Claims

1. Use of a recombinant polypeptide comprising a truncated von Willebrand Factor (VWF) in the preparation of a medicament for the treatment or prophylaxis of a blood coagulation disorder, wherein the blood coagulation disorder is hemophilia A or von-Willebrand disease, said treatment or prophylaxis comprising the recombinant polypeptide and a Factor VIII protein (FVIII) to be administered extravascularly to a subject having the blood coagulation disorder, wherein said recombinant polypeptide is capable of binding to said FVIII, wherein the truncated VWF comprises an amino acid sequence having a sequence identity of at least 90% to amino acids 764 to 1242 of SEQ ID NO:4, wherein said polypeptide comprises a half-life extending moiety (HLEM), wherein the polypeptide is present as a dimer wherein the ratio dimer : monomer of the polypeptide of the invention is at least 1.5, wherein the dimeric polypeptide has a FVIII binding affinity characterized by a dissociation constant K_D of less than 1 nM, and wherein the molar ratio of the recombinant polypeptide to be administered to the FVIII to be administered is higher than 50.

2. The use according to claim 1, wherein said treatment or prophylaxis comprises the recombinant polypeptide and the Factor VIII protein (FVIII) to be administered extravascularly to a subject having the blood coagulation disorder.

3. The use according to any one of the preceding claims, wherein the subject is a human subject.

4. The use according to any one of the preceding claims, wherein the dimeric polypeptide has a FVIII binding affinity characterized by a dissociation constant K_D of less than 500 pM, less than 200 pM, less than 100 pM, less than 90 pM or less than 80 pM.

5. The use according to any one of the preceding claims, wherein the polypeptide is to be administered either subcutaneously, intradermally or intramuscularly.

6. The use according to any one of the preceding claims, wherein the truncated VWF consists either of (a) amino acids 764 to 1242 of SEQ ID NO:4, or of (b) an amino acid sequence having a sequence identity of at least 90% to amino acids 764 to 1242 of SEQ ID NO:4.

7. The use according to any one of claims 1 to 6, wherein the HLEM is a heterologous amino acid sequence fused to the truncated VWF, wherein said heterologous amino acid sequence preferably comprises or consists of a polypeptide selected from the group consisting of albumin or fragments thereof, transferrin or fragments thereof, the C-terminal peptide of human chorionic gonadotropin, an XTEN sequence, homo-amino acid repeats (HAP), proline-alanine-serine repeats (PAS), afamin, alpha-fetoprotein, Vitamin D binding protein, polypeptides capable of binding under physiological conditions to albumin or to immunoglobulin constant regions, polypeptides capable of binding to the neonatal Fc receptor (FcRn), particularly immunoglobulin constant regions and portions thereof, preferably the Fc portion of immunoglobulin, and combinations thereof.

8. The use according to any one of claims 1 to 6, wherein the HLEM is conjugated to the recombinant polypeptide, wherein said HLEM is preferably selected from the group consisting of hydroxyethyl starch (HES), polyethylene glycol (PEG), polysialic acids (PSAs), elastin-like polypeptides, heparosan polymers, hyaluronic acid and albumin binding ligands, e.g. fatty acid chains, and combinations thereof.

9. The use according to any one of claims 1 to 8, wherein the mean residence time (MRT) of the FVIII to be administered is increased by the co-administration of the recombinant polypeptide, preferably by a factor of at least 1.5, at least 2, at least 3, at least 4 or at least 5, as compared to a reference treatment, wherein said reference treatment is identical to said treatment, except that the recombinant polypeptide to be administered does not comprise a HLEM and/or except that the molar ratio of the recombinant polypeptide to be administered to the FVIII to be administered is below 50.

10. The use according to any one of claims 1 to 9, wherein the mean residence time (MRT) of the recombinant polypeptide to be administered is increased by a factor of at least 1.5, at least 2 or at least 3, as compared to a reference treatment, wherein said reference treatment is identical to said treatment, except that the recombinant polypeptide to be administered does not comprise a HLEM and/or except that the molar ratio of the recombinant polypeptide to be administered to the FVIII to be administered is below 50.

11. The use according to any one of claims 1 to 10, wherein the terminal half-life of the FVIII to be administered is increased by the co-administration of the recombinant polypeptide,

preferably by a factor of at least 1.2, at least 1.5, at least 2, at least 2.5 or at least 3, as compared to a reference treatment, wherein said reference treatment is identical to said treatment, except that the recombinant polypeptide to be administered does not comprise a HLEM and/or except that the molar ratio of the recombinant polypeptide to be administered to the FVIII to be administered is below 50.

12. The use according to any one of claims 1 to 11, wherein the time period for reaching a 1% trough level of the FVIII co-administered with said polypeptide having a HLEM is prolonged compared to a reference treatment, wherein said reference treatment is identical to said treatment, except the FVIII is to be administered with a recombinant polypeptide without having said HLEM.

13. The use according to any one of the preceding claims, , wherein the plasma half-life of the polypeptide is at least 100%, at least 200% or preferably at least 400% higher compared to that of the endogenous VWF and/or compared to that of VWF of normal human plasma (NHP).

14. The use according to any one of the preceding claims, wherein co-administration of the recombinant polypeptide and the FVIII protein is achieved either (i) by administration together in a single composition comprising the recombinant polypeptide and the FVIII protein, or (ii) by administration of the recombinant polypeptide (first compound) and the FVIII protein (second compound) each provided in separate compositions, wherein the first compound is to be administered before, after or concurrently with the second compound.

15. The use according to any one of the preceding claims, wherein the FVIII is a plasma derived protein or a recombinant FVIII protein.

16. The use according to any one of the preceding claims, wherein FVIII is to be administered extravascularly and wherein the bioavailability of the to be administered FVIII following co-administration with the recombinant polypeptide is at least 2%, at least 3%, at least 5%, preferably at least 7%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35% or at least 40%.

17. The use according to any one of the preceding claims, wherein the bioavailability of the recombinant polypeptide is at least 30%, preferably at least 35%, more preferably at least 40%, at least 45%, at least 50%%, at least 55%, at least 60%, at least 65%, at least 70%, or at least 80%.

18. The use according to any one of the preceding claims, wherein the dosage of co-administered FVIII protein does not exceed 2500 IU/kg, 1500 IU/kg, 1000 IU/kg, 600 IU/kg, 500 IU/kg or 400 IU/kg.

19. The use according to any one of the preceding claims, wherein following co-administration of said recombinant polypeptide with FVIII the maximal concentration (C_{max}) for FVIII is at least 10 mIU/mL, at least 25 mIU/mL, at least 50 mIU/mL, at least 100 mIU/mL, at least 200 mIU/mL, at least 300 mIU/mL or at least 400 mIU/mL FVIII activity, preferably chromogenic FVIII activity.

20. The use according to any one of claims 1 to 19, wherein following co-administration of said recombinant polypeptide with FVIII the clearance (CL) value for the recombinant polypeptide is reduced by a factor of at least 2, at least 5 or at least 10, as compared to a reference treatment, wherein said reference treatment is identical to said treatment, except that the recombinant polypeptide to be administered does not comprise a HLEM and/or except that the molar ratio of the recombinant polypeptide to be administered to the FVIII to be administered is below 50.

21. The use according to any one of claims 1 to 20, wherein following co-administration of said recombinant polypeptide with FVIII the clearance (CL) value of the to be administered FVIII is reduced compared to a reference treatment, preferably by a factor of at least 1.5, at least 2, at least 3, at least 5, at least 7.5 or at least 10, wherein said reference treatment is identical to said treatment, except that the recombinant polypeptide to be administered does not comprise a HLEM and/or except that the molar ratio of the recombinant polypeptide to be administered to the FVIII to be administered is below 50.

22. The use according to any one of the preceding claims, wherein the molar ratio of the recombinant polypeptide to the FVIII to be administered is at least 75, at least 100, at least 200, at least 300, at least 400, at least 500 or at least 1000.