

What is claimed is:

1. Use of an injectable pharmaceutical composition comprising;
an angiopoietin-2 (Ang-2) inhibitor; and
a vascular endothelial growth factor (VEGF) antagonist in the manufacture of a medicament for the treatment of a vascular eye disease or disorder.
2. The use of claim 1, comprising 40 mg/mL of the VEGF antagonist, and 0.5 mg to 10 mg of the Ang-2 inhibitor.
3. The use of any one of claims 1 or 2, wherein the eye disease or disorder is selected from the group consisting of diabetic retinopathy, diabetic macular edema, age-related macular degeneration, retinal neovascularization, central retinal vein occlusion, branched retinal vein occlusion, polypoidal choroidal vasculopathy, and choroidal neovascularization.
4. Use of an injectable pharmaceutical composition comprising an Ang-2 inhibitor in combination with a VEGF antagonist in the manufacture of a medicament for treating retinal angiogenesis.
5. The use of claim 4, wherein the retinal angiogenesis is associated with an eye disease or disorder selected from the group consisting of diabetic retinopathy, diabetic macular edema, age-related macular degeneration, retinal neovascularization, central retinal vein occlusion, branched retinal vein occlusion, polypoidal choroidal vasculopathy, and choroidal neovascularization.
6. Use of an injectable pharmaceutical composition comprising an Ang-2 inhibitor in combination with a VEGF antagonist in the manufacture of a medicament for inhibiting neovascularization.
7. Use of an injectable pharmaceutical composition comprising an Ang-2 inhibitor in combination with a VEGF antagonist in the manufacture of a medicament for inhibiting vascular leak.

8. Use of an injectable pharmaceutical formulation in the manufacture of a medicament for reducing the number of intravitreal injections to be administered to a subject with an eye disease,

wherein the formulation is to be sequentially administered with a first initial dose following by one or more secondary doses of a pharmaceutical composition comprising a therapeutically effective amount of an Ang-2 inhibitor in combination with a VEGF antagonist;

whereby the formulation allows that intravitreal administration of the VEGF antagonist is reduced to once every 9 weeks as compared to a subject who has been administered the VEGF antagonist alone.

9. The use of claim 8, wherein the one or more secondary doses comprises 2 – 10 doses of the pharmaceutical composition.

10. The use of claim 9, wherein at least 2 secondary doses of the pharmaceutical composition are to be administered to the subject, and wherein each secondary dose is to be administered 1 to 4 weeks after the immediately preceding dose.

11. The use of any one of the preceding claims, wherein the Ang-2 inhibitor is an anti-Ang-2 antibody or antigen binding fragment thereof.

12. The use of claim 11, wherein the antibody or antigen binding fragment comprises the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) having the amino acid sequence of SEQ ID NO: 1 and the CDRs of a light chain variable region (LCVR) having the amino acid sequence of SEQ ID NO: 2.

13. The use of claim 12, wherein the antibody or antigen binding fragment comprises a heavy chain CDR1 (HCDR1) having the amino acid sequence of SEQ ID NO: 3, a HCDR2 having the amino acid sequence of SEQ ID NO: 4, a HCDR3 having the amino acid sequence of SEQ ID NO: 5, a light chain CDR1 (LCDR1) having the amino acid sequence of SEQ ID NO: 6, a LCDR2 having the amino acid sequence of SEQ ID NO: 7, and a LCDR3 having the amino acid sequence of SEQ ID NO: 8.

14. The use of claim 13, wherein the antibody or antigen binding fragment thereof comprises a HCVR having the amino acid sequence of SEQ ID NO: 1 and a LCVR having the amino acid sequence of SEQ ID NO: 2.

15. The use of any one of the preceding claims, wherein the VEGF antagonist comprises a VEGF receptor-based chimeric molecule (VEGF Trap).

16. The use of claim 15, wherein the VEGF Trap comprises one or more immunoglobulin (Ig)-like domains of VEGFR1, one or more Ig-like domains of VEGFR2, and a multimerizing domain.

17. The use of claim 16, wherein the VEGF Trap comprises Ig-like domain 2 of VEGFR1, Ig-like domain 3 of VEGFR2, and a multimerizing domain.

18. The use of claim 15, wherein the VEGF Trap is aflibercept.

19. The use of any one of the preceding claims, wherein the VEGF antagonist consists of a dimer of two polypeptides consisting of amino acids 27-457 of SEQ ID NO: 11.

20. A stable liquid formulation comprising: (i) a vascular endothelial growth factor (VEGF) antagonist; (ii) an antibody that binds specifically to human angiopoietin-2 (hAng-2); (iii) a buffer at pH of 6.2 ± 0.3 ; (iv) a non-ionic detergent; (v) a tonicity agent; and (vi) a stabilizer; wherein the VEGF antagonist consists of a dimer of two polypeptides consisting of amino acids 27-457 of SEQ ID NO: 11.

21. The formulation of claim 20, wherein the antibody comprises three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) wherein HCDR1 has SEQ ID NO: 3, HCDR2 has SEQ ID NO: 4, HCDR3 has SEQ ID NO: 5, and three light chain CDRs (LCDR1, LCDR2 and LCDR3), wherein LCDR1 has SEQ ID NO: 6, LCDR2 has SEQ ID NO: 7, and LCDR3 has SEQ ID NO: 8.

22. The formulation of any one of claims 20 and 21, wherein the antibody comprises a heavy chain variable region (HCVR) of SEQ ID NO: 1 and a light chain variable region (LCVR) of SEQ ID NO: 2.

23. The formulation of claim 22, wherein the VEGF antagonist concentration is about 40 mg/mL $\pm$ 1.5 mg/mL.

24. The formulation of claim 23, comprising about 10 – 120 mg/mL of the antibody.

25. The formulation of claim 24, comprising the antibody at a concentration selected from the group consisting of 10 mg/mL, 20 mg/mL, 60 mg/mL, and 120 mg/mL.

26. The formulation of claim 20, comprising about 5 – 100 mg/mL of the VEGF antagonist; about 10 – 120 mg/mL of the anti-Ang-2 antibody; about 5 – 50 mM sodium phosphate, pH about 6.2; about 0.01 – 0.1% (w/v) polysorbate; about 10 – 50 mM sodium chloride; and about 1 – 20% (w/v) sucrose.

27. The formulation of claim 26, comprising the antibody at a concentration selected from the group consisting of 10 mg/ml, 20 mg/ml, 60 mg/ml, and 120 mg/ml.

28. The formulation of claim 25, wherein (a) the buffer is sodium phosphate;

(b) the sodium phosphate concentration is 10 mM $\pm$ 1.5 mM;

(c) the non-ionic detergent is polysorbate 20;

(d) the polysorbate 20 concentration is 0.03% w/v $\pm$ 0.0045%;

(e) the tonicity agent is sodium chloride;

(f) the sodium chloride concentration is 40 mM $\pm$ 6.0 mM; and

(g) the stabilizer is sucrose is present in a concentration of 5% $\pm$ 0.75%.

29. The formulation of claim 20, wherein the VEGF antagonist concentration is 40 mg/mL $\pm$ 6.0 mg/mL, the antibody concentration is 10 mg/mL $\pm$ 1.5 mg/mL, the buffer is 10mM $\pm$ 1.5mM sodium phosphate, pH 6.2 $\pm$ 0.3, the non-ionic detergent is 0.03% w/v $\pm$ 0.0045% polysorbate 20, the tonicity agent is 40mM sodium chloride, and the stabilizer is 5% w/v $\pm$ 1.5% sucrose.

30. The formulation of claim 20, wherein the VEGF antagonist concentration is 40 mg/mL $\pm$ 6.0 mg/mL, the antibody concentration is 20 mg/mL $\pm$ 3.0 mg/mL, the buffer is 10mM $\pm$ 1.5mM sodium phosphate, pH 6.2 $\pm$ 0.3, the non-ionic detergent is 0.03% w/v $\pm$ 0.0045% polysorbate 20, the tonicity agent is 40mM sodium chloride, and the stabilizer is 5% w/v $\pm$ 1.5% sucrose.

31. The formulation of claim 20, wherein the VEGF antagonist concentration is 40 mg/mL $\pm$ 6.0 mg/mL, the antibody concentration is 60 mg/mL $\pm$ 9.0 mg/mL, the buffer is 10mM $\pm$ 1.5mM sodium phosphate, pH 6.2 $\pm$ 0.3, the non-ionic detergent is 0.03% w/v $\pm$ 0.0045% polysorbate 20, the tonicity agent is 40mM sodium chloride, and the stabilizer is 5% w/v $\pm$ 1.5% sucrose.

32. The formulation of claim 20, wherein the VEGF antagonist concentration is 40 mg/mL $\pm$ 6.0 mg/mL, the antibody concentration is 120 mg/mL $\pm$ 18.0 mg/mL, the buffer is 10mM $\pm$ 1.5mM sodium phosphate, pH 6.2 $\pm$ 0.3, the non-ionic detergent is 0.03% w/v $\pm$ 0.0045% polysorbate 20, the tonicity agent is 40mM sodium chloride, and the stabilizer is 5% w/v $\pm$ 1.5% sucrose.

33. Use of a formulation of any of claims 20-27 and 29-32 in the manufacture of a medicament for treating or ameliorating a vascular eye disease or disorder in a subject in need thereof.