 IU/kg rVWF:RCo activity, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In a specific embodiment,

the composition contains from 20 IU/kg to 30 IU/kg rVWF:RCo activity. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00265] In one embodiment, the method comprises administering a dosage of a rVWF/rFVIII composition containing from 25 IU/kg to 75 IU/kg rVWF:RCo activity, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In a specific embodiment, the composition contains from 40 IU/kg to 60 IU/kg rVWF:RCo activity. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00266] In one embodiment, the method comprises administering a dosage of a rVWF/rFVIII composition containing from 75 IU/kg to 125 IU/kg rVWF:RCo activity, wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In a specific embodiment, the composition contains from 75 IU/kg to 100 IU/kg rVWF:RCo activity. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00267] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the subject is administered a dose of rVWF selected from variations 2141 to 2338 in **Table 12**, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment,

FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00268] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher specific activity than a composition of pdVWF. In yet another embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers with a higher specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00269] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers in which at least 30% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00270] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers in which at least 50% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in

Table 20 to **Table 27**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00271] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers in which at least 70% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00272] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in **Table 3** to **Table 5**, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00273] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the rVWF in the composition has a specific activity of from 40 mU/μg to 60 mU/μg, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is

selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00274] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the rVWF in the composition has a specific activity of at least 60 mU/μg, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00275] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the rVWF in the composition has a specific activity of at least 80 mU/μg, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00276] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the rVWF in the composition has a specific activity selected from variations 1 to 133 found in **Table 1**, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean

residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00277] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher specific activity than a composition of pdVWF/FVIII. In yet another embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers with a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00278] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers in which at least 30% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00279] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers in which at least 50% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence

time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00280] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers in which at least 70% of rVWF molecules in the composition are present in a multimer of at least 10 subunits, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00281] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in **Table 3** to **Table 5**, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00282] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein FVIII in the subject is stabilized for at least 18 hours post-administration, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00283] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein FVIII in the subject is stabilized for at least 24 hours post-administration, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00284] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein FVIII in the subject is stabilized for at least 30 hours post-administration, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00285] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 4:1-3:2, and wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in **Table 3** to **Table 5**. In a specific embodiment, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 3:1-3:2. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00286] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:1-1:2, and wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in **Table 3** to **Table 5**. In a specific embodiment, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 3:2-2:3. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00287] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:3-1:6, and wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in **Table 3** to **Table 5**. In a specific embodiment, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:3-1:5. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00288] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is selected from variations 1988 to 2140 found in **Table 11**, and wherein the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers having a minimal percentage of rVWF molecules present in a particular higher-order rVWF multimer or larger multimer according to any one of variations 134 to 457 found in **Table 3** to **Table 5**. In one

embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00289] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, , wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is selected from variations 1988 to 2140 found in **Table 11**. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00290] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 4:1-3:2, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In a specific embodiment, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 3:1-3:2. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00291] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:1-1:2, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In a specific embodiment, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity

(IU rVWF:RCo) in the composition is from 3:2-2:3. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00292] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:3-1:6, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In a specific embodiment, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:3-1:5. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00293] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is selected from variations 1988 to 2140 found in **Table 11**, and wherein the combination of rVWF specific activity in the composition and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 2339 to 4868 in **Table 13** to **Table 19**. In one embodiment, the composition of rVWF/rFVIII administered to the subject is a composition of high molecular weight rVWF multimers. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00294] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 4:1-3:2, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject

administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In a specific embodiment, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 3:1-3:2. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00295] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:1-1:2, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In a specific embodiment, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 3:2-2:3. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00296] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:3-1:6, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In a specific embodiment, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:3-1:5. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00297] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is selected from variations 1988 to 2140 found in **Table 11**, and wherein the dose of rVWF and increase in FVIII stability, as compared to FVIII stability in a subject administered a composition of pdVWF/FVIII, is selected from variations 4869 to 8003 in **Table 20** to **Table 27**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00298] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 4:1-3:2, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In a specific embodiment, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 3:1-3:2. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00299] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:1-1:2, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In a specific embodiment, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 3:2-2:3. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence

time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00300] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:3-1:6, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In a specific embodiment, the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is from 2:3-1:5. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00301] In one embodiment, the method comprises administering a composition of rVWF/rFVIII, wherein the ratio of rFVIII procoagulant activity (IU rFVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) in the composition is selected from variations 1988 to 2140 found in **Table 11**, and wherein the dose of rVWF and specific activity of rVWF in the composition is selected from variations 8004 to 10625 in **Table 28** to **Table 34**. In one embodiment, the composition of rVWF/rFVIII administered to the subject has a higher VWF specific activity than a composition of pdVWF/FVIII. In one embodiment, FVIII stability is characterized by the half life of FVIII. In another embodiment, FVIII stability is characterized by mean residence time (MRT) of FVIII. In a further embodiment, the method is for treating any type of VWD. In a specific embodiment, the method is for treating Type 3 VWD.

[00302] The practice of the present invention may employ, unless otherwise indicated, conventional techniques and descriptions of organic chemistry, polymer technology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology, which are within the skill of the art. Such conventional techniques include polymer array synthesis, hybridization, ligation, and detection of hybridization using a label. Specific illustrations of suitable techniques can be had by reference to the example herein below. However, other equivalent conventional procedures can, of course, also be used. Such conventional techniques and descriptions can be found in standard laboratory manuals such as *Genome Analysis: A Laboratory Manual Series* (Vols. I-IV), *Using Antibodies: A Laboratory Manual, Cells: A Laboratory Manual, PCR Primer: A Laboratory Manual, and*

Molecular Cloning: A Laboratory Manual (all from Cold Spring Harbor Laboratory Press), Stryer, L. (1995) *Biochemistry* (4th Ed.) Freeman, Highly stabilized York, Gait, "*Oligonucleotide Synthesis: A Practical Approach"* 1984, IRL Press, London, Nelson and Cox (2000), *Lehninger, Principles of Biochemistry* 3rd Ed., W. H. Freeman Pub., Highly stabilized York, N.Y. and Berg et al. (2002) *Biochemistry*, 5th Ed., W. H. Freeman Pub., Highly stabilized York, N.Y., all of which are herein incorporated in their entirety by reference for all purposes.

[00303] Note that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a polymerase" refers to one agent or mixtures of such agents, and reference to "the method" includes reference to equivalent steps and methods known to those skilled in the art, and so forth.

[00304] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing devices, compositions, formulations and methodologies which are described in the publication and which might be used in connection with the presently described invention.

[00305] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention.

[00306] In the above description, numerous specific details are set forth to provide a more thorough understanding of the present invention. However, it will be apparent to one of skill in the art that the present invention may be practiced without one or more of these specific details. In other instances, well-known features and procedures well known to those skilled in the art have not been described in order to avoid obscuring the invention.

[00307] Although the present invention is described primarily with reference to specific embodiments, it is also envisioned that other embodiments will become apparent to those skilled in the art upon reading the present disclosure, and it is intended that such embodiments be contained within the present inventive methods.

EXAMPLES

Example 1

[00308] Study of rVWF:rFVIII co-administration. The immediate tolerability and safety after single doses of rVWF:rFVIII at 2 IU/kg, 7.5 IU/kg, 20 IU/kg and 50 IU/kg VWF:RCo was assessed as a primary endpoint of the study. Secondary endpoints included PK for VWF:RCo, VWF:CB, VWF:Ag, FVIII and multimeric composition of the VWF. An additional secondary endpoint was a PK comparison with pdVWF//pdFVIII [Cohort 4 (50 IU/kg VWF:RCo)]. See FIG. 1 for a schematic illustration of the study design.

[00309] Recombinant human Von Willebrand Factor (rVWF) was expressed in CHO cells. Propeptide removal was mediated in vitro through exposure of the pro-VWF to recombinant Furin. Fully glycosylated/ABO blood groups glycans were absent. The recombinant VWF has higher specific activity than plasma-derived VWF (pdVWF) and offers the therapeutic flexibility of dosing with or without rFVIII. The rVWF used in this study was not exposed to ADAMTS13, resulting in the presence of ultra-large VWF multimers and intact VWF subunits. ADAMTS13 results in subunit cleavage at TYR^{1605}-MET^{1606}.

[00310] VWF:RCo PK/VWF multimer kinetics showed highly similar PK for VWF:RCo (VWF activity) between rVWF and Humate P (FIG. 2A). Humate P is human derived medium purity Factor VIII concentrates complexed to VWF. A surrogate marker was used for efficacy and dosing recommendations. The data in FIG. 2A show that rVWF shows similar activity to that of plasma derived VW. Progressive loss of high molecular weight rVWF was seen upon exposure to ADAMTS13 (FIG. 2B), showing that rVWF is present in high molecular weight multimers prior to the ADAMTS13 exposure.

[00311] Higher FVIII levels were observed in rVWF patients as compared to Humate (FIG. 3). These data show that rVWF stabilizes endogenous FVIII *in vivo*. There was a difference in effects seen with different VWF:FVIII ratios (1.3:1 vs. ~2.1 VWF/FVIII). These different ratios suggest that less rVWF can be used to stabilize FVIII than is needed when using plasma derived VWF. The study design provided a flexibility of re-dosing with rVWF alone (no rFVIII) after the initial dose.

[00312] Ultra-large molecular weight multimers are present with rVWF – these ultra-large molecular weight multimers rapidly disappear following infusion. ADAMTS13 mediated cleavage fragments were seen in all subjects. The pharmacokinetic profile of VWF:RCo was similar to that of pdVWF. There was sustained stabilization of endogenous FVIII with rVWF which was comparable to that observed with pdVWF. The adverse drug reaction profile with

rVWF was similar to that of pdVWF/pdFVIII, and all related adverse events (AEs) were mild.

[00313] The overall safety and pharmacokinetic profile suggests that rVWF can be used for the treatment and preventing of bleeding episodes at doses comparable to pdVWF/pdFVIII, while enhancing the levels of FVIII as compared to the effect from the use of pdVWF. Without being limited by theory, it is possible that the high proportion of ultra-large multimers (decamers or higher) in the population of rVWF leads to the enhanced stabilization of FVIII seen with rVWF as compared to that by plasma derived VWF.

Example 2

[00314] In-human study evaluating pharmacokinetics demonstrating safety and tolerability in severe Von Willebrand Disease (VWD). This study compared the effects of pdVWF and rVWF in patients with type 3 VWD or severe Type 1 VWD.

[00315] The pdVWF used in this study was synthesized in endothelial cells and megakaryocytes. Post-translational modification of propeptide removal occurred intracellularly during passage of the protein to the Golgi and post-Golgi compartments. Glycosylation/ABO blood group glycans were present. The pdVWF consisted of VWF subunits that had been exposed to plasma ADAMTS13. There were no ultra-large VWF multimers in the pdVWF population and subunits were cleaved at TYR^{1605}-MET^{1606}. pdVWF concentrates contained other proteins, including ADAMTS13 and hemagglutins.

[00316] The rVWF used in this study was expressed in CHO cells. Propeptide removal was mediated in vitro through exposure of the pro-VWF to recombinant Furin. Fully glycosylated/ABO blood group glycans were absent. The rVWF was not exposed to ADAMTS13. The subunits of the rVWF were intact and ultra-large VWF multimers were present. Subunit cleavage did occur upon ADAMTS13 exposure. The rVWF showed higher specific activity than pdVWF.

[00317] The inclusion criteria for this study were:

- Type 3 VWD (VWF:Ag ≤ 3 IU/dL)
- Severe Type 1 VWD (VWF:RCo ≤ 10 IU/dL and FVIII:C < 20 IU/dL
- 18 to 60 years of age
- Previous coagulation factor replacement therapy (≥25 ED)
- Non-bleeding state

[00318] The exclusion criteria for this study were:

- Other coagulation disorders
- History of VWF and/or FVIII inhibitors

- Cardiovascular disease
- Medical history of thromboembolic event
- Medical history of other immunological disorders

[00319] The immediate tolerability and safety after single doses of rVWF:rFVIII at 2 IU/kg, 7.5 IU/kg, 20 IU/kg and 50 IU/kg VWF:RCo was assessed as a primary endpoint of this study. Secondary endpoints included PK for VWF:RCo, VWF:CB, VWF:Ag, FVIII and multimeric composition of the VWF. An additional secondary endpoint was a PK comparison with pdVWF//pdFVIII [Cohort 4 (50 IU/kg VWF:RCo)]. Patient demographics for this study are shown in FIG. 4. Pharmacokinetic analysis of Cohort 4A (Type 3 VWD) VWF:RCo/VWF:Ag is shown in FIG. 5. These data show that the total activities of rVWF were comparable to those of pdVWF. Progressive loss of high molecular weight rVWF was seen upon exposure to ADAMTS13 (FIG. 6). Further pharmacokinetic analysis of Cohort 4A (Type 3 VWD) FVIII:C is shown in FIG. 7. The data in FIG. 7 suggests that rVWF was more effective at stabilizing the *in vivo* activity of FVIII than pdVWF, resulting in increased FVIII procoagulant activity after treatment with rVWF/rVWF as compared to treatment with pdVWF/pdFVIII.

[00320] Ultra-large molecular weight multimers were present in rVWF and rapidly disappeared following infusion. ADAMTS13 mediated cleavage fragments were seen in all subjects. The pharmacokinetic profile of VWF:RCo was similar to that of pdVWF. There was sustained stabilization of endogenous FVIII that was comparable to that observed with pdVWF. The adverse drug reaction profile was similar to that of pdVWF/pdFVIII, and all related adverse events were mild.

[00321] The overall safety and pharmacokinetic profile suggests that rVWF can be used for the treatment and preventing of bleeding episodes at doses comparable to pdVWF/pdFVIII.

Example 3

[00322] Clinical study of rVWF:rFVIII complex. This study was a pharmacokinetics, immediate safety and tolerability study in congenital von Willebrand disease Type 3. FIG. 9 shows the rVWF PK parameters for three patients in the study.

[00323] FIG. 10 shows PK data for Patient 1. There was a good correlation between VWF:RCo and VWF:CBA. Activities were measurable up to 12 hours (both were below the limit of quantification at 24 hours). VWF:Ag was still measurable at 96 hours. Endogenous FVIII activity increased to a maximum of 0.13 IU/mL.

[00324] FIG. 11 shows PK data in Patient 2. As with Patient 1, there was a good correlation between VWF:RCo and VWF:CBA. Both activities were measurable (albeit at the limit of

quantification) up to 12 hours. VWF:Ag was still measurable at 72 hours (the 96 hour sample was not tested). Endogenous FVIII activity increased to a maximum of 0.18 IU/mL for this patient.

[00325] FIG. 12 shows PK data in Patient 3. VWF:RCo activity was measurable up to 24 hours (albeit at the limit of quantification), while VWF:CBA was below LoQ at 24 hours. VWF:Ag was still measurable up to 48 hours. Endogenous FVIII activity increased to a maximum of 0.13 IU/mL for this patient.

[00326] FIG. 13 shows data comparing the VWF parameters and FVIII activity for the three patients. There was a good correlation see in all three patients for all parameters tested (VWF:RCo, VWF:CBA, VWF:Ag, and FVII:Chr activity).

[00327] rVWF had ~ 100% recovery in all patients. The three patients showed slightly different rVWF PK. For VWF antigen, there was a maximum 0.06 IU/ml 30 minutes after application of 2 IU VWF:RCo/kg followed by a steady decline. For FVIII activity, the baseline FVIII activity increased to approximately 0.1 IU/ml 15 minutes after application of rVWF+rFVIII. Thereafter, activity further increased to 0.16 IU/ml, reached a plateau at 3-6 hours that stayed up to 28 hours followed by a steady decline. The delayed increase in FVIII indicates that the secondary rise was induced by rVWF.

Example 4

[00328] <u>rVWF study – FVII PK Assessment and TA assessment.</u> FIG. 14 shows data for FVIII activity across all cohorts. FIG. 15 shows data from Cohort 1 (2 IU/kg VWF:RCo/1.5 IU/kg FVIII). There was good correlation for all three patients in this cohort for all parameters tested.

[00329] FIG. 15 shows data from Cohort 2 (7.5 IU/kg VWF:RCo/5.8 IU/kg FVIII). FIG. 16 shows the pharmacokinetics data for this cohort for FVIII:C.

[00330] FIG. 17 shows data for Cohort 3 (20 IU/kg VWF:RCo/15.4 IU/kg FVIII). These data show a comparison of plasma parameters for VWF and FVIII. FIG. 18 shows the pharmacokinetics data for this cohort for FVIII:C.

[00331] FIG. 19 shows data for Cohort 4 (50 IU/kg VWF:RCo). FVIII dosing was 38.5 IU/kg rFVIII or 25 IU/kg pdFVIII. These data show that the parameters for rVWF are similar to those for pdVWF (Haemate), but that rVWF is more effective at stabilizing FVIII activity, resulting in an increase seen in FVIII activity as compared to that seen with pdVWF. FIG. 20 shows a summary of pharmacokinetics data for this cohort for FVIII:C. As can be seen in these data, the median and mean $T_{1/2}$ was increased for rVWF/FVIII as compared to

pdVWF/FVIII, suggesting that rVWF is more effective at stabilizing *in vivo* FVIII than is pdVWF resulting in increased half-life.

Example 5

[00332] Clinical study of rVWF effect on rFVIII half-life in the treatment of hemophilia A. This study evaluates the immediate tolerability and safety of rVWF after single doses of 50 IU/kg rFVIII (Advate) alone or in combination with rVWF at 10 or 50 IU/kg von Willebrand Factor:Ristocetin cofactor activity (VWF:RCo). This study also evaluates the pharmacokinetics after single doses of 50 IU/kg rFVIII (Advate) alone or in combination with rVWF at 10 or 50 IU/kg (VWF:RCo).

[00333] The population for the study is selected using the following criteria:

[00334] Inclusion criteria:

- Severe Hemophilia A (FVIII:C <1 IU/dL)
- 18 to 60 years of age
- Previous coagulation factor replacement therapy (≥150 ED)
- Non-bleeding state

[00335] Exclusion criteria:

- Other coagulation disorders
- History of VWF and/or FVIII inhibitors
- Cardiovascular disease
- Medical history of thromboembolic event
- Medical history of other immunological disorders (exceptions)

[00336] Subject participation is for 16 weeks with an overall study duration of 7 months.

[00337] The design of the study is a multicenter, uncontrolled, non randomized, open-label clinical study to assess safety, immediate tolerability and pharmacokinetics of rFVIII:rVWF in subjects with hereditary severe hemophilia A (FVIII:C <1%).

[00338] Each subject (N = 14) participating in the triple-period PK analysis receives in a non randomized fashion 50 IU/kg rFVIII (Advate) with no, 10 IU/kg VWF:RCo, or 50 IU/kg VWF:RCo rVWF, and is expected to participate for approximately 16 weeks.

[00339] The intra-individual pharmacokinetics are spaced at 5-14 days apart to ensure a "wash-out" period of at least 5 days and a timely completion of the study. Safety analyses are performed separately once 6 subjects have been dosed with 10 IU/KG VWF:RCo rVWF and once 6 subjects have been dosed with 50 IU/KG VWF:RCo rVWF.

[00340] Subjects should not have received cryoprecipitate, fresh frozen plasma or other drugs interfering with VWF or FVIII PK for at least 5 days before either of the infusions.

[00341] Dosage of rVWF is escalated when immediate tolerability and safety are demonstrated after a minimum of 6 subjects treated with 10 IU VWF:RCo rVWF. The effects of the investigational product on vital signs, hematology, and clinical chemistry parameters will determine short-term safety.

[00342] Samples for the determination of levels of FVIII activity (FVIII:C), VWF antigen (VWF:Ag), VWF activity (VWF:RCo), VWF:CB, (and VWF multimer distribution) are taken pre-infusion (within 30 minutes prior to the start of the infusion) and after the end of the infusion at 15 minutes (±5 minutes), 30 minutes (±5 minutes), 1 hour (±5 minutes), 3 hours (±10 minutes), 6 hours (±10 minutes), 9 hours (±15 minutes), 24 hours (±2 hours) and 48 hours (±2 hours), 72 hours (±2 hours), 96 hours (±2 hours), and 120 hours (±2 hours) (or at least every 24 hours thereafter until FVIII drops below <1%). FVIII activity is determined using both the chromogenic and one-stage aPTT-based assay methods performed at the local and central laboratory.

[00343] The effects of each infusion on vital signs and other symptoms indicative of an adverse event (AE), hematology, and clinical chemistry parameters are used as indicators of short-term safety. Vital signs, clinical chemistry, and hematology parameters are assessed pre-infusion and until 120 hours post-infusion. The occurrence of AEs are continuously monitored for up to 2 hours post-infusion (rVWF treated subjects) and at various time points during the follow-up period.

[00344] The presence of inhibitors to FVIII and VWF are assessed before investigational product infusion and at the study completion visit.

[00345] If at any time a serious AE related to the investigational product occurs, an independent data monitoring committee (DMC) will advise whether to continue the study.

[00346] Pharmacokinetic primary endpoints for the study include: AUC_{0}-∞/Dose (area under the plasma concentration/time curve from time 0 to infinity); $AUC_{0\text{-}96h}$/Dose (area under the plasma concentration/time curve from time 0 to 96 hours); mean residence time (MRT); clearance (CL); T1/2 (elimination phase half-life); Volume of distribution at steady state (Vss) of VWF:RCo, VWF:Ag ,VWF:CB, and FVIII.

[00347] Analysis for pharmacokinetic primary endpoints include $AUC_{0\text{-}96h}$/Dose, $AUC_{0\text{-}\infty}$/Dose, MRT, CL, $T_{1/2}$ and Vss summarized per treatment group (50 IU/kg rFVIII (Advate) alone, 50 IU/kg rFVIII (Advate) premixed with rVWF at 10 IU/kg VWF:RCo, 50 IU/kg rFVIII (Advate) premixed with rVWF at 50 IU/kg VWF:RCo) by median and two-sided 95% CIs for the median, mean, standard deviation, coefficient of variation and geometric mean. Descriptive statistics (medians and ranges) are used to summarize VWF:RCo, VWF:Ag, VWF:CB and FVIII levels over time.

[00348] Safety primary endpoint includes: occurrence of treatment related AEs. Analysis of the safety primary endpoint includes the number and percentage of subjects who experience a treatment related AE. The number and rate of treatment related AEs are tabulated.

[00349] Pharmacokinetic secondary endpoints include: In vivo recovery (IVR) and incremental recovery (IR) of FVIII, VWF:RCo, VWF:Ag and VWF:CB. Analysis of pharmacokinetic secondary endpoints includes determining IVR and IR of FVIII, VWF:RCo, VWF:Ag and VWF:CB by subject and summarizing by medians and ranges.

[00350] Safety secondary endpoints include: development of inhibitory and total binding anti-VWF antibodies, development of inhibitory antibodies to FVIII, development of antibodies to Chinese hamster ovary (CHO) proteins, mouse immunoglobulin G (IgG) and rFurin, occurrence of thrombotic events.

[00351] Safety secondary endpoints are analyzed by tabulating the number of subjects who experience an SAE and the number of SAEs . In addition, the number of subjects who experience a treatment related AE and the number and rate of treatment related AEs are subcategorized for thrombotic events, inhibitory and total binding anti-VWF antibodies, inhibitory antibodies to FVIII, antibodies to Chinese hamster ovary (CHO) proteins, antibodies to mouse immunoglobulin G (IgG) and antibodies to rFurin.

[00352] A listing of all AEs are presented by subject identifier, age, sex, preferred term and reported term of the AE, duration, severity, seriousness, action taken, outcome, causality assessment, onset date, stop date and medication or non-drug therapy to treat the AE. An overview table for AEs are provided, presenting the number of AEs, the number of subjects with AEs and the corresponding percent of subjects in total and by seriousness and relationship to treatment. An additional summary table presents the total number of (mild, moderate, severe) AEs by system organ class and preferred term with relationship to treatment.

[00353] No formal sample size calculation has been conducted for this study.

[00354] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

CLAIMS

1. Use of a recombinant Von Willebrand Factor (rVWF) and recombinant FVIII (rFVIII) in the manufacture of a medicament for treating Von Willebrand Disease,

wherein the rVWF is a high molecular weight VWF multimer composition comprising at least 20% VWF decamers or higher order multimers, wherein the rVWF is matured in vitro by treatment with Furin, wherein the ratio of rFVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCO) to be administered to the subject is between 2:1 and 1:4, and wherein the rVWF and rFVIII are to be administered together in an initial dose and then subsequent re-dosing is conducted with rVWF alone.

2. The use according to claim 1, wherein the rVWF has a specific activity of about 20-150 mU/µg, or about 30 to 120 mU/µg.

3. The use according to any one of claims 1 to 2, wherein the high molecular weight VWF multimer composition comprises at least 30% VWF decamers or higher order multimers, at least 40% VWF decamers or higher order multimers, at least 50% VWF decamers or higher order multimers, more preferably wherein the high molecular weight VWF multimer composition comprises at least 60% VWF decamers or higher order multimers, most preferably wherein the high molecular weight VWF multimer composition comprises at least 70% VWF decamers or higher order multimers.

4. The use according to any one of claims 1 to 3, wherein the subject is to be administered between 1.0 IU/kg VWF:RCo and 150 IU/kg VWF:RCo per dose, preferably wherein the subject is to be administered between 2 IU/kg VWF:RCo and 50 IU/kg VWF:RCo per dose, more preferred wherein the subject is to be administered between 5 IU/kg VWF:RCo and 40 IU/kg VWF:RCo per dose, very preferred wherein the subject is to be administered between 10 IU/kg VWF:RCo and 20 IU/kg VWF:RCo per dose.

5. The use according to any one of claims 1 to 4, wherein the rVWF is to be administered no more than once daily, no more than once every other day, no more than once every third day, no more than once every fourth day, no more than once every fifth day, no more than twice a week, no more than once a week, no more than once every two weeks, or no more than once a month.

6. The use according to any one of claims 1 to 5, wherein the rVWF is to be administered in multiple administrations.

7. The use according to any one of claims 1 to 6, wherein the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) to be administered is between 3:2 and 1:3, preferably wherein the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) to be administered is between 1:1 and 1:2, more preferably wherein the ratio of FVIII procoagulant activity (IU FVIII:C) to rVWF Ristocetin cofactor activity (IU rVWF:RCo) to be administered is about 3:4.

8. The use according to any one of claims 1 to 7, wherein the rVWF is produced through expression in a Chinese Hamster Ovary (CHO cell culture), preferably wherein the rFVIII and rVWF are produced through expression in the same cell culture.

9. The use according to any one of claims 1 to 8, wherein the rVWF and rFVIII are to be administered together in a single composition.

10. The use according to any one of claims 1 to 9, wherein the high molecular weight VWF multimer composition maintains the at least 20% VWF decamers or higher order multimers for at least 3 hours post-administration.

11. The use according to any one of claims 1 to 10, wherein the Factor VIII half-life is extended by at least 12 hours, preferably wherein the Factor VIII half-life is extended by at least 24 hours, more preferably wherein the Factor VIII half-life is extended by at least 36 hours, or most preferably wherein the Factor VIII half-life is extended by at least 48 or 72 hours.

12. The use according to any one of claims 1 to 11, wherein the FVIII half-life is at least 1.5 times higher as compared to FVIII half-life of plasma derived VWF when administered in said subject.

13. The use according to any one of claims 1 to 12, for treating Von Willebrand Disease Type 3.

TREATMENT OF COAGULATION DISEASE BY ADMINISTRATION OF RECOMBINANT VWF

ABSTRACT OF THE DISCLOSURE

The present invention provides methods of treating coagulation disease, including hemophilia and von Willebrand disease by administering recombinant von Willebrand Factor alone or in combination with Factor VIII.

Fig. 3