CLAIMS

1. A lyophilized formulation of an anti-tissue factor (TF) antibody-drug conjugate (ADC), the lyophilized formulation obtained by lyophilizing an aqueous formulation comprising said anti-TF ADC and pharmaceutically acceptable excipients, wherein the anti-TF antibody is conjugated to a hydrophobic drug and wherein the formulation is free of surfactant.

2. The lyophilized formulation of claim 1 wherein the pharmaceutically acceptable excipients comprises:

a) a buffer which limits pH shifts during the lyophilizing step so that pH is kept between about 5 and about 7,

b) at least one non-reducing sugar which forms an amorphous phase with the anti-TF ADC in solid state; and

c) at least one bulking agent.

3. The lyophilized formulation of claims 1 or 2, wherein the aqueous formulation comprises a buffer selected from the group consisting of histidine, citrate, phosphate, carbonic acid, succinate, glycolate and a combination of any thereof.

4. The lyophilized formulation of any of claims 2 or 3, wherein the buffer is histidine.

5. The lyophilized formulation of any of claims 2 to 4, wherein the aqueous formulation comprises the buffer at a concentration of about 20 to about 50 mM, such as from about 25 mM to about 40 mM buffer, such as from about 28 mM to about 34 mM, such as from about 29 mM to about 31 mM, such as about 30 mM buffer.

6. The lyophilized formulation of any of claims 2 to 5, wherein the non-reducing sugar is selected from sucrose, trehalose and a combination thereof.

7. The lyophilized formulation of claim 6, wherein the non-reducing sugar is sucrose.

8. The lyophilized formulation of any of claims 2 to 7, wherein the aqueous formulation comprises the non-reducing sugar at a concentration of about 10 to about 250 mM, such as from about 50 to about 225 mM, such as 84 to about 165 mM, such as from about 84 to about 146 mM sucrose, such as from about 84 to about 92 mM sucrose, such as about 88 mM.

9. The lyophilized formulation of any of claims 2 to 8 wherein the bulking agent is selected from mannitol and glycine.

10. The lyophilized formulation of claim 9, wherein the bulking agent is mannitol.

11. The lyophilized formulation of any of claims 2 to 10, wherein the aqueous formulation comprises the bulking agent at a concentration of about 50 mM to about 300 mM, such as from about 100 mM to about 274 mM , such as from about 158 to about 172 mM, such as about 165 mM.

12. The lyophilized formulation of any one of the preceding claims, wherein the aqueous formulation comprises from about 5 g/L to about 30 g/L anti-TF ADC, such as about 7 to about 20 g/L anti-TF ADC, such as from about 8 to about 15 g/L anti-TF ADC.

13. The lyophilized formulation of any one of the preceding claims, wherein the aqueous formulation comprises from about 9 to about 11 g/L anti-TF ADC such as about 10 g/L anti-TF ADC.

14. The lyophilized formulation of any one of the preceding claims, wherein the pH of the aqueous formulation is in a range from about 5.5 to 6.5, such as about 6.

15. The lyophilized formulation of any one of the preceding claims, comprising mannitol and sucrose, wherein the weight by weight ratio of mannitol to sucrose is at least about 1:1.

16. The lyophilized formulation of any one of the preceding claims, comprising mannitol and sucrose, wherein the weight by weight ratio of mannitol to sucrose is between about 1:1 and about 30:1, such as between 1:1 and about 10:1, such as between about 1:1 and about 2:1.

17. The lyophilized formulation of any one of the preceding claims, comprising mannitol and sucrose, wherein the weight by weight ratio of mannitol to sucrose is about 1:1.

18. The lyophilized formulation of any one of the preceding claims, comprising mannitol, wherein the weight by weight ratio of mannitol to anti-TF ADC is at least about 3:1.

19. The lyophilized formulation of any one of the preceding claims, comprising mannitol and sucrose, wherein the weight by weight ratio of mannitol to anti-TF ADC is about 3:1 and the weight by weight ratio of mannitol to sucrose is about 1:1.

20. The lyophilized formulation according to any one of the preceding claims, which is obtainable or obtained by lyophilizing an aqueous formulation comprising about 5 g/L to about 30 g/L anti-TF ADC and pharmaceutically acceptable excipients comprising;

a. about 20 to about 50 mM histidine or citrate buffer having a pH of about 5 to about 7;

b. about 10 to about 250 mM sucrose or trehalose; and

c. about 50 mM to about 300 mM mannitol or glycine.

21. The lyophilized formulation of any one of the preceding claims, wherein the aqueous formulation comprises from about 9 to about 11 g/L anti-TF ADC, such as about 10 mg/mL anti-TF ADC, about 30 mM histidine, about 88 mM sucrose and about 165 mM mannitol.

22. The lyophilized formulation of any one of the preceding claims, wherein the anti-TF antibody competes for binding to human TF with one or more reference anti-TF antibodies comprising VH and VL regions selected from the groups consisting of:

a. a VH region comprising an amino acid sequence of SEQ ID NO: 5 and a VL region comprising an amino acid sequence of SEQ ID NO: 45;

b. a VH region comprising an amino acid sequence of SEQ ID NO: 33 and a VL region comprising an amino acid sequence of SEQ ID NO: 73;

c. a VH region comprising an amino acid sequence of SEQ ID NO: 37 and a VL region comprising an amino acid sequence of SEQ ID NO: 77; or

d. a VH region comprising an amino acid sequence of SEQ ID NO: 1 and a VL region comprising an amino acid sequence of SEQ ID NO: 41.

23. The lyophilized formulation according to any of the above claims wherein the anti-TF antibody comprises:

a. a variable heavy (VH) region comprising a CDR1 region having the amino acid sequence set forth in SEQ ID NO: 6, a CDR2 region having the amino acid sequence set forth in SEQ ID NO: 7, and a CDR3 region having the amino acid sequence set forth in SEQ ID NO: 8, and a variable light (VL) region comprising a CDR1 region having the amino acid sequence set forth in SEQ ID NO:46, a CDR2 region having the amino acid sequence set forth in SEQ ID NO: 47, and a CDR3 region having the amino acid sequence set forth in SEQ ID NO: 48; or

b. a VH region comprising a CDR1 region having the amino acid sequence set forth in SEQ ID NO: 34, a CDR2 region having the amino acid sequence set forth in SEQ ID NO: 35, and a CDR3 region having the amino acid sequence set forth in SEQ ID NO: 36, and a VL region comprising a CDR1 region having the amino acid sequence set forth in SEQ ID NO: 74, a CDR2 region having the amino acid sequence set forth in SEQ ID NO: 75, and a CDR3 region having the amino acid sequence set forth in SEQ ID NO: 76, or

c. a VH region comprising a CDR1 region having the amino acid sequence set forth in SEQ ID NO: 38, a CDR2 region having the amino acid sequence set forth in SEQ ID NO: 39, and a CDR3 region having the amino acid sequence set forth in SEQ ID NO: 40, and a VL region comprising a CDR1 region having the amino acid sequence set forth in SEQ ID NO: 78, a CDR2 region having the amino acid sequence set forth in SEQ ID NO: 79. and a CDR3 region having the amino acid sequence set forth in SEQ ID NO: 80, or

d. a VH region comprising a CDR1 region having the amino acid sequence set forth in SEQ ID NO: 2; a CDR2 region having the amino acid sequence set forth in SEQ ID NO: 3, and a CDR3 region having the amino acid sequence set forth in SEQ ID NO: 4, and a VL region comprising a CDR1 region having the amino acid sequence set forth in SEQ ID NO: 42, a CDR2 region having the amino acid sequence set forth in SEQ ID NO: 43, and a CDR3 region having the amino acid sequence set forth in SEQ ID NO: 44, or

e. a variant of any of said antibodies as defined above in (a) to (d), wherein said variant preferably has at most 1, 2 or 3 amino acid modifications, more preferably amino acid substitutions, such as conservative amino acid substitutions in said amino acid sequences defined above in (a) to (d).

24. The lyophilized formulation of any one of the preceding claims, wherein the antibody comprises

a. a VH region comprising an amino acid sequence of SEQ ID NO: 5 and a VL region comprising an amino acid sequence of SEQ ID NO: 45;

b. a VH region comprising an amino acid sequence of SEQ ID NO: 33 and a VL region comprising an amino acid sequence of SEQ ID NO: 73;

c. a VH region comprising an amino acid sequence of SEQ ID NO: 37 and a VL region comprising an amino acid sequence of SEQ ID NO: 77; or

d. a VH region comprising an amino acid sequence of SEQ ID NO: 1 and a VL region comprising an amino acid sequence of SEQ ID NO: 41.

25. The lyophilized formulation of any one of the preceding claims, wherein the average absolute number of drug moieties per antibody molecule is 1, 2, 3, 4, 5, 6, 7, or 8, such as 3, 4 or 5, preferably 4.

26. The lyophilized formulation of any one of the preceding claims, wherein the drug is an auristatin or a functional peptide analogue or derivate thereof.

27. The lyophilized formulation of any one of the preceding claims, wherein the drug is linked to the anti-TF antibody via a linker attached to sulphydryl residues of the anti-TF antibody, which sulphydryl residues have been obtained by partial reduction of the anti-TF antibody.

28. The lyophilized formulation of any one of the preceding claims, wherein the drug is MMAE or MMAF.

29. The lyophilized formulation of any one of the preceding claims, wherein the drug is linked to the anti-TF antibody via a linker-drug which is selected from: mcMMAE, vcMMAE, vcMMAF or mcMMAF, most preferred vcMMAE.

30. The lyophilized formulation of any one of the preceding claims, wherein the anti-TF antibody is a full-length antibody.

31. The lyophilized formulation of any one of the preceding claims, wherein the anti-TF antibody is a full length fully human monoclonal IgG1 antibody, optionally human IgG1κ.

32. The lyophilized formulation of any one of the preceding claims, which is obtainable or obtained by lyophilizing an aqueous formulation comprising about 9 g/L to about 11 g/L anti-TF ADC and pharmaceutically acceptable excipients comprising: about 30 mM histidine buffer having a pH of about 5 to about 7; about 88 mM sucrose; and about 165 mM mannitol; wherein the antibody comprises a VH region comprising an amino acid sequence of SEQ ID NO: 5 and a VL region comprising an amino acid sequence of SEQ ID NO: 45; a VH region comprising an amino acid sequence of SEQ ID NO: 33 and a VL region comprising an amino acid sequence of SEQ ID NO: 73; a VH region comprising an amino acid sequence of SEQ ID NO: 37 and a VL region comprising an amino acid sequence of SEQ ID NO: 77; or a VH region comprising an amino acid sequence of SEQ ID NO: 1 and a VL region comprising an amino acid sequence of SEQ ID NO: 41, and wherein the linker-drug is vcMMAE, vcMMAF or mcMMAF.

33. The lyophilized formulation of claim 32 wherein the antibody comprises a VH region comprising an amino acid sequence of SEQ ID NO: 5 and a VL region comprising an amino acid sequence of SEQ ID NO: 45.

34. The lyophilized formulation of any of claims 32 or 33 wherein the anti-TF ADC is stable at 2-8 °C, such as at 5°C for pharmaceutical use for at least 6 months, such as for at least 9 months, such as for at least 15 months or preferably for at least 18 months, or even more preferred for at least 24 months, or most preferred for at least 36 months.

35. The lyophilized formulation of claim 34, wherein the formulation is stable when it has less than 3.0% aggregates, such as less than 2.0% aggregates when stored at 5°C for at least 6 months, such as for at least 9 months, such as for at least 15 months or preferably for at least 18 months, or even more preferred for at least 24 months, or most preferred for at least 36 months.

36. The lyophilized formulation of claim 34 or 35 wherein the stability is determined by SEC analysis according to Example 10.

37. The lyophilized formulation of any one of the preceding claims which lyophilized formulation contains less than 3.0 wt. % moisture, such as less than 2.0 wt. % moisture, such as less than 1 wt. % moisture, or less than 0.5 wt. % moisture.

38. The lyophilized formulation of any one of the preceding claims wherein the formulation is free of any inorganic salts.

39. An aqueous solution suitable for preparing a lyophilized formulation of an anti-TF ADC, wherein said aqueous solution does not contain a surfactant, said solution comprising:

a. from about 7 to about 20 g/L anti-TF ADC, optionally wherein the antibody portion comprises the VH and VL sequences of any one of claims 22 to 24 and a combination of any two of b, c or d or all of b, c or d:

b. about 28 to 34 mM histidine;

c. about 84 to about 146 mM sucrose;

d. about 158 to about 274 mannitol.

40. A pharmaceutically acceptable liquid formulation obtained by reconstituting the lyophilized formulation of any one of claims 1-38 in a sterile aqueous diluent.

41. The liquid formulation of claim 40, comprising about 5 g/L to about 30 g/L anti-TF ADC, about 20 to about 50 mM histidine having a pH of about 5 to about 7; about 10 to about 250 mM sucrose or trehalose; and about 50 mM to about 300 mM mannitol or glycine.

42. The liquid formulation of claim 41, comprising about 9 to about 11 mg/mL anti-TF ADC, about 28 to about 34 mM histidine, about 84 to about 92 mM sucrose and about 158 to about 274 mM mannitol.

43. A method for preparing a lyophilized formulation of any of claims 1-38 comprising the steps of:

a. cooling the aqueous solution at a rate of from 0.5°C/min to 1°C/min to a temperature of -40°C or less;
b. holding isothermally for at least 120 min;
c. warming to between -20°C and -15°C at a rate of from 0.5°C/min to 3°C/min;
d. holding isothermally for at least 180 min;
e. applying vacuum using a pressure between 50 mTorr and 200 mTorr at a temperature between -30°C and -10°C;
f. increasing the temperature to between 35°C and 50°C at a rate of from 0.5°C/min and 1°C/min and
g. holding isothermally for at least 10 hours.

44. A method of preparing an injectable solution of an anti-TF ADC, comprising the step of reconstituting the lyophilized formulation of any one of claims 1 to 38 in a sterile aqueous diluent.