Claims

1. A liquid pharmaceutical formulation comprising at least 100 mg/ml of a protein comprising an antigen binding domain that binds to or specifically binds to Factor XII and/or an activated form thereof, an organic acid buffer, a non-ionic surfactant and an amino acid stabiliser, wherein the formulation has a pH of 5.0 to 6.5 and a viscosity of less than about 30 mPa*s at 20 °C.

2. The formulation according to claim 1, wherein the protein is present in the formulation at a concentration of at least 150 mg/ml.

3. The formulation according to claim 1 or 2, wherein the protein is present in the formulation at a concentration between 160 mg/ml and 180 mg/ml.

4. The formulation according to any one of claims 1 to 3, wherein the formulation is an aqueous formulation.

5. The formulation according to any one of claims 1 to 4, wherein the organic acid buffer is selected from the group consisting of a histidine buffer and a glutamate buffer.

6. The formulation according to any one of claims 1 to 5, wherein the non-ionic surfactant is selected from the group consisting of polysorbate 80, polysorbate 20 and poloxamer 188.

7. The formulation according to any one of claims 1 to 6, wherein the amino acid stabiliser is selected from the group consisting of proline, arginine, salts thereof and a combination thereof.

8. The formulation according to any one of claims 1 to 7, wherein the formulation further comprises a polyol.

9. The formulation according to any one of claims 1 to 8, wherein the formulation comprises a histidine buffer, proline and polysorbate 80.

10. The formulation according to claim 9, wherein the formulation further comprises arginine monohydrochloride.

11. A pharmaceutical formulation comprising between 100 mg/ml and 110 mg/ml of a protein comprising an antigen binding domain that binds to or specifically binds to Factor XII and/or an activated form thereof, a histidine buffer, polysorbate 80 and proline and arginine monohydrochloride as stabilisers, wherein the formulation has a pH of 5.5 to 6.5 and a viscosity of less than about 10 mPa*s at 20 °C.

12. A pharmaceutical formulation comprising between 160 mg/ml and 180 mg/ml of a protein comprising an antigen binding domain that binds to or specifically binds to Factor XII and/or an activated form thereof, a histidine buffer, polysorbate 80 and proline and arginine monohydrochloride as stabilisers, wherein the formulation has a pH of 5.5 to 6.5 and a viscosity of less than about 10 mPa*s at 20 C.

13. The formulation according to any one of claims 1 to 12, wherein the formulation has a pH of 5.8 to 6.4 and comprises 12 mM to 25 mM L-histidine buffer, 0.01 % to 0.03 % (w/v) polysorbate 80, 90 mM to 150 mM L-proline and 100 mM to 160 mM L-arginine monohydrochloride.

14. The formulation according to any one of claims 1 to 13, wherein the formulation has a pH of 5.8 to 6.4 and comprises about 20 mM L-histidine buffer, 0.02 % (w/v) polysorbate 80, 140 mM L-proline and 150 mM L-arginine monohydrochloride.

15. The formulation according to any one of claims 1 to 14, wherein the viscosity of the formulation is less than about 9 mPa*s at 20 °C.

16. The formulation according to any one of claims 1 to 15, wherein the formulation has a density between 1.00 to 1.10 g/cm^3 at 20 °C.

17. The formulation according to any one of claims 1 to 16, wherein the formulation comprises less than about 10 % total aggregates of the protein.

18. The formulation according to any one of claims 1 to 17, wherein at least 90 % of the protein in the formulation is a monomer.

19. The formulation according to any one of claims 1 to 18, wherein the antigen binding domain binds to or specifically binds to Factor XII and/or an activated form thereof and antagonises activity of the Factor XII and/or an activated form thereof and/or antagonises activation of the Factor XII and/or an activated form thereof.

20. The formulation according to any one of claims 1 to 19, wherein the protein comprises an antigen binding domain of an antibody.

21. The formulation according to any one of claims 1 to 20, wherein the protein is selected from the group consisting of:
    (i) a single chain Fv fragment (scFv);
    (ii) a dimeric scFv (di-scFv);
    (iii) a diabody;
    (iv) a triabody;
    (v) a tetrabody;
    (vi) a Fab;
    (vii) a F(ab')2;
    (viii) a Fv;
    (ix) one of (i) to (viii) is linked to a constant region of an antibody, Fc or a heavy chain constant domain (C_H) C_H2 and/or C_H3; or
    (x) an antibody.

22. The formulation according to any one of claims 1 to 21, wherein the protein comprises:
    (i) a V_H comprising an amino acid sequence set forth in SEQ ID NO: 1 and a V_L comprising an amino acid sequence set forth in SEQ ID NO: 2
    (ii) a V_H comprising an amino acid sequence set forth in SEQ ID NO: 3 and a V_L comprising an amino acid sequence set forth in SEQ ID NO: 4; or
    (iii) a V_H comprising an amino acid sequence set forth in SEQ ID NO: 5 and a V_L comprising an amino acid sequence set forth in SEQ ID NO: 6.

23. The formulation according to any one of claims 1 to 21, wherein the protein comprises:
    (i) a V_H comprising:
        (a) a CDR1 comprising a sequence set forth in SEQ ID NO: 7; a CDR2 comprising a sequence set forth in SEQ ID NO: 8; and a CDR3 comprising a sequence set forth in SEQ ID NO: 9; or
        (b) a CDR1 comprising a sequence set forth in SEQ ID NO: 7; a CDR2 comprising a sequence set forth in SEQ ID NO: 10; and a CDR3 comprising a sequence set forth in SEQ ID NO: 11; or
        (c) a CDR1 comprising a sequence set forth in SEQ ID NO: 7; a CDR2 comprising a sequence set forth in SEQ ID NO: 10; and a CDR3 comprising a sequence set forth in SEQ ID NO: 9; or

(d) a CDR1 comprising a sequence set forth in SEQ ID NO: 7; a CDR2 comprising a sequence set forth in SEQ ID NO: 16; and a CDR3 comprising a sequence set forth in SEQ ID NO: 9; and/or

(ii) a V_L comprising:

(a) a CDR1 comprising a sequence set forth in SEQ ID NO: 12; a CDR2 comprising a sequence set forth in SEQ ID NO: 13; and a CDR3 comprising a sequence set forth in SEQ ID NO: 14; or

(b) a CDR1 comprising a sequence set forth in SEQ ID NO: 12; a CDR2 comprising a sequence set forth in SEQ ID NO: 13; and a CDR3 comprising a sequence set forth in SEQ ID NO: 15.

24. The formulation according to claim 23, wherein the protein comprises a V_H comprising a CDR2 set forth in SEQ ID NO: 10 wherein the X at position 3 is D, the X at position 4 is I, the X at position 5 is P, the X at position 6 is T, the X at position 7 is K, and the X at position 8 is G.

25. A pharmaceutical formulation comprising between 100 mg/ml and 170 mg/ml of a protein comprising an antigen binding domain that binds to or specifically binds to Factor XII and/or an activated form thereof, a histidine buffer, polysorbate 80 and proline and arginine monohydrochloride as stabilisers, wherein the formulation has a pH of 5.5 to 6.5 and a viscosity of less than about 30 mPa*s at 20 °C and wherein the protein comprises a V_H comprising an amino acid sequence set forth in SEQ ID NO: 5 and a V_L comprising an amino acid sequence set forth in SEQ ID NO: 6.

26. A pharmaceutical formulation comprising between 100 mg/ml and 170 mg/ml of a protein comprising an antigen binding domain that binds to or specifically binds to Factor XII and/or an activated form thereof, a histidine buffer, polysorbate 80 and proline and arginine monohydrochloride as stabilisers, wherein the formulation has a pH of 5.5 to 6.5 and a viscosity of less than about 30 mPa*s at 20 °C and wherein the protein comprises:

(i) a V_H comprising a CDR1 comprising a sequence set forth in SEQ ID NO: 7; a CDR2 comprising a sequence set forth in SEQ ID NO: 16; and a CDR3 comprising a sequence set forth in SEQ ID NO: 9; and

(ii) a V_L comprising a CDR1 comprising a sequence set forth in SEQ ID NO: 12; a CDR2 comprising a sequence set forth in SEQ ID NO: 13; and a CDR3 comprising a sequence set forth in SEQ ID NO: 14.

27. A pharmaceutical formulation according to any one of claims 1 to 26, for use in antagonising activity and/or antagonising activation of Factor XII and/or an activated form thereof.

28. Use of the pharmaceutical formulation according to any one of claims 1 to 26, in the manufacture of a medicament for antagonising activation of Factor XII and/or an activated form thereof in a subject.

29. A pharmaceutical formulation according to any one of claims 1 to 26, for use in treating or preventing a disease or condition in a subject.

30. Use of the pharmaceutical formulation according to any one of claims 1 to 26, in the manufacture of a medicament for the treatment or prevention of a disease or condition in a subject, wherein the disease or condition is a thrombotic disorder, an inflammatory disorder and/or a thrombo-inflammatory disorder.

31. The formulation for use according to claim 29, wherein the disease or condition is a thrombotic disorder, an inflammatory disorder and/or a thrombo-inflammatory disorder.

32. The formulation for use according to claim 29 or the use according to claim 30, wherein the disease or condition is selected from the group consisting of venous, arterial or capillary thrombus formation (such as stroke, myocardial infarction, deep vein thrombosis (DVT), portal vein thrombosis, renal vein thrombosis, jugular vein thrombosis, cerebral sinus thrombosis, Budd-Chiari syndrome, Paget-Schroetter disease or silent brain ischemia), thrombus formation in the heart, thromboembolism, thrombus formation during and/or after contacting blood of a human or animal subject with artificial surfaces, disseminated intravascular coagulation (DIC), atrial fibrillation, acute coronary syndromes (ACS), atherosclerotic disease, ischaemic stroke with reperfusion, a disease associated with ischemia-reperfusion injury (IRI, such as trauma, organ transplantation), neurotraumatic disorder (such as such as traumatic brain injury, spinal cord injury), a neurological inflammatory disease (such as multiples sclerosis), an interstitial lung disease (such as idiopathic pulmonary fibrosis (IPF)), pneumonia, fibrinolysis, a disease related to FXII/FXIIa-induced kinin formation (such as hereditary angioedema (HAE)), sepsis, a disease related to FXII/FXIIa-mediated complement activation, acute respiratory distress syndrome (ARDS), organ and cell transplantation, sickle cell disease and a condition associated with increased vascular permeability.

33. A kit for use in antagonising activity and/or antagonising activation of Factor XII and/or an activated form thereof in a subject, the kit comprising:
    (a) at least one pharmaceutical formulation according to any one of claims 1 to 26;
    (b) instructions for using the kit in antagonising activity and/or antagonising activation of Factor XII and/or an activated form thereof in the subject; and
    (c) optionally, at least one further therapeutically active compound or drug.

34. A kit for use in treating or preventing a disease or condition in a subject, the kit comprising:
    (a) at least one pharmaceutical formulation according to any one of claims 1 to 26;
    (b) instructions for using the kit in treating or preventing the disease or condition in the subject; and
    (c) optionally, at least one further therapeutically active compound or drug.

35. The kit according to any one of claims 33 or 34, wherein the formulation is present in a vial, a prefilled syringe or an autoinjector device.

36. A prefilled syringe comprising the pharmaceutical formulation according to any one of claims 1 to 26.

37. An autoinjector device comprising the pharmaceutical formulation according to any one of claims 1 to 26.