

CLAIMS

1. A pharmaceutical composition comprising or consisting essentially of:
- 50 to 120 mg/mL of a bispecific antibody binding to human CD3 and human CD20,
 - 20 to 40 mM acetate
 - 140 to 160 mM sorbitol

where the pH of the composition is from 5 to 6 and where the bispecific antibody comprises a first binding region binding to human CD3 which comprises the CDR sequences:

VH-CDR1: SEQ ID NO: 1

VH-CDR2: SEQ ID NO: 2

VH-CDR3: SEQ ID NO: 3

VL-CDR1: SEQ ID NO: 4

VL-CDR2: GTN, and

VL-CDR3: SEQ ID NO: 5

and a second binding region binding to human CD20 which comprises the CDR sequences:

VH-CDR1: SEQ ID NO: 8

VH-CDR2: SEQ ID NO: 9

VH-CDR3: SEQ ID NO: 10

VL-CDR1: SEQ ID NO: 11

VL-CDR2: DAS, and

VL-CDR3: SEQ ID NO: 12.

2. The pharmaceutical composition of claim 1 wherein the first binding region of the bispecific antibody binding to CD3 comprises a VH and a VL sequence having at least 90% sequence identity to the VH and VL sequences of SEQ ID: 6 and 7, such as at least 95%, 96%, 97%, 98%, 99% or 100% sequence identity to the VH and VL sequences of SEQ ID: 6 and 7.

3. The pharmaceutical composition of claim 1 or 2 wherein the second binding region of the bispecific antibody binding to CD20 comprises a VH and a VL sequence having at least 90% sequence identity to the VH and VL sequences of SEQ ID: 13 and 14, such as at least 95%, 96%, 97%, 98%, 99% or 100% sequence identity to the VH and VL sequences of SEQ ID: 13 and 14.

4. The pharmaceutical composition of any of claims 1-3 wherein the bispecific antibody is an IgG1 antibody.
5. The pharmaceutical composition of any one of claims 1-4 wherein the bispecific antibody comprises a first and a second light chain which comprises a first and a second light chain constant region which is selected between a lambda light chain constant region and a kappa light chain constant region such as the light chain constant regions of SEQ ID Nos 22 and 23.
6. The pharmaceutical composition of any one of the above claims wherein the bispecific antibody comprises an Fc region which comprises a first and second heavy chain, wherein said Fc region has been modified so that it has reduced effector functions compared to the bispecific antibody comprising a wild-type IgG1 Fc region.
7. The pharmaceutical composition of any one of the above claims wherein the bispecific antibody comprises an Fc region which has been modified so that binding of C1q to said antibody is reduced compared to the bispecific antibody having a wild-type IgG1 Fc region by at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, or 100%, wherein C1q binding is determined by ELISA.
8. The pharmaceutical composition of any one of the above claims wherein the bispecific antibody comprises a first and second heavy chain each comprising at least a hinge region, a CH2 and CH3 region, wherein in said first heavy chain at least one of the amino acids in the positions corresponding to a positions selected from the group consisting of T366, L368, K370, D399, F405, Y407, and K409 in a human IgG1 heavy chain has been substituted, and in said second heavy chain at least one of the amino acids in the positions corresponding to a position selected from the group consisting of T366, L368, K370, D399, F405, Y407, and K409 in a human IgG1 heavy chain has been substituted, and wherein said first and said second heavy chains are not substituted in the same positions.
9. The pharmaceutical composition of any one of the above claims wherein (i) the amino acid in the position corresponding to F405 in a human IgG1 heavy chain is L in said first heavy chain, and the amino acid in the position corresponding to K409 in a human IgG1 heavy chain is R in said second heavy chain, or (ii) the amino acid in the position

corresponding to K409 in a human IgG1 heavy chain is R in said first heavy chain, and the amino acid in the position corresponding to F405 in a human IgG1 heavy chain is L in said second heavy chain.

- 5 10. The pharmaceutical composition of any one of the above claims wherein the positions corresponding to positions L234 and L235 in the human IgG1 heavy chain of both the first heavy chain and the second heavy chain of the bispecific antibody are F and E, respectively.
- 10 11. The pharmaceutical composition of any one of the above claims wherein the positions corresponding to positions L234, L235, and D265 in the human IgG1 heavy chain of both the first heavy chain and the second heavy chain of the bispecific antibody are F, E, and A, respectively.
- 15 12. The pharmaceutical composition of any one of the above claims wherein the positions corresponding to positions L234, L235, and D265 in the human IgG1 heavy chain of both the first constant heavy chain and the second constant heavy chain of the bispecific antibody are F, E, and A, respectively, and wherein the position corresponding to F405 in the human IgG1 heavy chain of the first constant heavy chain is L, and the position corresponding to K409 in the human IgG1 heavy chain of the second constant heavy chain is R.
- 20
- 25 13. The pharmaceutical composition of any one of the above claims wherein the first and second constant heavy chains comprises an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO:16.
- 30 14. The pharmaceutical composition of any one of the above claims wherein the first and second constant heavy chains comprise the amino acid sequence of SEQ ID Nos: 19 and 20, respectively.
- 35 15. The pharmaceutical composition of any one of the above claims wherein a. is 50 to 120 mg/mL such as 50 to 110 mg/mL, or such as 50 to 100 mg/mL, such as 50 to 90mg/mL, such as 50 to 80mg/mL, such as 50 to 70mg/mL, such as 55 to 65 mg/ml, such as 58 to 62 mg/ml, such as 60 mg/mL or a is about 120 mg/mL.

16. The pharmaceutical composition of any one of the above claims wherein b. is 28 to 32 mM such as 30 mM.
17. The pharmaceutical composition of any one of the above claims wherein c. is 145 to 155 mM such as 148 to 152 mM such as 150 mM.
18. The pharmaceutical composition of any one of the above claims wherein pH is 5.3 to 5.6, such as 5.4 to 5.6 such as about 5.5.
19. The pharmaceutical composition of any one of the above claims wherein the composition has a pH of 5.4 to 5.6, such as 5.5 and consists essentially of:
- a. 50 to 120 mg/mL of the bispecific antibody
 - b. 20 to 40 mM acetate
 - c. 140 to 160 mM sorbitol.
20. The pharmaceutical composition of any one of the above claims wherein the composition has a pH of 5.4 to 5.6 and consists essentially of:
- a. 58 to 62 mg/mL of the bispecific antibody
 - b. 28 to 32 mM acetate
 - c. 145 to 155 mM sorbitol
21. The pharmaceutical composition of any one of the above claims wherein the composition has a pH of 5.5 and consists essentially of:
- a. 60 mg/mL of the bispecific antibody
 - b. 30 mM acetate
 - c. 150 mM sorbitol
22. The pharmaceutical composition of any one of the above claims 1 to 19 wherein the composition has a pH of 5.4 to 5.6 and consists essentially of:
- a. 110 to 130 mg/mL of the bispecific antibody
 - b. 28 to 32 mM acetate
 - c. 145 to 155 mM sorbitol
23. The pharmaceutical composition of any one of the above claim 22 wherein the composition has a pH of 5.5 and consists essentially of:
- a. 120 mg/mL of the bispecific antibody

- b. 30 mM acetate
- c. 150 mM sorbitol

- 5 24. The pharmaceutical composition of any one of the above claims wherein the composition does not comprise a surfactant.
25. The pharmaceutical composition of any one of the above claims wherein the composition does not comprise a hyaluronidase.
- 10 26. The pharmaceutical composition of any one of the above claims wherein the composition is a subcutaneous composition.
27. The pharmaceutical composition of any one of the above claims wherein the composition is an intravenous composition.
- 15 28. The pharmaceutical composition of any one of the above claims wherein the composition is for use in the treatment of cancer.
29. The pharmaceutical composition of any one of the above claims wherein the composition is for use in subcutaneous administration.
- 20 30. The pharmaceutical composition of any one of the above claims 1-24 wherein the composition is for use in intravenous administration.
- 25 31. The pharmaceutical composition of any one of the above claims 1-30 which is in a dosage unit form.
32. The pharmaceutical composition of any one of the above claims which composition is stable for pharmaceutical use for at least 6 months, such as at least 9 month or at least
- 30 12 months at a storage temperature of 2-8°C, such as 5°C.
33. Use of the pharmaceutical composition of any one of claims 1-25 for subcutaneous administration.

34. Use of the pharmaceutical composition of any one of claims 1-25 for intravenous administration.
35. The use of any one of claims 33 or 34 wherein the use is for the treatment of cancer.
36. A method of treating cancer in a subject comprising administering to a subject in need thereof the pharmaceutical composition of any one of claims 1 to 32 for a time sufficient to treat the cancer.
37. The method of claim 36 wherein the composition is administered subcutaneously or intravenously.
38. The method of any one of claims 36 or 37 wherein the cancer is a B-cell malignancy.
39. A unit dosage form, comprising or consisting essentially of
- a. a bispecific antibody comprising a first binding region binding to human CD3 which comprises the CDR sequences:
VH-CDR1: SEQ ID NO: 1
VH-CDR2: SEQ ID NO: 2
VH-CDR3: SEQ ID NO: 3
VL-CDR1: SEQ ID NO: 4
VL-CDR2: GTN, and
VL-CDR3: SEQ ID NO: 5,
and a second binding region binding to human CD20 which comprises the CDR sequences:
VH-CDR1: SEQ ID NO: 8
VH-CDR2: SEQ ID NO: 9
VH-CDR3: SEQ ID NO: 10
VL-CDR1: SEQ ID NO: 11
VL-CDR2: DAS, and
VL-CDR3: SEQ ID NO: 12
in an amount of from 5 µg to 50 mg,
 - b. acetate buffer and sorbitol in a ratio of between 1:5 and 1:10 wherein the osmolality of the unit dosage form is from 210 to 250 and the pH is from 5.4 to 5.6.

40. A unit dosage form, comprising or consisting essentially of:

- a. a bispecific antibody comprising a first binding region binding to human CD3 which comprises the CDR sequences:

VH-CDR1: SEQ ID NO: 1

VH-CDR2: SEQ ID NO: 2

VH-CDR3: SEQ ID NO: 3

VL-CDR1: SEQ ID NO: 4

VL-CDR2: GTN, and

VL-CDR3: SEQ ID NO: 5,

and a second binding region binding to human CD20 which comprises the CDR sequences:

VH-CDR1: SEQ ID NO: 8

VH-CDR2: SEQ ID NO: 9

VH-CDR3: SEQ ID NO: 10

VL-CDR1: SEQ ID NO: 11

VL-CDR2: DAS, and

VL-CDR3: SEQ ID NO: 12

in an amount of from 5 µg to 50 mg,

- b. acetate at a concentration of 30 mM,

- c. sorbitol at a concentration of 150 mM,

at a pH of 5.5.

41. The unit dosage form of any one of claims 39 or 40 wherein the first binding region of the bispecific antibody binding to human CD3 comprises the VH and VL sequences of SEQ ID: 6 and 7 and the second binding region of the bispecific antibody binding to human CD20 comprises the VH and VL sequences of SEQ ID: 13 and 14.

42. The unit dosage form of claim 41 wherein the bispecific antibody comprises the first and second constant region heavy chains of SEQ ID NOs: 19 and 20 respectively.

43. The unit dosage form of any one of claims 39 to 42 wherein the amount of the bispecific antibody is from 50 µg to 40 mg.

44. The unit dosage form of any one of claims 39 to 43 wherein the amount of the bispecific antibody is from 100 µg to 30 mg, such as 150 µg, 200 µg, 250 µg, 300 µg, 350 µg, 400 µg, 450 µg, 500 µg, 600 µg, 700 µg, 800 µg, 900 µg, 1 mg, 2 mg, 3 mg, 4 mg, 5

mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg such as 30 mg.

5 45. The unit dosage form of any one of claim 39 to 44 wherein the total volume is from 0.5 mL to 2 mL, such as 1 mL.

46. The unit dosage form of claim 45 which unit dosage form is for subcutaneous administration.

10

47. The unit dosage form of any one of claim 39 to 44 wherein the total volume is from 20 mL to 200 mL wherein the dosage form is for I.V. administration.

15

48. A method of treating cancer in a subject comprising administering to a subject in need thereof the unit dosage form of any one of claims 39 to 47 for a time sufficient to treat the cancer.

49. The unit dosage form of any one of claims 39 to 47 for use in the treatment of cancer.

20

50. A container comprising the unit dosage form of any one of claims 39 to 45.

51. A kit-of-parts comprising:

25

- a. the pharmaceutical composition of any one of claims 1 to 25
- b. a diluent comprising acetate and sorbitol
- c. a receptacle for the unit dosage form
- d. directions for dilution and/or for use.

52. The kit-of-parts of claim 51 wherein the ratio of the concentrations of acetate and sorbitol is identical in the diluent and the pharmaceutical composition.

30

53. The kit-of-parts of any one of claims 51 or 52 wherein

35

- a. the pharmaceutical composition comprises:
 - i. 60 mg/mL of the bispecific antibody
 - ii. 30 mM acetate buffer
 - iii. 150 mM sorbitol
 - iv. pH is 5.5

- b. the diluent comprises:
 - i. 30 mM acetate buffer
 - ii. 150 mM sorbitol
- c. a receptacle for the unit dosage form, and
- d. directions for dilution and/or for use.

54. A method of preparing a pharmaceutical composition as defined in any one of claims 1 to 32, comprising the steps of mixing in water for injection:

- a. 60 to 120 mg/mL of a bispecific antibody comprising a first binding region binding to human CD3 which comprises the CDR sequences:
 - VH-CDR1: SEQ ID NO: 1
 - VH-CDR2: SEQ ID NO: 2
 - VH-CDR3: SEQ ID NO: 3
 - VL-CDR1: SEQ ID NO: 4
 - VL-CDR2: GTN, and
 - VL-CDR3: SEQ ID NO: 5,
- and a second binding region binding to human CD20 which comprises the CDR sequences:
 - VH-CDR1: SEQ ID NO: 8
 - VH-CDR2: SEQ ID NO: 9
 - VH-CDR3: SEQ ID NO: 10
 - VL-CDR1: SEQ ID NO: 11
 - VL-CDR2: DAS, and
 - VL-CDR3: SEQ ID NO: 12
- b. 3.53 mg/mL of sodium acetate trihydrate
- c. 0.32 mg/mL of acetic acid
- d. 27.3 mg/mL of sorbitol

and adjusting the pH to 5.5 by adding sodium hydroxide.

55. The method of claim 54 wherein a. is 60 mg/mL.

56. The method of claim 54 wherein a. is 120 mg/mL.

57. A method of preparing a unit dosage form as defined in any one of claims 39 to 45, comprising the steps of:

- a. preparing the pharmaceutical composition by the method of any of claims 54 to 56
- 5 b. preparing a diluent in water for injection comprising:
 - i. 3.53 mg/mL of sodium acetate trihydrate
 - ii. 0.32 mg/mL of acetic acid
 - iii. 27.3 mg/mL of sorbitol
 - iv. sodium hydroxide to adjust pH to 5.5
- 10 c. mixing the pharmaceutical composition and the diluent to a desired bispecific antibody concentration.

58. A pharmaceutical composition or a unit dosage form, which is obtainable by the method
15 as defined in any one of claims 54 to 57.