WHAT IS CLAIMED IS:

1. A method of administering Factor VIII to a human subject in need thereof, comprising administering to the subject a therapeutic dose of a chimeric polypeptide comprising a Factor VIII portion and a second portion at a dosing interval at least about one and one-half times longer than the dosing interval required for an equivalent dose of a polypeptide consisting of said Factor VIII portion.wherein said Factor VIII portion comprises processed Factor VIII, which has two chains, a first chain comprising a heavy chain and a second chain comprising a light chain, wherein said first chain and said second chain are associated by a metal bond.

2. The method of claim 1, wherein at least about 50%, about 60%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 99% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

3. The method of claim 2, wherein about 100% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

4. The method of any one of claims 1 or 2, wherein said Factor VIII portion comprises single chain Factor VIII, which is a single chain.

5. The method of claim 4, wherein said single chain Factor VIII contains an intact intracellular processing site.

6. The method of claim 5, wherein said intracellular processing site corresponds to Arginine at residue 1648 of full-length Factor VIII (Arginine residue 1667 of amino acids 20-2351 of SEQ ID NO: 6).

7. The method of any one of claims 3-6, wherein at least about 1%, about 5%, about 10%, about 15%, about 20%, or about 25% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII.

8. The method of claim 7, wherein about 25% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 75% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

9. The method of claim 7, wherein about 20% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 80% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

10. The method of claim 7, wherein about 15% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 85% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

11. The method of claim 7, wherein about 10% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 90% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

12. The method of claim 7, wherein about 5% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 95% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

13. The method of claim 7, wherein about 1% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 99% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

14. The method of any one of claims 3-6, wherein at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, or about 99% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII.

15. The method of claim 14, wherein about 30% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 70% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

16. The method of claim 14, wherein about 40% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 60% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

17. The method of claim 14, wherein about 50% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 50% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

18. The method of claim 14, wherein about 60% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 40% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

19. The method of claim 14, wherein about 70% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 30% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

20. The method of claim 14, wherein about 80% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 20% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

21. The method of claim 14, wherein about 85% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 15% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

22. The method of claim 14, wherein about 90% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 10% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

23. The method of claim 14, wherein about 95% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 5% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

24. The method of claim 14, wherein about 99% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 1% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

25. The method of claim 14, wherein about 100% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII.

26. The method of any one of claims 4-25, wherein the chimeric polypeptide comprising single chain Factor VIII has Factor VIII activity at a level comparable to a chimeric polypeptide consisting of two Fc portions and processed Factor VIII, which is fused to one of the two Fc portions, when the Factor VIII activity is measured in vitro by a chromogenic assay.

27. The method of any one of claims 4-26, wherein said chimeric polypeptide comprising single chain Factor VIII has Factor VIII activity in vivo comparable to a chimeric polypeptide consisting of two Fc portions and processed Factor VIII, which is fused to one of the two Fc portions.

28. The method of any one of claims 4-27, wherein said chimeric polypeptide comprising single chain Factor VIII has a Factor Xa generation rate comparable to a chimeric polypeptide consisting of two Fc portions and processed Factor VIII, which is fused to one of the two Fc portions.

29. The method of any one of claims 4-28, wherein said single chain Factor VIII in the chimeric polypeptide is inactivated by activated Protein C at a level comparable to processed Factor VIII in a chimeric polypeptide consisting of two Fc portions and processed Factor VIII.

30. The method of any one of claims 4-29, wherein said single chain Factor VIII in the chimeric polypeptide has a Factor IXa interaction rate comparable to processed Factor VIII in a chimeric polypeptide consisting of two Fc portions and processed Factor VIII.

31. The method of any one of claims 4-30, wherein said single chain Factor VIII in the chimeric polypeptide binds to von Willebrand Factor at a level comparable to processed Factor VIII in a chimeric polypeptide consisting of two Fc portions and processed Factor VIII.

32. The method of any one of claims 1-31, wherein said chimeric polypeptide has one or more characteristics selected from the group consisting of:

an ability to interact with phospholipid vesicles comparable to the ability of a polypeptide consisting of said Factor VIII portion;

an ability to form a Xase complex that activates Factor X comparable to the ability of a polypeptide consisting of said Factor VIII portion;

an ability to be activated by alpha-thrombin within five minutes comparable to the ability of a polypeptide consisting of said Factor VIII portion; and

an ability to interact with Factor IXa comparable to the ability of a polypeptide consisting of said Factor VIII portion.

33. The method of claim 32, wherein said chimeric polypeptide has one or more characteristics selected from the group consisting of:

forms a Xase complex that activates Factor X at a Km within about one, about one and one half, or about two standard deviations of the Km of a polypeptide consisting of said Factor VIII portion, wherein Km is measured as a function of Factor X concentration;

forms a Xase complex that activates Factor X at a Vmax within about one, about one and one half, or about two standard deviations of the Vmax of a polypeptide consisting of said Factor VIII portion, wherein Vmax is measured as a function of Factor X concentration;

forms a Xase complex that activates Factor X at a Kd within about one, about one and one half, or about two standard deviations of the Kd of a polypeptide consisting of said Factor VIII portion, wherein Kd is measured as a function of Factor IXa concentration; and

forms a Xase complex that activates Factor X at a Vmax within about one, about one and one half, or about two standard deviations of the Vmax of a polypeptide consisting of said Factor VIII portion, wherein Vmax is measured as a function of Factor IXa concentration.

34. The method of any of claims 1-33, wherein said dose has a mean incremental recovery (K-Value) (activity; observed) greater that 1.38 IU/dL per IU/kg.

35. The method of any of claims 34, wherein said dose has a mean incremental recovery (K-Value) (activity; observed) of at least about 1.5, at least about 1.85, or at least about 2.46 IU/dL per IU/kg.

36. The method of any of claims 1-35, wherein said chimeric polypeptide exhibits one or more pharmacokinetic parameters, in said patient population or in said subject, selected from the group consisting of:

a C_{max}_OBS in said subject administered with 25 IU/kg of the chimeric polypeptide is comparable to the C_{max}_OBS in a subject administered with 25 IU/kg of a polypeptide consisting of the full-length, mature Factor VIII when measured by a one stage (aPTT) assay or a two stage (chromogenic) assay;

a C_{max}_OBS in said subject of about 60.5 IU/dL as measured by a one stage (aPTT) assay when about 25 IU/kg of the chimeric polypeptide is administered;

a C_{max}_OBS in said subject of about 53.1 – 69 IU/dL as measured by a one stage (aPTT) assay when about 25 IU/kg of the chimeric polypeptide is administered;

a C_{max}_OBS in said subject of about 119 IU/dL as measured by a one stage (aPTT) assay when about 65 IU/kg of the chimeric polypeptide is administered;

a C_{max}_OBS in said subject of about 103 – 136 IU/dL as measured by a one stage (aPTT) assay when about 65 IU/kg of the chimeric polypeptide is administered;

a C_{max}_OBS in said subject of about 76.5 IU/dL as measured by a two stage (chromogenic) assay when about 25 IU/kg of the chimeric polypeptide is administered;

a C_{max}_OBS in said subject of about 64.9 – 90.1 IU/dL as measured by a two stage (chromogenic) assay when about 25 IU/kg of the chimeric polypeptide is administered;

a C_{max}_OBS in said subject of about 182 IU/dL as measured by a two stage (chromogenic) assay when about 65 IU/kg of the chimeric polypeptide is administered;

a C_{max}_OBS in said subject of about 146 – 227 IU/dL as measured by a two stage (chromogenic) assay when about 65 IU/kg of the chimeric polypeptide is administered;

a mean clearance (CL) (activity) in said patient population of about 2.33 ± 1.08 mL/hour/kg or less;

a mean clearance (CL) (activity) in said patient population of about 1.8-2.69 mL/hour/kg;

a mean clearance (CL) (activity) in said patient population that is about 65% of the clearance of a polypeptide consisting of said Factor VIII portion;

a clearance (CL) (activity) in said subject of about 1.22 - 5.19 mL/hour/kg;

a clearance (CL) (activity) in said subject is 0.51, 0.52, 0.53, 0.54, 0.55, 0.56, 0.57, 0.58, 0.59, 0.60, 0.61, 0.62, 0.63, 0.64, 0.65, 0.66, 0.67, 0.68, 0.69, or 0.70 times lower than the clearance in a subject administered with the same amount of a polypeptide consisting of the full-length, mature Factor VIII when measured by a one stage (aPTT) assay or a two stage (chromogenic) assay;

a clearance (CL) (activity) in said subject of about 1.68 mL/hour/kg as measured by a one stage (aPTT) assay when about 25 IU/kg of the chimeric polypeptide is administered;

a clearance (CL) (activity) in said subject of about 1.31 – 2.15 mL/hour/kg as measured by a one stage (aPTT) assay when about 25 IU/kg of the chimeric polypeptide is administered;

a clearance (CL) (activity) in said subject of about 2.32 mL/hour/kg as measured by a one stage (aPTT) assay when about 65 IU/kg of the chimeric polypeptide is administered;

a clearance (CL) (activity) in said subject of about 1.64 – 3.29 mL/hour/kg as measured by oa ne stage (aPTT) assay when about 65 IU/kg of the chimeric polypeptide is administered;

a clearance (CL) (activity) in said subject of about 1.49 mL/hour/kg as measured by a two stage (chromogenic) assay when about 25 IU/kg of the chimeric polypeptide is administered;

a clearance (CL) (activity) in said subject of about 1.16 – 1.92 mL/hour/kg as measured by a two stage (chromogenic) assay when about 25 IU/kg of the chimeric polypeptide is administered;

a clearance (CL) (activity) in said subject of about 1.52 mL/hour/kg as measured by a two stage (chromogenic) assay when about 65 IU/kg of the chimeric polypeptide is administered;

a clearance (CL) (activity) in said subject of about 1.05-2.20 mL/hour/kg as measured by a two stage (chromogenic) assay when about 65 IU/kg of the chimeric polypeptide is administered;

a mean mean residence time (MRT) (activity) in said patient population of at least about 26.3 ± 8.33 hours;

a mean MRT (activity) in said patient population of about 25.9 - 26.5 hours;

a mean MRT (activity) in said patent population that is about 1.5 fold longer than the mean MRT of a polypeptide consisting of said Factor VIII portion;

a mean residence time (MRT) (activity) in said subject of about 14 – 41.3 hours;

a MRT in said subject is at least 1.50, 1.51, 1.52, 1.53, 1.54, 1.55, 1.56, 1.57, 1.58, 1.59, 1.60, 1.61, 1.62, 1.63, 1.64, 1.65, 1.66, 1.67, 1.68, 1.69, 1.70, 1.71, 1.72, 1.73, 1.74, 1.75, 1.76, 1.77, 1.78, 1.79,

1.80, 1.81, 1.82, 1.83, 1.84, 1.85, 1.86, 1.87, 1.88, 1.89, or 1.90 times higher than the MRT in a subject administered with the same amount of a polypeptide consisting of the full-length, mature Factor VIII when meansured by a one stage (aPTT) assay or a two stage (chromogenic) assay;

a MRT (activity) in said subject of about 27 hours as meansured by a one stage (aPTT) assay;

a MRT (activity) in said subject of about 20.6 – 35.3 hours as meansured by a one stage (aPTT) assay;

a MRT (activity) in said subject of about 23.9 – 28.5 hours as measured by a two stage (chromogenic) assay;

a MRT (activity) in said subject of about 19.8 – 28.9 hours as measured by a two stage (chromogenic) assay;

a MRT (activity) in said subject of about 20.5 – 39.6 hours as measured by a two stage (chromogenic) assay;

a mean t1/2beta (activity) in said patient population of about 18.3 ± 5.79 hours;

a mean t1/2beta (activity)in said patient population that is about 18 - 18.4 hours;

a mean t1/2beta (activity) in said patient population that is about 1.5 fold longer than the mean t1/2beta of a polypeptide consisting of said Factor VIII portion;

a t1/2beta (activity) in said subject of about 11 – 26.4 hours;

a t1/2beta (activity) in said subject that is at least 1.50, 1.51, 1.52, 1.53, 1.54, 1.55, 1.56, 1.57, 1.58, 1.59, 1.60, 1.61, 1.62, 1.63, 1.64, 1.65, 1.66, 1.67, 1.68, 1.69, 1.70, 1.71, 1.72, 1.73, 1.74, 1.75, 1.76, 1.77, 1.78, 1.79, 1.80, 1.81, 1.82, 1.83, 1.84, 1.85, 1.86, or 1.87 times higher than the t1/2beta (activity) in a subject administered with the same amount of a polypeptide consisting of the full-length, mature Factor VIII when measured by a one stage (aPTT) assay or a two stage (chromogenic) assay;

a t1/2beta (activity) in said subject of about 18.8 hours as measured by a one stage (aPTT) assay;

a t1/2beta (activity) in said subject of about 14.3 – 24.5 hours as measured by a one stage (aPTT) assay;

a t1/2beta (activity) in said subject of about 16.7 hours as measured by a two stage (chromogenic) assay;

a t1/2beta (activity) in said subject of about 13.8 – 20.1 hours as measured by a two stage (chromogenic) assay;

a t1/2beta (activity) in said subject of about 19.8 hours as measured by a two stage (chromogenic) assay;

a t1/2beta (activity) in said subject of about 14.3 – 27.5 hours as measured by a two stage (chromogenic) assay;

a mean incremental recovery (K value) (activity; observed) in said patient population of about 2.01 ± 0.44 IU/dL per IU/kg;

a mean incremental recovery (K value) (activity; observed) in said patient population of about 1.85 - 2.46 IU/dL per IU/kg;

a mean incremental recovery (K value) (activity; observed) in said patient population that is about 90 % of the mean incremental recovery of a polypeptide consisting of said Factor VIII portion;

an incremental recovery (K value) (activity; observed) in said subject of about 1.38 - 2.88 IU/dL per IU/kg;

an incremental recovery in said subject that is comparable to the Incremental Recovery in a subject administered with a polypeptide consisting of the full-length, mature Factor VIII when measured by a one stage (aPTT) assay or a two stage (chromogenic) assay;

an incremental recovery in said subject of about 2.44 IU/dL per IU/kg as measured by a one stage (aPTT) assay when about 25 IU/kg of the chimeric polypeptide is administered;

an incremental recovery in said subject of about 2.12 – 2.81 IU/dL per IU/kg as measured by a one stage (aPTT) assay when about 25 IU/kg of the chimeric polypeptide is administered;

an incremental recovery in said subject of about 1.83 IU/dL per IU/kg as measured by a one stage (aPTT) assay when about 65 IU/kg of the chimeric polypeptide is administered;

an incremental recovery in said subject of about 1.59 – 2.10 IU/dL per IU/kg as measured by a one stage (aPTT) assay when about 65 IU/kg of the chimeric polypeptide is administered;

an incremental recovery in said subject of about 3.09 IU/dL per IU/kg as measured by a two stage (chromogenic) assay when about 25 IU/kg of the chimeric polypeptide is administered;

an incremental recovery in said subject of about 2.80 IU/dL per IU/kg as measured by a two stage (chromogenic) assay when about 65 IU/kg of the chimeric polypeptide is administered;

an incremental recovery in said subject of about 2.61-3.66 IU/dL per IU/kg as measured by a two stage (chromogenic) assay when about 25 IU/kg of the chimeric polypeptide is administered; and

an incremental recovery in said subject of about 2.24-3.50 IU/dL per IU/kg as measured by a two stage (chromogenic) assay when about 65 IU/kg of the chimeric polypeptide is administered;

a mean Vss (activity) in said patient population of about 55.1 ± 12.3 mL/kg;

a mean Vss (activity) in said patient population of about 45.3 - 56.1 mL/kg;

a Vss (activity) in said subject of about 37.7 - 79.4 mL/kg;

a Vss (activity) in said subject that is comparable to the Vss (activity) in a subject administered with the same amount of a polypeptide consisting of the full-length, mature Factor VIII when measured by a one stage (aPTT) assay or a two stage (chromogenic) assay;

a Vss (activity) in said subject of about 45.5 mL/kg as measured by a one stage (aPTT) assay when about 25 IU/kg of the chimeric polypeptide is administered;

a Vss (activity) in said subject of about 39.3 – 52.5 mL/kg as measured by a one stage (aPTT) assay when about 25 IU/kg of the chimeric polypeptide is administered;

a Vss (activity) in said subject of about 62.8 mL/kg as measured by a one stage (aPTT) assay when about 65 IU/kg of the chimeric polypeptide is administered;

a Vss (activity) in said subject of about 55.2 – 71.5 mL/kg as measured by a one stage (aPTT) assay when about 65 IU/kg of the chimeric polypeptide is administered;

a Vss (activity) in said subject of about 35.9 mL/kg as measured by a two stage (chromogenic) assay when about 25 IU/kg of the chimeric polypeptide is administered;

a Vss (activity) in said subject of about 30.4-42.3 mL/kg as measured by a two stage (chromogenic) assay when about 25 IU/kg of the chimeric polypeptide is administered;

a Vss (activity) in said subject of about 43.4 mL/kg as measured by a two stage (chromogenic) assay when about 65 IU/kg of the chimeric polypeptide is administered;

a Vss (activity) in said subject of about 38.2-49.2 mL/kg as measured by a two stage (chromogenic) assay when about 65 IU/kg of the chimeric polypeptide is administered;

a mean AUC/dose (activity) in said patient population of about 49.9 ± 18.2 IU*h/dL per IU/kg;

a mean AUC/dose (activity) in said patient population of about 44.8 - 57.6 IU*h/dL per IU/kg; and

an AUC/dose in said subject of about 19.2 - 81.7 IU*h/dL per IU/kg;

an AUC_{INF} in said subject that is at least 1.45, 1.46, 1.47, 1.48, 1.49, 1.50, 1.51, 1.52, 1.53, 1.54, 1.55, 1.56, 1.57, 1.58, 1.59, 1.60, 1.61, 1.62, 1.63, 1.64, 1.65, 1.66, 1.67, 1.68, 1.69, 1.70, 1.71, 1.72, 1.73, 1.74, 1.75, 1.76, 1.77, 1.78, 1.79, 1.80, 1.81, 1.82, 1.83, 1.84, 1.85, 1.86, 1.87, 1.88, 1.89, 1.90 times higher than the AUC_{INF} in a subject administered with the same amount of a polypeptide consisting of the full-length, mature Factor VIII when measured by a one stage (aPTT) assay or a two stage (chromogenic) assay;

an AUC_{INF} in said subject of about 1440 ± 316 hr*IU/dL per IU/kg as measured by a one stage (aPTT) assay when about 25 IU/kg of the chimeric polypeptide is administered;

an AUC_{INF} in said subject of about 1160 - 1880 hr*IU/dL per IU/kg as measured by a one stage (aPTT) assay when about 25 IU/kg of the chimeric polypeptide is administered;

an AUC_{INF} in said subject of about 1480 hr*IU/dL per IU/kg as measured by a one stage (aPTT) assay when about 25 IU/kg of the chimeric polypeptide is administered;

an AUC_{INF} in said subject of about 2910 ± 1320 hr*IU/dL per IU/kg as measured by a one stage (aPTT) assay when about 65 IU/kg of the chimeric polypeptide is administered;

an AUC_{INF} in said subject of about 1980 - 3970 hr*IU/dL per IU/kg as measured by a one stage (aPTT) assay when about 65 IU/kg of the chimeric polypeptide is administered;

an AUC_{INF} in said subject of about 2800 hr*IU/dL per IU/kg as measured by a one stage (aPTT) assay when about 65 IU/kg of the chimeric polypeptide is administered;

an AUC_{INF} in said subject of about 1660 hr*IU/dL per IU/kg as measured by a two stage (chromogenic) assay when about 25 IU/kg of the chimeric polypeptide is administered;

an AUC_{INF} in said subject of about 1300 - 2120 hr*IU/dL per IU/kg as measured by a two stage (chromogenic) assay when about 25 IU/kg of the chimeric polypeptide is administered;

an AUC_{INF} in said subject of about 4280 hr*IU/dL per IU/kg as measured by a two stage (chromogenic) assay when about 65 IU/kg of the chimeric polypeptide is administered;

an AUC_{INF} in said subject of about 2960 - 6190 hr*IU/dL per IU/kg as measured by a two stage (chromogenic) assay when about 65 IU/kg of the chimeric polypeptide is administered.

37. The method of any of claims 1-36, wherein the therapeutic dose is about 10 to about 150, 100-110, 110-120, 120-130, 130-140, 140-150, 110, 115, 120, 125, 130, 135, 140, 145, or 150 IU/kg.

38. The method of any of claims 1-37, wherein the dosing interval is one and one-half to 5, one and one-half, 2, 3, 4, or 5 days or longer.

39. A composition comprising a chimeric polypeptide having Factor VIII activity, wherein at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100% of said polypeptide comprises a Factor VIII portion, which is single chain Factor VIII, and a second portion, wherein said single chain Factor VIII is at least 90% or 95% identical to a Factor VIII amino acid sequence shown in Table 2 without a signal sequence (amino acids 20 to 1457 of SEQ ID NO:2 or amino acids 20 to 2351 of SEQ ID NO:6).

40. The composition of claim 39, wherein said single chain Factor VIII is identical to a Factor VIII amino acid sequence shown in Table 2 without a signal sequence (amino acids 20 to 1457 of SEQ ID NO:2 or amino acids 20 to 2351 of SEQ ID NO:6).

41. A composition comprising a chimeric polypeptide having Factor VIII activity, wherein at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100% of said polypeptide comprises a Factor VIII portion, which is single chain Factor VIII, and a second portion, wherein said single chain Factor VIII is at least 90% or 95% identical to a Factor VIII amino acid sequence shown in Table 2 with a signal sequence (amino acids 1 to 1457 of SEQ ID NO:2 or amino acids 1 to 2351 of SEQ ID NO:6).

42. The composition of claim 41, wherein said single chain Factor VIII is identical to a Factor VIII amino acid sequence shown in Table 2 with a signal sequence (amino acids 1 to 1457 of SEQ ID NO:2 or amino acids 1 to 2351 of SEQ ID NO:6).

43. The composition of any of claims 39 to 42, wherein said second portion is an Fc region, albumin, a PAS sequence, transferrin or CTP (28 amino acid C-terminal peptide (CTP) of hCG with its 4 O-glycans), polyethylene glycol (PEG), hydroxyethyl starch (HES), albumin binding polypeptide, albumin-binding small molecules, or any combinations thereof.

44. The composition of any of claims 43, wherein said second portion is an Fc region.

45. The composition of claim 44, wherein said Fc is at least 90% or 95% identical to the Fc amino acid sequence shown in Table 2 (amino acids 1458 to 1684 of SEQ ID NO:2 or amino acids 2352 to 2578 of SEQ ID NO:6)

46. The composition of claim 45, wherein said Fc is identical to the Fc amino acid sequence shown in Table 2 (amino acids 1458 to 1684 of SEQ ID NO:2 or amino acids 2352 to 2578 of SEQ ID NO:6).

47. The composition of claim 39, wherein said polypeptide comprises a sequence at least 90% or 95% identical to the Factor VIII and Fc amino acid sequences shown in Table 2A(i) without a signal sequence (amino acids 20 to 1684 of SEQ ID NO:2) or at least 90% or 95% identical to the Factor VIII and Fc amino acid sequence shown in Table 2A(i) with a signal sequence (amino acids 1 to 1684 of SEQ ID NO:2).

48. The composition of claim 39, wherein said polypeptide comprises a sequence identical to the Factor VIII and Fc amino acid sequences shown in Table 2A(i) without a signal sequence (amino acids 20 to 1684 of SEQ ID NO:2) or at least 90% or 95% identical to the Factor VIII and Fc amino acid sequence shown in Table 2A(i) with a signal sequence (amino acids 1 to 1684 of SEQ ID NO:2).

49. The composition of any of claims 39-48, wherein said polypeptide is in the form of a hybrid comprising a second polypeptide, wherein said second polypeptide consists essentially of an Fc.

50. The composition of claim 49, wherein said second polypeptide consists essentially of a sequence at least 90% or 95% identical to the amino acid sequence shown in Table 2A(ii) without a signal sequence (amino acids 21 to 247 of SEQ ID NO:4) or at least 90% or 95% identical to the amino acid sequence shown in Table 2A(ii) with a signal sequence (amino acids 1 to 247 of SEQ ID NO:4).

51. The composition of claim 50, wherein said second polypeptide consists essentially of a sequence identical to the amino acid sequence shown in Table 2A(ii) without a signal sequence (amino acids 21 to 247 of SEQ ID NO:4) or at least 90% or 95% identical to the amino acid sequence shown in Table 2A(ii) with a signal sequence (amino acids 1 to 247 of SEQ ID NO:4).

52. The composition of any of claims 39-51, wherein said polypeptide has a half-life at least one and one-half to six times longer, one and one-half to five times longer, one and one-half to four times longer, one and one-half to three times longer, or one and one-half to two times longer to a polypeptide consisting of said Factor VIII.

53. The composition of any one of claims 39-52, which has one, about one and one half, or about two or more characteristics selected from the group consisting of:

an ability to interact with phospholipid vesicles comparable to the ability of a polypeptide consisting of said Factor VIII portion;

an ability to form a Xase complex that activates Factor X comparable to the ability of a polypeptide consisting of said Factor VIII portion;

an ability to be activated by alpha-thrombin within five minutes comparable to the ability of a polypeptide consisting of said Factor VIII portion; and

an ability to interact with Factor IXa comparable to the ability of a polypeptide consisting of said Factor VIII portion.

54. The composition of any one of claims 39-53, wherein about 70%, about 60%, about 50%, about 40%, about 30%, about 20%, about 10%, about 5%, about 4%, about 3%, about 2%, or about 1% of the Factor VIII portion of said polypeptide is processed Factor VIII.

55. The composition of any one of claims 39-54, wherein said chimeric polypeptide comprising single chain Factor VIII has Factor VIII activity comparable to a chimeric polypeptide consisting of two Fc portions and processed Factor VIII, wherein said processed Factor VIII is fused to one Fc of the two Fc portions, when the Factor VIII is measured in vitro by a chromogenic assay.

56. The composition of any one of claims 39-55, wherein said chimeric polypeptide comprising single chain Factor VIII has a Factor Xa generation rate comparable to processed Factor VIII.

57. The composition of any one of claims 39-56, wherein said chimeric polypeptide comprising single chain Factor VIII has a Factor Xa generation rate comparable to a chimeric polypeptide consisting of two Fc portions and processed Factor VIII, which is fused to one of the two Fc portions.

58. The composition of any one of claims 39-57, wherein said single chain Factor VIII in the chimeric polypeptide has a Factor IXa interaction rate comparable to processed Factor VIII in a chimeric polypeptide consisting of two Fc portions and processed Factor VIII.

59. The composition of any one of claims 39-58, wherein said single chain Factor VIII in the chimeric polypeptide is inactivated by activated Protein C at a level comparable to processed Factor VIII in a chimeric polypeptide consisting of two Fc portions and processed Factor VIII.

60. The composition of any one of claims 39-59, wherein said single chain Factor VIII in the chimeric polypeptide binds to von Willebrand Factor at a level comparable to processed Factor VIII in a chimeric polypeptide consisting of two Fc portions and processed Factor VIII.

61. The composition of any one of claims 39-60, wherein said chimeric polypeptide comprising single chain Factor VIII has Factor VIII activity in vivo comparable to a chimeric polypeptide consisting of two Fc portions and processed Factor VIII, which is fused to one of the two Fc portions.

62. The composition of any one of claims 39-61, wherein about 30% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 70% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

63. The composition of any one of claims 39-61, wherein about 40% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 60% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

64. The composition of any one of claims 39-61, wherein about 50% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 50% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

65. The composition of any one of claims 39-61, wherein about 60% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 40% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

66. The composition of any one of claims 39-61, wherein about 70% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 30% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

67. The composition of any one of claims 39-61, wherein about 80% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 20% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

68. The composition of any one of claims 39-61, wherein about 90% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 10% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

69. The composition of any one of claims 39-61, wherein about 95% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 5% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

70. The composition of any one of claims 39-61, wherein about 99% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII and about 5% of the Factor VIII portion of the chimeric polypeptide is processed Factor VIII.

71. The composition of any one of claims 39-61, wherein about 100% of the Factor VIII portion of the chimeric polypeptide is single chain Factor VIII.

72. A composition of any one of claims 39-71, which is a pharmaceutical composition further comprising an excipient.

73. A method of treating a bleeding condition comprising administering a therapeutically effective amount of the composition of any one of claims 39-72.

74. The method of claim 73, wherein said treatment is prophylactic treatment.

75. The method of claim 73, wherein said treatment is on-demand treatment.

76. The method of any one of claims 73-75, wherein said bleeding condition is selected from the group consisting of a bleeding coagulation disorder, hemarthrosis, muscle bleed, oral bleed, hemorrhage, hemorrhage into muscles, oral hemorrhage, trauma, trauma capitis, gastrointestinal bleeding, intracranial hemorrhage, intra-abdominal hemorrhage, intrathoracic hemorrhage, bone fracture, central nervous system bleeding, bleeding in the retropharyngeal space, bleeding in the retroperitoneal space, and bleeding in the illiopsoas sheath.

77. The method of claim 76, wherein said bleeding coagulation disorder is hemophilia.

78. The method of claim 77, wherein said bleeding coagulation disorder is hemophilia A.

79. The method of any one of claims 1 to 38 and 73 to 78, wherein said administration maintains a Factor VIII trough level in at least 90% of said patient population at a level above 1%.

80. The method of any one of claims 1 to 38 and 73 to 78, wherein said administration maintains a Factor VIII trough level in at least 60% of said population at a level above 3%.

81. A method of maintaining Factor VIII in a patient population at a level above 1% for at least one day, two days, or three days comprising administering a therapeutically effective amount of rFVIIIFc to said population, wherein the therapeutically effective amount is at least 25 IU/kg of rFVIIIFc and wherein at least 90% of said population maintains the Factor VIII trough level at least 1% or more.

82. A method of maintaining Factor VIII in a patient population at a level above 3% for at least one day, two days, three days comprising administering a therapeutically effective amount of rFVIIIFc to said population, wherein the therapeutically effective amount is at least 65 IU/kg of rFVIIIFc and wherein at least 90% of said population maintains the Factor VIII trough level at least 3% or more.

83. The method of any one of claims 4 to 38 and 73 to 82, wherein the single chain Factor VIII comprises a substitution or mutation at an amino acid position corresponding to Arginine 1645.

84. The method of any one of claims 4 to 38 and 73 to 83, wherein the single chain Factor VIII comprises a substitution or mutation at an amino acid position corresponding to Arginine 1648.

85. The method of any one of claims 4 to 38 and 73 to 84, wherein the single chain Factor VIII comprises a substitution or mutation at amino acid positions corresponding to Arginine 1645 and Arginine 1648 in full-length Factor VIII.

86. The method of claim 85, wherein the amino acid substituted at the amino acid position corresponding to Arginine 1645 is a different amino acid from the amino acid substituted at the amino acid position corresponding to Arginine 1648.

87. The method of any one of claims 83-86, wherein the substitution or mutation is an amino acid other than arginine.

88. The composition of any one of claims 39 to 72, wherein the single chain FVIII comprises an intact intracellular processing site.

89. The composition of any one of claims 39 to 72, wherein the single chain Factor VIII comprises a substitution or mutation at an amino acid position corresponding to Arginine 1645 in full-length mature Factor VIII.

90. The composition of any one of claims 39 to 72, wherein the single chain Factor VIII comprises a substitution or mutation at an amino acid position corresponding to Arginine 1648 in full-length mature Factor VIII.

91. The composition of any one of claims 39 to 72, wherein the single chain Factor VIII comprises a substitution or mutation at amino acid positions corresponding to Arginine 1645 and Arginine 1648 in full-length Factor VIII.

92. The composition of claim 91, wherein the amino acid substituted at the amino acid position corresponding to Arginine 1645 is a different amino acid than the amino acid substituted at the amino acid position corresponding to Arginine 1648.

93. The composition of any one of claims 89 to 92, wherein the substitution or mutation is an amino acid other than arginine.

94. The method of any one of claims 73 to 82, wherein the single chain Factor VIII comprises an intact intracellular processing site.

95. The method of any one of claims 73 to 82, wherein the single chain Factor VIII comprises a substitution or mutation at an amino acid position corresponding to Arginine 1645 in full-length mature Factor VIII.

96. The method of any one of claims 73 to 82, wherein the single chain Factor VIII comprises a substitution or mutation at an amino acid position corresponding to Arginine 1648 in full-length mature Factor VIII.

97. The method of any one of claims 73 to 82, wherein the single chain Factor VIII comprises a substitution or mutation at amino acid positions corresponding to Arginine 1645 and Arginine 1648 in full-length Factor VIII.

98. The method of claim 97, wherein the amino acid substituted at the amino acid position corresponding to Arginine 1645 is a different amino acid than the amino acid substituted at the amino acid position corresponding to Arginine 1648 in full-length Factor VIII.

99. The method of any one of claims 95 to 98, wherein the substitution or mutation is an amino acid other than arginine.

100. The method of claim 87 or 99, wherein the amino acid residue other than arginine is selected from the group consisting of isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, alanine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, proline, selenocysteine, serine, tyrosine, histidine, ornithine, pyrrolysine, or taurine.

101. The composition of claim 93, wherein the amino acid residue other than arginine is selected from the group consisting of isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, alanine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, proline, selenocysteine, serine, tyrosine, histidine, ornithine, pyrrolysine, or taurine.

102. The method of any one of claims 1 to 38, 73 to 87, or 94 to 100, wherein said subject is a pediatric subject.

103. A method of preventing, decreasing, or treating a bleeding episode in a subject comprising administering to the subject an effective amount of a long-acting Factor VIII (FVIII) protein, wherein the subject expresses a high level of von Willebrand Factor (VWF) in plasma.

104. A method of claim 103, wherein the subject has been identified as expressing a high level of VWF in plasma.

105. A method of preventing, decreasing, or treating a bleeding episode in a subject comprising:

(a) identifying a subject having high levels of VWF by measuring the level of VWF in the plasma of said subject, wherein a VWF level of at least about 100 IU/dL identifies the subject as having a high level of VWF; and

(b) administering to the subject an effective amount of a long-acting FVIII protein.

106. The method of any of claims 103-105, wherein the subject is a human.

107. The method of any of claims 103-106, wherein the subject is a pediatric subject.

108. The method of any of claims 103-107, wherein the subject has hemophilia A.

109. The method of any of claims 103-108, wherein the high level of VWF is at least about 100 IU/dL.

110. The method of any of claims 103-109, wherein the high level of VWF is between about 100 IU/dL and about 200 IU/dL.

111. The method of claim 110, wherein the high level of VWF is about 110 IU/dL, about 120 IU/dL, about 130 IU/dL, about 140 IU/dL, about 150 IU/dL, about 160 IU/dL, about 170 IU/dL, about 180 IU/dL, about 190 IU/dL, or about 200 IU/dL.

112. The method of any of claims 103-111, wherein the subject has the blood serotype A, B, or AB.

113. The method of any of claims 103-112, wherein said long-acting FVIII protein has a half-life in said subject of between about 20 and about 40 hours.

114. The method of claim 113, wherein said long-acting FVIII protein has a half-life of about 21 hours, 22 hours, 23 hours, 24 hours, 25 hours, 26 hours, 27 hours, 28 hours, 29 hours, 30 hours, 31 hours, 31 hours, 32 hours, 33 hours, 34 hours, 35 hours, 36 hours, 37 hours, 38 hours, 39 hours, or 40 hours.

115. The method of claim 114, wherein said long-acting FVIII protein has a half-life of between about 20 and 27 hours.

116. The method of any of claims 103-115, wherein said long-acting FVIII protein has a half-life that is at least about 1.2 times greater than the half-life of said said long-acting FVIII protein when administered to an individual having average levels of VWF.

117. The method of claim 116, wherein said long-acting FVIII protein has a half-life that is at least about about 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, or 2.5-fold times greater than the half-life of said said long-acting FVIII protein when administered to an individual having average levels of VWF.

118. The method of any one of claims 103-117, wherein the effective amount is at least about 20IU/kg, at least about 25 IU/kg, at least about 30IU/kg, at least about 35 IU/kg, at least about 40IU/kg, at least about 45 IU/kg, at least about 50IU/kg, at least about 55 IU/kg, at least about 60IU/kg, at least about 65IU/kg, at least about 70IU/kg, at least about 75IU/kg, at least about 80IU/kg, at least about 85IU/kg, or at least about 90IU/kg.

119. The method of any of claims 103-118, wherein the effective amount is at least about 65IU/kg to at least about 90IU/kg.

120. The method of claim 119, wherein the effective amount is 80 IU/kg.

121. The method of any of claims 103-120, wherein the long-acting FVIII protein is administered every 72 hours or longer.

122. The method of claim 121, wherein the long-acting FVIII protein is administered about once a week or longer.

123. The method of claim 121, wherein the effective amount of the long-acting FVIII protein is administered about once every 10 days, about once every two weeks, about once every 15 days, about once every 20 days, about once every three weeks, about once every 25 days, about once every four weeks, or about once every one month.

124. The method of claim 121, wherein the long-acting FVIII is administered at a dosage of 80 IU/kg once every 72 hours.

125. The method of claim 124, wherein the subject is a pediatric subject.

126. The method of any of claims 103-125, wherein the administration resolves greater than 5-20%, greater than 5-15%, greater than 5-10%, greater than 10-20%, or greater than 10-15% of bleeding episodes.

127. The method of any of claims 103-126, wherein a trough level of plasma Factor VIII:C in the subjects is maintained above 1-3 or 3-5 IU/dl.

128. The method of any of claims 103-127, wherein the administration prevents a bleeding episode in the subject.

129. The method of claim 128, wherein the bleeding episode is spontaneous.

130. The method of claim 129, wherein the administration resolves greater than 80-100%, greater than 80-90%, greater than 85-90%, greater than 90-100%, greater than 90-95%, or greater than 95-100% of bleeding episodes.

131. The method of any of claims 103-130, wherein the administration maintains homeostatis in the population of the subjects in need of a surgery.

132. The method of any of claims 103-131, wherein the long-acting FVIII protein is administered prior to, during, or after the surgery.

133. The method of claim 132, wherein the surgery is minor surgery, major surgery, tooth extraction, tonsillectomy, inguinal herniotomy, synovectomy, total knee replacement, craniotomy, osteosynthesis, trauma surgery, intracranial surgery, intra-abdominal surgery, intrathoracic surgery, or joint replacement surgery.

134. The method of claims 131-133, wherein the surgery is an emergency surgery.

135. The method of any of claims 103-134, wherein the long-acting FVIII protein has a half-life longer than a polypeptide consisting of FVIII.

136. The method of any of claims 103-135, wherein the long-acting FVIII protein is pegylated, hesylated, or polysialylated.

137. The method of any of claims 103-136, wherein the long-acting FVIII protein is a chimeric protein comprising a FVIII portion and a second portion.

138. The method of claim 137, wherein the second portion is an Fc region, albumin, a PAS sequence, transferrin or CTP (28 amino acid C-terminal peptide (CTP) of hCG with its 4 O-glycans), polyethylene glycol (PEG), hydroxyethyl starch (HES), albumin binding polypeptide, albumin-binding small molecules, or any combinations thereof.

139. The method of claims 137 or 138, wherein the second portion is fused to the amino-terminus or the carboxy-terminus of the FVIII portion.

140. The method of claims 137 or 138, wherein the second portion is inserted between two amino acids in the FVIII portion.

141. The method of any of claims 137-140, wherein the chimeric protein is a FVIIIFc monomer dimer hybrid.

142. The method of claim 141, wherein the FVIII portion is a single chain.

143. The method of claim 142, wherein the FVIII portion comprises a heavy chain and a light chain.

144. The method of any of claims 137-143, wherein the FVIII portion comprises full-length factor VIII, mature factor VIII, or factor VIII with a full or partial deletion of the B domain.

145. The method of claim 141, wherein the FVIII portion comprises an amino acid sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to amino acids 1 to 1438 of SEQ ID NO: 2 or amino acids 1 to 2332 of SEQ ID NO: 6.

146. The method of claim 145, wherein the FVIII portion comprises amino acids 1 to 1438 of SEQ ID NO: 2 or amino acids 1 to 2332 of SEQ ID NO: 6.

147. The method of any of claims 137-146, wherein the second portion of the chimeric polypeptide comprises an Fc region which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to amino acids 1439 to 1665 of SEQ ID NO: 2 or amino acids 2333 to 2559 of SEQ ID NO: 6.

148. The method of claim 147, wherein the second portion comprises amino acids 1439 to 1665 of SEQ ID NO: 2 or amino acids 2333 to 2559 of SEQ ID NO: 6.

149. The method of any one of claims 103-148, wherein the long-acting FVIII polypeptide is administered as part of a pharmaceutical composition comprising at least one excipient.

150. A method of treating a subject diagnosed with bleeding disorder, comprising measuring the half-life of FVIII-Fc in said subject, wherein a half-life that is at least about 1.2 times greater than the half-life of FVIII-Fc in a normal subject indicates the subject is a candidate for long interval dosing, and administering a FVIII-Fc polypeptide in an effective amount and at a dosing interval of at least 3 days.

151. A method of treating a subject diagnosed with bleeding disorder, comprising administering a FVIII-Fc polypeptide in an effective amount and at a dosing interval of at least 3 days to a

subject, wherein the half-life of FVIII-Fc in said subject is at least about 1.2 times greater than the half-life of FVIII-Fc when administered to a subject having average levels of VWF.

152. The method of claims 150 or 151, wherein the plasma half-life of FVIII-Fc in said subject is at least about 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, or 2.5-fold times greater than the plasma half-life of FVIII-Fc when administered to a subject having average levels of VWF.

153. The method of any of claims 150-152, wherein said FVIII-Fc plasma half-life is between 20-40 hours.

154. The method of claim 153, wherein said long-acting FVIII protein has a half-life of about 21 hours, 22 hours, 23 hours, 24 hours, 25 hours, 26 hours, 27 hours, 28 hours, 29 hours, 30 hours, 31 hours, 31 hours, 32 hours, 33 hours, 34 hours, 35 hours, 36 hours, 37 hours, 38 hours, 39 hours, or 40 hours.

155. The method of claim 154, wherein said long-acting FVIII protein has a half-life of between about 20 and 27 hours.

156. A method of treating a subject diagnosed with bleeding disorder, comprising measuring the half-life of a short-acting FVIII administered to said subject, wherein a half-life that is at least about 1.2 times greater than the half-life of said short-acting FVIII in a subject having average VWF levels indicates that the subject is a candidate for long interval dosing, and administering a long-acting FVIII-Fc polypeptide in an effective amount and at a dosing interval of at least 3 days.

157. The method of claim 156, wherein the half-life of the short-acting FVIII in said subject is at least about 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, or 2.5-fold greater than the half-life of a short-acting FVIII when administered to a subject having average levels of VWF.

158. The method of any of claims 150-157, wherein the subject is a human.

159. The method of any of claims 150-158, wherein the subject is a pediatric subject.

160. The method of any of claims 150-159, wherein the subject has hemophilia A.

161. The method of any of claims 150-160, wherein the subject has the blood serotype A, B, or AB.

162. The method of any of claims 150-161, wherein the long-acting FVIII-Fc is administered in an effective amount that is at least about 20IU/kg, at least about 25 IU/kg, at least about 30IU/kg, at least about 35 IU/kg, at least about 40IU/kg, at least about 45 IU/kg, at least about 50IU/kg, at least about 55 IU/kg, at least about 60IU/kg, at least about 65IU/kg, at least about 70IU/kg, at least about 75IU/kg, at least about 80IU/kg, at least about 85IU/kg, or at least about 90IU/kg.

163. The method of any of claims 150-161, wherein the effective amount is at least about 65IU/kg to at least about 90IU/kg.

164. The method of any of claims 150-163, wherein the effective amount of the FVIII-Fc protein is administered about once every week, about once every 10 days, about once every two weeks,

about once every 15 days, about once every 20 days, about once every three weeks, about once every 25 days, about once every four weeks, or about once every one month.

165. The method of any of claims 150-164, wherein the administration resolves greater than 5-20%, greater than 5-15%, greater than 5-10%, greater than 10-20%, or greater than 10-15% of bleeding episodes.

166. The method of any of claims 150-165, wherein a trough level of plasma Factor VIII:C in the subjects is maintained above 1-3 or 3-5 IU/dl.

167. The method of any of claims 150-166, wherein the administration prevents a bleeding episode in the subject.

168. The method of claim 167, wherein the bleeding episode is spontaneous.

169. The method of claim 167, wherein the administration resolves greater than 80-100%, greater than 80-90%, greater than 85-90%, greater than 90-100%, greater than 90-95%, or greater than 95-100% of bleeding episodes.

170. The method of any of claims 150-169, wherein the administration maintains homeostatis in the population of the subjects in need of a surgery.

171. The method of any of claims 150-170, wherein the FVIII-Fc protein is administered prior to, during, or after the surgery.

172. The method of claims 170 or 171, wherein the surgery is minor surgery, major surgery, tooth extraction, tonsillectomy, inguinal herniotomy, synovectomy, total knee replacement, craniotomy, osteosynthesis, trauma surgery, intracranial surgery, intra-abdominal surgery, intrathoracic surgery, or joint replacement surgery.

173. The method of any of claims 170-172, wherein the surgery is an emergency surgery.

174. The method of any of claims 150-173, wherein the FVIII-Fc protein has a half-life longer than a polypeptide consisting of FVIII.

175. The method of any of claims 150-174, wherein the FVIII-Fc protein is pegylated, hesylated, or polysialylated.

176. The method of claims 174 or 175, wherein the FVIII-Fc protein is a FVIIIFc monomer dimer hybrid.

177. The method of any of claims 172-176, wherein the FVIII portion is a single chain.

178. The method of claim 177, wherein the FVIII portion comprises a heavy chain and a light chain.

179. The method of any 174-178, wherein the FVIII portion comprises full-length factor VIII, mature factor VIII, or factor VIII with a full or partial deletion of the B domain.

180. The method of claim 179, wherein the FVIII portion comprises an amino acid sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to amino acids 1 to 1438 of SEQ ID NO: 2 or amino acids 1 to 2332 of SEQ ID NO: 6.

181. The method of claim 180, wherein the FVIII portion comprises amino acids 1 to 1438 of SEQ ID NO: 2 or amino acids 1 to 2332 of SEQ ID NO: 6.

182. The method of 174-181, wherein the second portion of the chimeric polypeptide comprises an Fc region which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to amino acids 1439 to 1665 of SEQ ID NO: 2 or amino acids 2333 to 2559 of SEQ ID NO: 6.

183. The method of claim 182, wherein the second portion comprises amino acids 1439 to 1665 of SEQ ID NO: 2 or amino acids 2333 to 2559 of SEQ ID NO: 6.

184. The method of any of claims 150-183, wherein the FVIII-Fc polypeptide is administered as part of a pharmaceutical composition comprising at least one excipient.

185. A method for determining whether a subject diagnosed with bleeding disorder is a candidate for long interval dosing with a long-acting FVIII polypeptide, comprising measuring the expression levels of plasma VWF, wherein an VWF expression level of at least 100 IU/dL indicates that the subject is a candidate for long interval dosing using a long-acting FVIII polypeptide.

186. The method of claim 185, wherein said VWF expression level is at least about 110 IU/dL, about 120 IU/dL, about 130 IU/dL, about 140 IU/dL, about 150 IU/dL, about 160 IU/dL, about 170 IU/dL, about 180 IU/dL, about 190 IU/dL, or about 200 IU/dL.

187. A method for determining whether a subject diagnosed with bleeding disorder is a candidate for long interval dosing of a long-acting FVIII polypeptide, comprising measuring the half-life of FVIII-Fc in said subject, wherein a half-life that is at least about 1.2-fold greater than the half-life of FVIII-Fc when administered to a subject having average VWF levels indicates the subject is a candidate for long interval dosing.

188. The method of claim 187, wherein the half-life of FVIII-Fc is at least about 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, or 2.5-fold greater than the half-life of FVIII-Fc when administered to a subject having average levels of VWF.

189. A method for determining whether a subject diagnosed with bleeding disorder is a candidate for long interval dosing of a long-acting FVIII polypeptide, comprising measuring the half-life of short-acting FVIII in said subject, wherein a half-life that is at least about 1.2-fold greater than the half-life of short-acting FVIII when administered to a subject having average VWF levels indicates the subject is a candidate for long interval dosing.

190. The method of claim 189, wherein the half-life is at least about 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, or 2.5-fold greater than the half-life of FVIII-Fc when administered to a subject having average levels of VWF.

191. The method of any of claims 1-38, 73-87, 94-100, and 102-190, wherein said chimeric polypeptide comprises a Fc portion.

192. The method of claim 191, where said dosing interval is at least about one and one-half to six times longer, one and one-half to five times longer, one and one-half to four times longer, one and one-

half to three times longer, or one and one-half to two times longer, than the dosing interval required for an equivalent dose of a polypeptide consisting of said Factor VIII portion.

193. The method of claim 192, where said dosing interval is at least about one and one-half, two, two and one-half, three, three and one-half, four, four and one-half, five, five and one-half or six times longer than the dosing interval required for an equivalent dose of a polypeptide consisting of said Factor VIII portion.

194. The method of any of claims 1-38, 73-87, 94-100, and 102-193, wherein said dosing interval of said chimeric polypeptide is about every three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, or fourteen days or longer.

195. The method of any of claims 1-38, 73-87, 94-100, and 102-194, wherein said subject is in need of prophylactic treatment.

196. The method of any of claims 1-38, 73-87, 94-100, and 102-193, wherein said subject is in need of on-demand treatment.

197. The method of claim 196, wherein said subject is in need of treatment for a bleeding episode.

198. The method of claim 197, wherein said subject is in need of treatment for hemarthrosis, muscle bleed, oral bleed, hemorrhage, hemorrhage into muscles, oral hemorrhage, trauma, trauma capitis, gastrointestinal bleeding, intracranial hemorrhage, intra-abdominal hemorrhage, intrathoracic hemorrhage, bone fracture, central nervous system bleeding, bleeding in the retropharyngeal space, bleeding in the retroperitoneal space, or bleeding in the illiopsoas sheath.

199. The method of claim 196, wherein said subject is in need of surgical prophylaxis, peri-operative management, or treatment for surgery.

200. The method of claim 199, wherein said surgery is minor surgery, major surgery, tooth extraction, tonsillectomy, inguinal herniotomy, synovectomy, total knee replacement, craniotomy, osteosynthesis, trauma surgery, intracranial surgery, intra-abdominal surgery, intrathoracic surgery, or joint replacement surgery.

201. The method of any of claims 196-200, wherein said dosing interval of said chimeric polypeptide is about once every 24-36, 24-48, 24-72, 24-96, 24-120, 24-144, 24-168, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, or 72 hours or longer.

202. The method of any of claims 1-38, 73-87, 94-100, and 102-201, wherein said therapeutic dose is 10-100 IU/kg.

203. The method of claim 201, wherein said therapeutic dose is 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, or 90-100 IU/kg.

204. The method of claim 202, wherein said therapeutic dose is 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 IU/kg.

205. The method of any of claims 1-38, 73-87, 94-100, and 102-204, wherein said Factor VIII is human Factor VIII.

206. The method of any of claims 1-38, 73-87, 94-100, and 102-205, wherein said Factor VIII has a full or partial deletion of the B domain.

207. The method of claim 205, wherein the Factor VIII portion of said chimeric polypeptide is at least 90% or 95% identical to a Factor VIII amino acid sequence shown in Table 2 without a signal sequence (amino acids 20 to 1457 of SEQ ID NO:2; amino acids 20 to 2351 of SEQ ID NO:6).

208. The method of claim 207, wherein the Factor VIII portion of said chimeric polypeptide is identical to a Factor VIII amino acid sequence shown in Table 2 without a signal sequence (amino acids 20 to 1457 of SEQ ID NO:2 or amino acids 20 to 2351 of SEQ ID NO:6).

209. The method of claim 205, wherein the Factor VIII portion of said chimeric polypeptide is at least 90% or 95% identical to a Factor VIII amino acid sequence shown in Table 2 with a signal sequence (amino acids 1 to 1457 of SEQ ID NO:2 or amino acids 1 to 2351 of SEQ ID NO:6).

210. The method of claim 209, wherein the Factor VIII portion of said chimeric polypeptide is identical to a Factor VIII amino acid sequence shown in Table 2 with a signal sequence (amino acids 1 to 1457 of SEQ ID NO:2 or amino acids 1 to 2351 of SEQ ID NO:6).

211. The method of claim 205 or 206, wherein said second portion of said chimeric polypeptide is at least 90% or 95% identical to the Fc amino acid sequence shown in Table 2 (amino acids 1458 to 1684 of SEQ ID NO:2; or amino acids 2352 to 2578 of SEQ ID NO:6).

212. The method of claim 211, wherein said second portion of said chimeric polypeptide is identical to the Fc amino acid sequence shown in Table 2 (amino acids 1458 to 1684 of SEQ ID NO:2 or amino acids 2352 to 2578 of SEQ ID NO:6).

213. The method of any of claims 1-38, 73-87, 94-100, and 102-212, wherein said chimeric polypeptide is in the form of a hybrid comprising a second polypeptide in association with said chimeric polypeptide, wherein said second polypeptide consists essentially of an Fc.

214. The method of claim 213, wherein said chimeric polypeptide comprises a sequence at least 90% or 95% identical to the Factor VIII and Fc amino acid sequence shown in Table 2A(i) without a signal sequence (amino acids 20 to 1684 of SEQ ID NO:2) or at least 90% or 95% identical to the Factor VIII and Fc amino acid sequence shown in Table 2A(i) with a signal sequence (amino acids 1to 1684 of SEQ ID NO:2).

215. The method of claim 214, wherein said chimeric polypeptide comprises a sequence identical to the Factor VIII and Fc amino acid sequence shown in Table 2A(i) without a signal sequence (amino acids 20 to 1684 of SEQ ID NO:2) or identical to the Factor VIII and Fc amino acid sequence shown in Table 2A(i) with a signal sequence (amino acids 1 to 1684 of SEQ ID NO:2).

216. The method of any of claims 213-215, wherein said second polypeptide consists essentially of a sequence at least 90% or 95% identical to the amino acid sequence shown in Table 2A(ii) without a

signal sequence (amino acids 21 to 247 of SEQ ID NO:4) or at least 90% or 95% identical to the amino acid sequence shown in Table 2A(ii) with a signal sequence (amino acids 1 to 247 of SEQ ID NO:4).

217. The method of claim 216, wherein said second polypeptide consists essentially of a sequence identical to the amino acid sequence shown in Table 2A(ii) without a signal sequence (amino acids 21 to 247 of SEQ ID NO:4) or identical to the amino acid sequence shown in Table 2A(ii) with a signal sequence (amino acids 1 to 247 of SEQ ID NO:4).

218. The method of any of claims 1-38, 73-87, 94-100, and 102-217, wherein said chimeric polypeptide is administered as part of a pharmaceutical composition comprising at least one excipient.

219. A method of administering Factor VIII to a human subject in need thereof, comprising administering to the subject a therapeutic dose of a chimeric polypeptide comprising a Factor VIII portion and a second portion to obtain an area under the plasma concentration versus time curve (AUC) at least about one and one-quarter times greater than the AUC obtained by an equivalent dose of a polypeptide consisting of said Factor VIII portion.

220. The method of claim 219, wherein said chimeric polypeptide is administered at a dosing interval of about every three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, or fourteen days or longer.

221. The method of claim 219 or 220, wherein said subject is in need of prophylactic treatment.

222. The method of claim 219 or 220, wherein said subject is in need of on-demand treatment.

223. The method of any of claims 219-222, wherein said subject is in need of treatment for a bleeding episode.

224. The method of any of claim 219-222, wherein said subject is in need of treatment for hemarthrosis, muscle bleed, oral bleed, hemorrhage, hemorrhage into muscles, oral hemorrhage, trauma, trauma capitis, gastrointestinal bleeding, intracranial hemorrhage, intra-abdominal hemorrhage, intrathoracic hemorrhage, bone fracture, central nervous system bleeding, bleeding in the retropharyngeal space, bleeding in the retroperitoneal space, or bleeding in the illiopsoas sheath.

225. The method of claim 222, wherein said subject is in need of surgical prophylaxis, peri-operative management, or treatment for surgery.

226. The method of claim 225, wherein said surgery is minor surgery, major surgery, tooth extraction, tonsillectomy, inguinal herniotomy, synovectomy, total knee replacement, craniotomy, osteosynthesis, trauma surgery, intracranial surgery, intra-abdominal surgery, intrathoracic surgery, or joint replacement surgery.

227. The method of any of claims 219-226, wherein said dosing interval of said chimeric polypeptide is about once every 24-36, 24-48, 24-72, 24-96, 24-120, 24-144, 24-168, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, or 72 hours or longer.

228. The method of any of claims 219-227, wherein said therapeutic dose is 10-100 IU/kg.

229. The method of claim 228, wherein said therapeutic dose is 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, or 90-100 IU/kg.

230. The method of claim 229, wherein said therapeutic dose is 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 IU/kg.

231. The method of any of claims 219-230, wherein said Factor VIII is human Factor VIII.

232. The method of any of claims 219-231, wherein said Factor VIII has a full or partial deletion of the B domain.

233. The method of claim 231, wherein the Factor VIII portion of said chimeric polypeptide is at least 90% or 95% identical to a Factor VIII amino acid sequence shown in Table 2 without a signal sequence (amino acids 20 to 1457 of SEQ ID NO:2 or amino acids 20 to 2351 of SEQ ID NO:6).

234. The method of claim 233, wherein the Factor VIII portion of said chimeric polypeptide is identical to a Factor VIII amino acid sequence shown in Table 2 without a signal sequence (amino acids 20 to 1457 of SEQ ID NO:2 or amino acids 20 to 2351 of SEQ ID NO:6).

235. The method of claim 231, wherein the Factor VIII portion of said chimeric polypeptide is at least 90% or 95% identical to a Factor VIII amino acid sequence shown in Table 2 with a signal sequence (amino acids 1 to 1457 of SEQ ID NO:2 or amino acids 1 to 2351 of SEQ ID NO:6).

236. The method of claim 235, wherein the Factor VIII portion of said chimeric polypeptide is identical to a Factor VIII amino acid sequence shown in Table 2 with a signal sequence (amino acids 1 to 1457 of SEQ ID NO:2 or amino acids 1 to 2351 of SEQ ID NO:6).

237. The method of claim 231 or 232, wherein said second portion of said chimeric polypeptide is at least 90% or 95% identical to the Fc amino acid sequence shown in Table 2 (amino acids 1458 to 1684 of SEQ ID NO:2 or amino acids 2352 to 2578 of SEQ ID NO:6).

238. The method of claim 237, wherein said second portion of said chimeric polypeptide is identical to the Fc amino acid sequence shown in Table 2 (amino acids 1458 to 1684 of SEQ ID NO: or; amino acids 2352 to 2578 of SEQ ID NO:6).

239. The method of any of claims 219-238, wherein said chimeric polypeptide is in the form of a hybrid comprising a second polypeptide in association with said chimeric polypeptide, wherein said second polypeptide consists essentially of an Fc.

240. The method of claim 239, wherein said chimeric polypeptide comprises a sequence at least 90% or 95% identical to the Factor VIII and Fc amino acid sequence shown in Table 2A(i) without a signal sequence (amino acids 20 to 1684 of SEQ ID NO:2) or at least 90% or 95% identical to the Factor VIII and Fc amino acid sequence shown in Table 2A(i) with a signal sequence (amino acids 1 to 1684 of SEQ ID NO:2).

241. The method of claim 240, wherein said chimeric polypeptide comprises a sequence identical to the Factor VIII and Fc amino acid sequence shown in Table 2A(i) without a signal sequence (amino

acids 20 to 1684 of SEQ ID NO:2) or at least 90% or 95% identical to the Factor VIII and Fc amino acid sequence shown in Table 2A(i) with a signal sequence (amino acids 1 to 1684 of SEQ ID NO:2).

242. The method of any of claims 239-241, wherein said second polypeptide consists essentially of a sequence at least 90% or 95% identical to the amino acid sequence shown in Table 2A(ii) without a signal sequence (amino acids 21 to 247 of SEQ ID NO:4) or at least 90% or 95% identical to the amino acid sequence shown in Table 2A(ii) with a signal sequence (amino acids 1 to 247 of SEQ ID NO:4).

243. The method of claim 242, wherein said second polypeptide consists essentially of a sequence identical to the amino acid sequence shown in Table 2A(ii) without a signal sequence (amino acids 21 to 247 of SEQ ID NO:4) or at least 90% or 95% identical to the amino acid sequence shown in Table 2A(ii) with a signal sequence (amino acids 1 to 247 of SEQ ID NO:4).

244. The method of any of claims 219-243, wherein said chimeric polypeptide is administered as part of a pharmaceutical composition comprising at least one excipient.

245. A method of administering Factor VIII to a human subject in need thereof, comprising

administering to the subject a therapeutic dose of a polypeptide comprising a Factor VIII and an Fc at a dosing interval of about every three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, or fourteen days or longer.

246. The method of any of claim 245, wherein said subject is in need of prophylactic treatment.

247. The method of claim 245 or 246, wherein said therapeutic dose is 10-100 IU/kg.

248. The method of claim 247, wherein said therapeutic dose is 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, or 90-100 IU/kg.

249. The method of claim 248, wherein said therapeutic dose is 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 IU/kg.

250. The method of any of claims 245-249, wherein said Factor VIII is human Factor VIII.

251. The method of any of claims 245-250, wherein said Factor VIII has a full or partial deletion of the B domain.

252. The method of claim 250, wherein said Factor VIII is at least 90% or 95% identical to a Factor VIII amino acid sequence shown in Table 2 without a signal sequence (amino acids 20 to 1457 of SEQ ID NO:2 or amino acids 20 to 2351 of SEQ ID NO:6).

253. The method of claim 252, wherein said Factor VIII is identical to a Factor VIII amino acid sequence shown in Table 2 without a signal sequence (amino acids 20 to 1457 of SEQ ID NO:2 or amino acids 20 to 2351 of SEQ ID NO:6).

254. The method of claim 250, wherein said Factor VIII is at least 90% or 95% identical to a Factor VIII amino acid sequence shown in Table 2 with a signal sequence (amino acids 1 to 1457 of SEQ ID NO:2 or amino acids 1 to 2351 of SEQ ID NO:6).

255. The method of claim 254, wherein said Factor VIII is identical to a Factor VIII amino acid sequence shown in Table 2 with a signal sequence (amino acids 1 to 1457 of SEQ ID NO:2 or amino acids 1 to 2351 of SEQ ID NO:6).

256. The method of claim 250 or 251, wherein said second portion is at least 90% or 95% identical to the Fc amino acid sequence shown in Table 2 (amino acids 1458 to 1684 of SEQ ID NO:2 or amino acids 2352 to 2578 of SEQ ID NO:6).

257. The method of claim 256, wherein said second portion is identical to the Fc amino acid sequence shown in Table 2 (amino acids 1458 to 1684 of SEQ ID NO:2 or amino acids 2352 to 2578 of SEQ ID NO:6).

258. The method of any of claims 245-257, wherein said chimeric polypeptide is a Factor VIII-Fc chimeric polypeptide in the form of a hybrid comprising a second polypeptide in association with said chimeric polypeptide, wherein said second polypeptide consists essentially of an Fc.

259. The method of claim 258, wherein said chimeric polypeptide comprises a sequence at least 90% or 95% identical to the Factor VIII and Fc amino acid sequence shown in Table 2A(i) without a signal sequence (amino acids 20 to 1684 of SEQ ID NO:2) or at least 90% or 95% identical to the Factor VIII and Fc amino acid sequence shown in Table 2A(i) with a signal sequence (amino acids 1 to 1684 of SEQ ID NO:2).

260. The method of claim 259, wherein said chimeric polypeptide comprises a sequence identical to the Factor VIII and Fc amino acid sequence shown in Table 2A(i) without a signal sequence (amino acids 20 to 1684 of SEQ ID NO:2) or at least 90% or 95% identical to the Factor VIII and Fc amino acid sequence shown in Table 2A(i) with a signal sequence (amino acids 1 to 1684 of SEQ ID NO:2).

261. The method of any of claims 258-260, wherein said second polypeptide consists essentially of a sequence at least 90% or 95% identical to the amino acid sequence shown in Table 2A(ii) without a signal sequence (amino acids 21 to 247 of SEQ ID NO:4) or at least 90% or 95% identical to the amino acid sequence shown in Table 2A(ii) with a signal sequence (amino acids 1 to 247 of SEQ ID NO:4).

262. The method of claim 261, wherein said second polypeptide consists essentially of a sequence identical to the amino acid sequence shown in Table 2A(ii) without a signal sequence (amino acids 21 to 247 of SEQ ID NO:4) or at least 90% or 95% identical to the amino acid sequence shown in Table 2A(ii) with a signal sequence (amino acids 1 to 247 of SEQ ID NO:4).

263. The method of any of claims 1-38, 73-87, 94-100, and 102-262, wherein said polypeptide is administered as part of a pharmaceutical composition comprising at least one excipient.

264. The method of any one of claims 1-38, 73-87, 94-100, and 102-263, wherein said chimeric polypeptide has Factor VIII activity.

CLAIMS

1. A pharmaceutical composition comprising: (i) a chimeric polypeptide, which comprises a Factor VIII (FVIII) portion and a second portion; and (ii) at least one pharmaceutically acceptable excipient, wherein about 15% to about 25% of the FVIII portion of the chimeric polypeptide comprises single chain FVIII and about 75% to about 85% of the FVIII portion of the chimeric polypeptide comprises processed FVIII.

2. The pharmaceutical composition of claim 1, wherein:

(i) about 25% of the FVIII portion of the chimeric polypeptide comprises a single chain FVIII and about 75% of the FVIII portion of the chimeric polypeptide comprises processed FVIII;

(ii) about 20% of the FVIII portion of the chimeric polypeptide comprises a single chain FVIII and about 80% of the FVIII portion of the chimeric polypeptide comprises processed FVIII; or

(iii) about 15% of the FVIII portion of the chimeric polypeptide comprises a single chain FVIII and about 85% of the FVIII portion of the chimeric polypeptide comprises processed FVIII.

3. The pharmaceutical composition of claim 1 or claim 2, wherein the single chain FVIII comprises a heavy chain and a light chain connected by a peptide bond.

4. The pharmaceutical composition of any one of claims 1 to 3, wherein the single chain FVIII has FVIII activity comparable to a polypeptide consisting of processed FVIII.

5. The pharmaceutical composition of any one of claims 1 to 4, wherein the processed FVIII comprises two chains including a first chain comprising a heavy chain of FVIII and a second chain comprising a light chain of FVIII, wherein the first chain and the second chain are associated by a metal bond.

6. The pharmaceutical composition of any one of claims 1 to 5, wherein the chimeric polypeptide is a long-acting FVIII polypeptide.

7. The pharmaceutical composition of any one of claims 1 to 6, wherein the second portion comprises an Fc region, an albumin, a PAS sequence, a transferrin, a 28 amino acid C-terminal peptide of hCG with its 4 O-glycans (CTP), a polyethylene glycol (PEG), a hydroxyethyl starch

(HES), an albumin binding polypeptide, an albumin-binding small molecule or any combination thereof.

8. The pharmaceutical composition of any one of claims 1 to 7, wherein the second portion comprises an Fc region.

9. The pharmaceutical composition of any one of claims 1 to 8, wherein the chimeric polypeptide is a FVIIIFc monomer dimer hybrid.

10. The pharmaceutical composition of any one of claims 1 to 9, wherein the FVIII portion comprises B-domain deleted FVIII or full-length mature FVIII.

11. The pharmaceutical composition of claim 10, wherein the single chain FVIII or the processed FVIII comprises B-domain deleted FVIII.

12. The pharmaceutical composition of any one of claims 1 to 11, wherein residue 1645 and/or residue 1648 corresponding to full-length mature FVIII is/are arginine in the single chain FVIII.

13. The pharmaceutical composition of any one of claims 1 to 11, wherein residue 1645 and/or residue 1648 corresponding to full-length mature FVIII is/are substituted or mutated in the single chain FVIII compared to wild type FVIII.

14. The pharmaceutical composition of any one of claims 4 to 13, wherein the FVIII activity is measured *in vitro* by a chromogenic assay.

15. The pharmaceutical composition of any one of claims 1 to 14, wherein the chimeric polypeptide has a half-life longer than a polypeptide consisting of the FVIII portion.

16. The pharmaceutical composition of claim 15, wherein the half-life is at least about 1.5 fold longer than the half-life of the polypeptide consisting of the FVIII portion.

17. The pharmaceutical composition of any one of claims 1 to 16, wherein the composition is more stable than a composition comprising processed FVIII without single chain FVIII.

18. The pharmaceutical composition of any one of claims 1 to 17, wherein said composition is formulated for administration to a human.

19. The pharmaceutical composition of any one of claims 1 to 18, wherein said composition is formulated for parenteral administration to a human.

20. The pharmaceutical composition of any one of claims 1 to 19, wherein said composition is formulated for subcutaneous, intradermal, intravascular, intravenous, intramuscular, spinal, intracranial, intrathecal, intraocular, periocular, intraorbital, intrasynovial or intraperitoneal injection to a human.

21. The pharmaceutical composition of any one of claims 1 to 20, wherein said composition is lyophilized.