

particularly difficult to obtain when the formulation should include antibodies in a high concentration.

It is therefore an object of the present invention to provide a liquid, in particular high concentration, formulation of a bispecific VEGF/ANG2 antibody with as few as necessary excipients, which enables the desired dosing and allows convenient intravitreal administration of the bispecific antibody through thin needles to a patient.

Summary

The present disclosure relates to a liquid pharmaceutical formulation of a bispecific anti-VEGF/ANG2 antibody, a method for the preparation and uses of the formulation. In particular, the pharmaceutical formulations of the present disclosure are for use in intravitreal administration for the treatment of ophthalmologic diseases like AMD and DME.

The disclosure refers to a liquid pharmaceutical formulation, comprising:

- 20 to 150 mg/ml of a bispecific anti-VEGF/ANG2 antibody comprising a constant heavy chain region of human IgG1 subclass

- 15 to 35 mM of sodium chloride

- 15 to 25 mM of a histidine acetate buffer

at a pH of 5.5 ± 0.5 ; wherein

the bispecific anti-VEGF/ANG2 antibody is bivalent and comprises a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2, wherein

- i) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 1, a CDR2H region of SEQ ID NO: 2, and a CDR1H region of SEQ ID NO:3, and in the light chain variable domain a CDR3L region of SEQ ID NO: 4, a CDR2L region of SEQ ID NO:5, and a CDR1L region of SEQ ID NO:6; and

- ii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3H region of SEQ

ID NO: 9, a CDR2H region of, SEQ ID NO: 10, and a CDR1H region of SEQ ID NO: 11, and in the light chain variable domain a CDR3L region of SEQ ID NO: 12, a CDR2L region of SEQ ID NO: 13, and a CDR1L region of SEQ ID NO: 14, and wherein

iii) the bispecific antibody comprises a constant heavy chain region of human IgG1 subclass comprising the mutations I253A, H310A, and H435A and the mutations L234A, L235A and P329G (numberings according to EU Index of Kabat.

In one aspect, the disclosure refers to a liquid pharmaceutical formulation comprising:

- 120 mg/ml $\pm$ 18 mg/ml of a bispecific anti-VEGF/ANG2 antibody comprising a constant heavy chain region of human IgG1 subclass,

- 15 to 35 mM of sodium chloride,

- 15 to 25 mM of a histidine acetate buffer,

at a pH of 5.5 ± 0.5 ;

wherein the bispecific anti-VEGF/ANG2 antibody is bivalent and comprises a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2, wherein

i) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 1, a CDR2H region of SEQ ID NO: 2, and a CDR1H region of SEQ ID NO:3, and in the light chain variable domain a CDR3L region of SEQ ID NO: 4, a CDR2L region of SEQ ID NO:5, and a CDR1L region of SEQ ID NO:6; and

- 5 ii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 9, a CDR2H region of, SEQ ID NO: 10, and a CDR1H region of SEQ ID NO: 11, and in the light chain variable domain a CDR3L region of SEQ ID NO: 12, a CDR2L region of SEQ ID NO: 13, and a CDR1L region of SEQ ID NO: 14, and wherein
- 10 iii) the bispecific antibody comprises a constant heavy chain region of human IgG1 subclass comprising the mutations I253A, H310A, and H435A and the mutations L234A, L235A and P329G (numberings according to EU Index of Kabat.

In one example the bispecific anti-VEGF/ANG2 antibody is bivalent and comprises the amino acid sequences of SEQ ID NO: 17, of SEQ ID NO: 18, of SEQ ID NO: 19, and of SEQ ID NO: 20.

15 In one example the bispecific anti-VEGF/ANG2 antibody is faricimab.

In one example the formulation further comprises

- 1 to 20mM of at least one stabilizer.

In one example the formulation further comprises

- 7.0 mM $\pm$ 2.0 mM methionine.

20 In one example the formulation further comprises

- 0.01-0.07% (w/v) of a surfactant.

In one example the formulation further comprises

- 0.04% (w/v) $\pm$ 0.02% (w/v) polysorbate 20.

In one example the formulation further comprises

25 - 50-250 mM of a tonicity agent.

In one example the formulation further comprises

- 160 mM $\pm$ 24 mM sucrose.

In one example the formulation is essentially free of visible particles.

In one example the formulation is a stable formulation.

In one example the osmolality of the formulation is 300 ± 100 mOsm/kg.

In one example the formulation is for intravitreal administration.

- 5 The formulation is for use in the treatment of an ocular vascular disease. In another aspect, the present disclosure provides the pharmaceutical formulation for use in the treatment of an ocular vascular disease.

10 In one example the ocular vascular disease is selected from the group consisting of diabetic retinopathy (DR), diabetic macular edema (DME), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), macular degeneration, wet age-related macular degeneration (wet AMD), retinopathy of prematurity (ROP), neovascular glaucoma, retinitis pigmentosa (RP), retinal angiomatous proliferation, macular telangiectasia, ischemic retinopathy, iris neovascularization, intraocular neovascularization, corneal neovascularization, retinal neovascularization, choroidal neovascularization, and retinal degeneration, in particular from the group consisting of diabetic retinopathy (DR), diabetic macular edema (DME), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), wet age-related macular degeneration (wet AMD).

- 20 The disclosure provides a method for the preparation of the pharmaceutical formulation according to the disclosure. In another aspect, the present disclosure provides a method for the preparation of the pharmaceutical formulation according to the disclosure, the method comprising the steps of

25 -buffer exchange of the bispecific antibody bulk solution a) against a diafiltration buffer by ultra-filtration and diafiltration or b) by dialysis using a dialysis buffer, the buffers containing a histidine-acetate buffer or a histidine-acetate buffer and sodium chloride, or a histidine-acetate buffer, sodium chloride and methionine, or a histidine-acetate buffer, sodium chloride, methionine and sucrose

- concentration of the buffer exchanged bulk solution by ultrafiltration
- adjustment of the final composition of the pharmaceutical formulation by addition of stock solutions of the respective excipients or by an appropriate conditioning buffer and homogenization of the liquid pharmaceutical formulation is homogenized by mixing.

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One aspect of the disclosure is a vial comprising the pharmaceutical formulation according to the disclosure.

One aspect of the disclosure is a prefilled syringe comprising the pharmaceutical formulation according to the disclosure.

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One aspect of the disclosure is a lyophilised form of the liquid pharmaceutical formulation according to the disclosure.

The present disclosure provides a liquid pharmaceutical formulation of a bispecific anti-VEGF/ANG2 antibody (with IgG1 constant region) which has valuable properties useful for ophthalmologic use and intravitreal application: the formulation has low viscosity and low turbidity (even at high

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Patent Claims

1. A liquid pharmaceutical formulation comprising:

- 120 mg/ml $\pm$ 18 mg/ml of a bispecific anti-VEGF/ANG2 antibody comprising a constant heavy chain region of human IgG1 subclass,

5 - 15 to 35 mM of sodium chloride,

- 15 to 25 mM of a histidine acetate buffer,

at a pH of 5.5 ± 0.5 ;

wherein the bispecific anti-VEGF/ANG2 antibody is bivalent and comprises a first antigen-binding site that specifically binds to human VEGF and a second
10 antigen-binding site that specifically binds to human ANG-2, wherein

i) said first antigen-binding site specifically binding to VEGF comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 1, a CDR2H region of SEQ ID NO: 2, and a CDR1H region of SEQ ID NO:3, and in the light chain variable domain a CDR3L region of SEQ
15 ID NO: 4, a CDR2L region of SEQ ID NO:5, and a CDR1L region of SEQ ID NO:6; and

ii) said second antigen-binding site specifically binding to ANG-2 comprises in the heavy chain variable domain a CDR3H region of SEQ ID NO: 9, a CDR2H region of, SEQ ID NO: 10, and a CDR1H region
20 of SEQ ID NO: 11, and in the light chain variable domain a CDR3L region of SEQ ID NO: 12, a CDR2L region of SEQ ID NO: 13, and a CDR1L region of SEQ ID NO: 14, and wherein

iii) the bispecific antibody comprises a constant heavy chain region of
25 human IgG1 subclass comprising the mutations I253A, H310A, and H435A and the mutations L234A, L235A and P329G, numberings according to EU Index of Kabat.

2. The pharmaceutical formulation according to claim 1, wherein the bispecific anti-VEGF/ANG2 antibody is bivalent and comprises a first antigen-binding

site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2, wherein

5 i) said first antigen-binding site specifically binding to VEGF comprises as heavy chain variable domain VH an amino acid sequence of SEQ ID NO: 7, and as light chain variable domain VL an amino acid sequence of SEQ ID NO: 8, and

10 ii) said second antigen-binding site specifically binding to ANG-2 comprises as heavy chain variable domain VH an amino acid sequence of SEQ ID NO: 15, and as light chain variable domain VL an amino acid sequence of SEQ ID NO: 16.

3. The pharmaceutical formulation according to claim 2, wherein the bispecific anti-VEGF/ANG2 antibody is bivalent and comprises a first antigen-binding site that specifically binds to human VEGF and a second antigen-binding site that specifically binds to human ANG-2,

15 wherein

iv) in the constant heavy chain region a S354C and T366W mutations are comprised in one CH3 domain and Y349C, T366S, L368A and Y407V mutations are comprised the other CH3 domain, numberings according to EU Index of Kabat.

20 4. The pharmaceutical formulation according to any one of claims 1 to 3, wherein the bispecific anti-VEGF/ANG2 antibody is bivalent and comprises the amino acid sequences of SEQ ID NO: 17, of SEQ ID NO: 18, of SEQ ID NO: 19, and of SEQ ID NO: 20

25 5. The pharmaceutical formulation according to any one of claims 1 to 3, wherein the bispecific anti-VEGF/ANG2 antibody is faricimab.

6. The pharmaceutical formulation according to any one of claims 1 to 5 for intravitreal administration.

7. The pharmaceutical formulation according to any one of claims 1 to 6, wherein the formulation is essentially free of visible particles.

8. The pharmaceutical formulation according to any one of claims 1 to 7, wherein the formulation further comprises
- 1 to 20mM of at least one stabilizer.
- 5 9. The pharmaceutical formulation according to any one of claims 1 to 7, wherein the formulation further comprises
- 7.0 mM $\pm$ 2.0 mM methionine.
- 10 10. The pharmaceutical formulation according to any one of claims 1 to 9, wherein the formulation further comprises
- 0.01-0.07%(w/v) of a surfactant.
- 10 11. The pharmaceutical formulation according to any one of claims 1 to 9, wherein the formulation further comprises
- 0.03% to 0.07% (w/v) polysorbate 20.
12. The pharmaceutical formulation according to any one of claims 1 to 11, wherein the formulation further comprises
- 15 - 50-250 mM of a tonicity agent.
13. The pharmaceutical formulation according to any one of claims 1 to 11, wherein the formulation further comprises
- 160 mM $\pm$ 24 mM sucrose.
14. The pharmaceutical formulation according to any one of claims 1 to 13, wherein the formulation has a viscosity of 20 mPas or less.
- 20 15. The pharmaceutical formulation according to any one of claims 1 to 14, wherein the formulation has a turbidity of 30 FTU or less.
16. The pharmaceutical formulation according to any one of claims 1 to 15, wherein the formulation has an ionic strength between 20 and 50.
- 25 17. The pharmaceutical formulation according to any one of claims 1 to 16, wherein formulation is a stable formulation.

18. The pharmaceutical formulation according to any one of claims 1 to 17, wherein the high molecular weight species (HMW) content of the bispecific antibody in the pharmaceutical formulation is below 10% after 8 weeks at 25°C or after 52 weeks at 25°C.
- 5 19. The pharmaceutical formulation according to any one of claims 1 to 18, wherein the osmolality of the formulation is 300±100 mOsm/kg.
20. The pharmaceutical formulation according to any one of claims 1 to 19 for use in the treatment of an ocular vascular disease.
- 10 21. The pharmaceutical formulation for use according to claim 20, wherein the ocular vascular diseases is selected from the group consisting of diabetic retinopathy (DR), diabetic macular edema (DME), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), macular degeneration, wet age-related macular degeneration (wet AMD), retinopathy of prematurity (ROP), neovascular glaucoma, retinitis pigmentosa (RP), retinal angiomatous proliferation, macular telangiectasia, ischemic retinopathy, iris neovascularization, intraocular neovascularization, corneal neovascularization, retinal neovascularization, choroidal neovascularization, and retinal degeneration, in particular from the group consisting of diabetic retinopathy (DR), diabetic macular edema (DME), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), wet age-related macular degeneration (wet AMD).
- 15 22. A method for the preparation of the pharmaceutical formulation of any one of claims 1 to 19,
- 20 the method comprising the steps of
- 25 -buffer exchange of the bispecific antibody bulk solution a) against a diafiltration buffer by ultra-filtration and diafiltration or b) by dialysis using a dialysis buffer, the buffers containing a histidine-acetate buffer or a histidine-acetate buffer and sodium chloride, or a histidine-acetate buffer, sodium chloride and methionine, or a histidine-acetate buffer, sodium chloride,
- 30 methionine and sucrose
- concentration of the buffer exchanged bulk solution by ultrafiltration

- adjustment of the final composition of the pharmaceutical formulation by addition of stock solutions of the respective excipients or by an appropriate conditioning buffer and homogenization of the liquid pharmaceutical formulation is homogenized by mixing.

- 5 23. A vial comprising the pharmaceutical formulation of any one of claims 1 to 19.
24. A prefilled syringe comprising the pharmaceutical formulation of any one of claims 1 to 19.
25. A lyophilised form of the liquid pharmaceutical formulation of any one of claims 1 to 19.