

CLAIMS

1. A pharmaceutical composition comprising or consisting essentially of:

- a. ~~2-50~~ to ~~15~~20 mg/mL of a bispecific antibody binding to human CD3 and human CD20,
- b. ~~20 to 40~~30 mM acetate
- c. ~~150 140 to 160~~ mM sorbitol

where the pH of the composition is ~~from 5 to 6~~5.5 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.

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.

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.

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.

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.

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.

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. ~~16. The pharmaceutical composition of any one of the above claims 1-15 wherein the composition has a pH of 5.4 to 5.6, such as 5.5 and consists essentially of:~~

- a. ~~is 50 to 120 mg/mL of the bispecific antibody~~
- b. ~~20 to 40 mM acetate~~
- c. ~~140 to 160 mM sorbitol.~~

20. ~~17. 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. ~~is 58 to 62 mg/mL of the bispecific antibody~~
- b. ~~28 to 32 mM acetate~~
- c. ~~145 to 155 mM sorbitol~~

21. ~~18. The pharmaceutical composition of any one of the above claims wherein the composition has a pH of 5.5 and consists essentially of:~~

- a. ~~is 60 mg/mL of the bispecific antibody~~
- b. ~~30 mM acetate~~
- c. ~~150 mM sorbitol~~

22. ~~19. The pharmaceutical composition of any one of the above claims 1 to 159 wherein the composition has a pH of 5.4 to 5.6 and consists essentially of:~~

- a. ~~is 110 to 130 mg/mL of the bispecific antibody~~
- b. ~~28 to 32 mM acetate~~
- c. ~~145 to 155 mM sorbitol~~

23. ~~20. The pharmaceutical composition of any one of the above claims 1-16 or 192-22 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 ~~24-21.~~ ____ The pharmaceutical composition of any one of the above claims wherein the composition does not comprise a surfactant.

~~25-22.~~ ____ The pharmaceutical composition of any one of the above claims wherein the composition does not comprise a hyaluronidase.

10 ~~26-23.~~ ____ The pharmaceutical composition of any one of the above claims wherein the composition is a subcutaneous composition.

~~27-24.~~ ____ The pharmaceutical composition of any one of the above claims wherein the composition is an intravenous composition.

15 ~~28-25.~~ ____ The pharmaceutical composition of any one of the above claims wherein the composition is for use in the treatment of cancer.

20 ~~29-26.~~ ____ The pharmaceutical composition of any one of the above claims wherein the composition is for use in subcutaneous administration.

~~30-27.~~ ____ The pharmaceutical composition of any one of the above claims 1-~~24-21~~ wherein the composition is for use in intravenous administration.

25 ~~31-28.~~ ____ The pharmaceutical composition of any one of the above claims 1-~~30-27~~ which is in a dosage unit form.

30 ~~32-29.~~ ____ 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 12 months at a storage temperature of 2-8°C, such as 5°C.

~~33-30.~~ ____ Use of the pharmaceutical composition of any one of claims 1-~~25-22~~, in the manufacture of a medicament for subcutaneous administration for the treatment of cancer.

~~34-31.~~ Use of the pharmaceutical composition of any one of claims 1-~~2522~~, in the manufacture of a medicament for intravenous administration for the treatment of cancer.

~~35-32.~~ Use of the pharmaceutical composition of any one of claims 1 to ~~3229~~, in the manufacture of a medicament for a time-sufficient-treatment of the cancer, wherein the medicament is to be administered to a subject in need thereof.

~~36-33.~~ The use of claim ~~35-32~~ wherein the composition is to be administered subcutaneously or intravenously.

~~37-34.~~ The use of any one of claims ~~35-32~~ or ~~36-33~~ wherein the cancer is a B-cell malignancy.

~~38-35.~~ 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.

39-36. 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.

40-37. The unit dosage form of any one of claims 38-35 or 39-36 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.

41-38. The unit dosage form of claim 40-37 wherein the bispecific antibody comprises the first and second constant region heavy chains of SEQ ID NOs: 19 and 20 respectively.

42-39. The unit dosage form of any one of claims 38-35 to 41-38 wherein the amount of the bispecific antibody is from 50 µg to 40 mg.

5 | ~~43-40.~~ The unit dosage form of any one of claims ~~38-35~~ to ~~42-39~~ 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.

10 | ~~44-41.~~ The unit dosage form of any one of claim ~~38-35~~ to ~~43-40~~ wherein the total volume is from 0.5 mL to 2 mL, such as 1 mL.

15 | ~~45-42.~~ The unit dosage form of claim ~~45-41~~ which unit dosage form is for subcutaneous administration.

20 | ~~46-43.~~ The unit dosage form of any one of claim ~~38-35~~ to ~~43-40~~ wherein the total volume is from 20 mL to 200 mL wherein the dosage form is for I.V. administration.

25 | ~~47-44.~~ Use of the unit dosage form of any one of claims ~~38-35~~ to ~~46-43~~, in the manufacture of a medicament, for a time-sufficient treatment of the cancer, wherein the medicament is to be administered to a subject in need thereof.

30 | ~~48-45.~~ The unit dosage form of any one of claims ~~38-35~~ to ~~46-43~~ for use in the treatment of cancer.

35 | ~~49-46.~~ A container comprising the unit dosage form of any one of claims ~~38-35~~ to ~~44-41~~.

40 | ~~50-47.~~ A kit-of-parts comprising:

- a. the pharmaceutical composition of any one of claims 1 to ~~25-22~~
- b. a diluent comprising acetate and sorbitol
- c. a receptacle for the unit dosage form
- d. directions for dilution and/or for use.

45 | ~~51-48.~~ The kit-of-parts of claim ~~50-47~~ wherein the ratio of the concentrations of acetate and sorbitol is identical in the diluent and the pharmaceutical composition.

50 | ~~52-49.~~ The kit-of-parts of any one of claims ~~50-47~~ or ~~51-48~~ wherein

- 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

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- 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.

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~~53-50.~~ 50. A method of preparing a pharmaceutical composition as defined in any one of claims 1 to ~~3229~~, comprising the steps of mixing in water for injection:

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- 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.

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54.~~51.~~____The method of claim ~~53-50~~ wherein a. is 60 mg/mL.

55.~~52.~~____The method of claim ~~53-50~~ wherein a. is 120 mg/mL.

5 56.~~53.~~____A method of preparing a unit dosage form as defined in any one of claims ~~38-35~~
to ~~4441~~, comprising the steps of:

a. preparing the pharmaceutical composition by the method of any of claims ~~53-50~~
to ~~5552~~

b. preparing a diluent in water for injection comprising:

10 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

c. mixing the pharmaceutical composition and the diluent to a desired bispecific
15 antibody concentration.

57.~~54.~~____A pharmaceutical composition or a unit dosage form, which is obtainable by the
method as defined in any one of claims ~~53-50~~ to ~~5653~~.