## CLAIMS

**WHAT IS CLAIMED IS:**

1. A method for treating or preventing wet age-related macular degeneration (wet AMD), comprising administering to a subject in need thereof (a) Antagonist A or another pharmaceutically acceptable salt thereof and (b) an VEGF antagonist, wherein (a) and (b) are administered in an amount that is effective for treating or preventing wet AMD, and wherein the administering occurs once every month, ± about seven days, for a first administration period of at least 3 consecutive months, followed by administering (a) and (b) for a second administration period at a frequency of at least every other month ± about seven days beginning at two months ± about seven days after the day of the last month of the first administration period on which (a) and (b) are administered.

2. The method of claim 1, wherein (a) and (b) are administered within about 60 minutes of each other.

3. The method of claim 1, wherein the VEGF antagonist is ranibizumab, bevacizumab, pegaptanib sodium, ESBA 1008 or aflibercept.

4. The method of claim 1, wherein the VEGF antagonist is ranibizumab or bevacizumab, wherein (a) and (b) are administered at a frequency of once every month ± about seven days during the second administration period and wherein the second administration period is at least about nine months.

5. The method of claim 4, further comprising measuring the subject's visual acuity.

6. The method of claim 5, further comprising administering to the subject (a) and (b) in an amount that is effective for treating or preventing wet AMD, until the subject's visual acuity on the last two of any three consecutive months is ≤ a five-ETDRS-letter difference from the subject's visual acuity on the first of the three consecutive months.

7. The method of claim 5, further comprising administering to the subject (a) and (b) every other month in an amount that is effective for treating or preventing wet AMD, wherein

the subject's visual acuity on the last two of any three consecutive months is ≤ a five-ETDRS-letter difference from the subject's visual acuity on the first of the three consecutive months.

8. The method of claim 7, further comprising administering to the subject (a) and (b) every month in an amount that is effective for treating or preventing wet AMD, until the subject's visual acuity on the last two of any three consecutive months is ≤ a five-ETDRS-letter difference from the subject's visual acuity on the first of the three consecutive months.

9. The method of claim 1, wherein the VEGF antagonist is aflibercept.

10. The method of claim 1, wherein the total number of months does not exceed 24.

11. The method of claim 4, wherein the subject has intraretinal or sub-retinal hemorrhage or a ≥ 50 μm increase in foveal intraretinal fluid at one month, ± about seven days, immediately following the second administration period.

12. The method of claim 11, further comprising: administering to the subject on each month ± about seven days, beginning on the month that immediately follows the second administration period (a) and (b) in an amount that is effective for treating or preventing wet AMD, until the subject's visual acuity on the last two of any three consecutive months that follow the 12 consecutive months is ≤ a five-ETDRS-letter difference from the subject's visual acuity on the first of the three consecutive months.

13. The method of claim 12, wherein the total number of months does not exceed 24.

14. The method of claim 1, wherein Antagonist A or another pharmaceutically acceptable salt thereof is administered intravitreally in an amount of about 1.5 mg/eye.

15. The method of claim 4, wherein the VEGF antagonist is bevacizumab and is administered intravitreally in an amount of about 1.25 mg/eye.

16. The method of claim 9, wherein the VEGF antagonist is administered intravitreally in an amount of about 2 mg/eye.

17. The method of claim 4, wherein the VEGF antagonist is ranibizumab and is administered intravitreally in an amount of about 0.5 mg/eye.

18. The method of claim 1, further comprising administering an anti-C5 agent.

19. The method of claim 1, further comprising administering (a) and (b) on a month in which the subject has intraretinal or sub-retinal hemorrhage or a $\geq$ 50 μm increase in foveal intraretinal fluid.

20. A method for treating or preventing sub-retinal fibrosis, comprising administering to a subject in need thereof (a) Antagonist A or another pharmaceutically acceptable salt thereof in an amount that is effective for treating or preventing sub-retinal fibrosis.

21. The method of claim 20, further comprising administering to the subject (b) a VEGF antagonist, wherein (a) and (b) are administered in an amount that is effective for treating or preventing sub-retinal fibrosis.

22. The method of claim 20, wherein the subject has wet age-related macular degeneration (wet AMD).

23. The method of claim 22, wherein the sub-retinal fibrosis is associated with the wet AMD.

24. The method of claim 20, wherein administering Antagonist A or another pharmacetically acceptable salt thereof results in a decrease in the size of sub-retinal hyper-reflective material (SHRM) as evidenced by spectral domain optical coherence tomography (SD-OCT) or results in stabilization of the subject's vision.

25. The method of claim 20, wherein Antagonist A or another pharmaceutically acceptable salt thereof is administered intravitreally in an amount of about 1.5 mg/eye.

26. The method of claim 21, wherein the VEGF antagonist is bevacizumab, ranibizumab, aflibercept, pegaptanib sodium or ESBA1008.

27. The method of claim 26, wherein the VEGF antagonist is bevacizumab and is administered intravitreally in an amount of about 1.25 mg/eye.

28. The method of claim 26, wherein the VEGF antagonist is aflibercept and is administered intravitreally in an amount of about 2 mg/eye.

29. The method of claim 26, wherein the VEGF antagonist is ranibizumab and is administered intravitreally in an amount of about 0.5 mg/eye.

30. The method of claim 21, further comprising administering an anti-C5 agent.

31. A method for treating or preventing von Hippel-Lindau (VHL) disease, comprising administering to a subject in need thereof Antagonist A or another pharmaceutically acceptable salt thereof in an amount that is effective for treating or preventing VHL disease.

32. The method of claim 31, further comprising administering a VEGF antagonist.

33. The method of claim 31, wherein Antagonist A or another pharmaceutically acceptable salt thereof is administered intravitreally in an amount of about 1.5 mg/eye.

34. The method of claim 32, wherein the VEGF antagonist is bevacizumab and is administered intravitreally in an amount of about 1.25 mg/eye.

35. The method of claim 32, wherein the VEGF antagonist is aflibercept and is administered intravitreally in an amount of about 2 mg/eye.

36. The method of claim 32, wherein the VEGF antagonist is ranibizumab and is administered intravitreally in an amount of about 0.5 mg/eye.

37. The method of claim 32, further comprising administering an anti-C5 agent.

## CLAIMS

1. Use of (a) Antagonist A or another pharmaceutically acceptable salt thereof and (b) an VEGF antagonist in the preparation of a medicament for the treatment or prevention of wet age-related macular degeneration (wet AMD), wherein (a) and (b) are for administration in an amount that is effective for treating or preventing wet AMD, and wherein the administration occurs once every month, ± about seven days, for a first administration period of at least 3 consecutive months, followed by administering (a) and (b) for a second administration period at a frequency of at least every other month ± about seven days beginning at two months ± about seven days after the day of the last month of the first administration period on which (a) and (b) are administered.

2. The use of claim 1, wherein (a) and (b) are for administration within about 60 minutes of each other.

3. The use of any one of claims 1 to 2, wherein the VEGF antagonist is ranibizumab, bevacizumab, pegaptanib sodium, ESBA 1008 or aflibercept.

4. The use of any one of claims 1 to 3, wherein the VEGF antagonist is ranibizumab or bevacizumab, wherein (a) and (b) are for administration at a frequency of once every month ± about seven days during the second administration period and wherein the second administration period is at least about nine months.

5. The use of any one of claims 1 to 4, further comprising measuring the subject's visual acuity.

6. The use of claim 5, further comprising administering to the subject (a) and (b) in an amount that is effective for treating or preventing wet AMD, until the subject's visual acuity on the last two of any three consecutive months is ≤ a five-ETDRS-letter difference from the subject's visual acuity on the first of the three consecutive months.

7. The use of claim 5, further comprising administering to the subject (a) and (b) every other month in an amount that is effective for treating or preventing wet AMD, wherein the subject's visual acuity on the last two of any three consecutive months is ≤ a five-ETDRS-letter difference from the subject's visual acuity on the first of the three consecutive months.

8. The use of claim 7, further comprising administering to the subject (a) and (b) every month in an amount that is effective for treating or preventing wet AMD, until the subject's visual acuity on the last two of any three consecutive months is ≤ a five- ETDRS-letter difference from the subject's visual acuity on the first of the three consecutive months.

9. The use of any one of claims 1 to 8, wherein the VEGF antagonist is aflibercept.

10. The use of any one of claims 1 9, wherein the total number of months does not exceed 24.

11. The use of claim 4, wherein the subject has intraretinal or sub-retinal hemorrhage or a ≥ 50 μm increase in foveal intraretinal fluid at one month, ± about seven days, immediately following the second administration period.

12. The use of claim 11, further comprising: administering to the subject on each month ± about seven days, beginning on the month that immediately follows the second administration period (a) and (b) in an amount that is effective for treating or preventing wet AMD, until the subject's visual acuity on the last two of any three consecutive months that follow the 12 consecutive months is ≤ a five-ETDRS-letter difference from the subject's visual acuity on the first of the three consecutive months.

13. The use of claim 12, wherein the total number of months does not exceed 24.

14. The use of any one of claims 1 to 13, wherein Antagonist A or another pharmaceutically acceptable salt thereof is for intravitreal administrationin an amount of about 1.5 mg/eye.

15. The use of claim 4, wherein the VEGF antagonist is bevacizumab and is for intravitreal administration in an amount of about 1.25 mg/eye.

16. The use of claim 9, wherein the VEGF antagonist is for intravitreal administration in an amount of about 2 mg/eye.

17. The use of claim 4, wherein the VEGF antagonist is ranibizumab and is for intravitreal administration in an amount of about 0.5 mg/eye.

18. The use of any one of claims 1 to 17, further comprising administering an anti-C5 agent.

19. The use of any one of claims 1 to 18, further comprising administering (a) and (b) on a month in which the subject has intraretinal or sub-retinal hemorrhage or a ≥ 50 μιη increase in foveal intraretinal fluid.

20. Use of (a) Antagonist A or another pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment or prevention of sub-retinal fibrosis.

21. The use of claim 20, further comprising administering to the subject (b) a VEGF antagonist, wherein (a) and (b) are for administration in an amount that is effective for treating or preventing sub-retinal fibrosis.

22. The use of claim 20, wherein the subject has wet age-related macular degeneration (wet AMD).

23. The use of claim 22, wherein the sub-retinal fibrosis is associated with the wet AMD.

24. The use of claim 20, wherein administering Antagonist A or another pharmacetically acceptable salt thereof results in a decrease in the size of sub-retinal hyper-reflective material (SHRM) as evidenced by spectral domain optical coherence tomography (SD-OCT) or results in stabilization of the subject's vision.

25. The use of any one of claims 20 to 24, wherein Antagonist A or another pharmaceutically acceptable salt thereof is administered intravitreally in an amount of about 1.5 mg/eye.

26. The use of claim 21, wherein the VEGF antagonist is bevacizumab, ranibizumab, aflibercept, pegaptanib sodium or ESBA1008.

27. The use of claim 26, wherein the VEGF antagonist is bevacizumab and is administered intravitreally in an amount of about 1.25 mg/eye.

28. The use of claim 26, wherein the VEGF antagonist is aflibercept and is administered intravitreally in an amount of about 2 mg/eye.

29. The use of claim 26, wherein the VEGF antagonist is ranibizumab and is administered intravitreally in an amount of about 0.5 mg/eye.

30. The use of claim 21, further comprising administering an anti-C5 agent.

31. Use of Antagonist A or another pharmaceutically acceptable salt in the preparation of a medicament for the treatment or prevention of von Hippel-Lindau (VHL) disease.

32. The use of claim 31, further comprising administering a VEGF antagonist.

33. The use of claim 31, wherein Antagonist A or another pharmaceutically acceptable salt thereof is for intravitreal administration in an amount of about 1.5 mg/eye.

34. The use of claim 32, wherein the VEGF antagonist is bevacizumab and is for intravitreal administration in an amount of about 1.25 mg/eye.

35. The use of claim 32, wherein the VEGF antagonist is aflibercept and is for intravitreal administration in an amount of about 2 mg/eye.

36. The use of claim 32, wherein the VEGF antagonist is ranibizumab and is for intravitreal administration in an amount of about 0.5 mg/eye.

37. The use of claim 32, further comprising administering an anti-C5 agent.

38. A composition comprising:

a) Antagonist A or another pharmaceutically acceptable salt thereof; and

b) a pharmaceutically acceptable excipient, buffering agent, aqueous carrier, or combination thereof, wherein

the composition has a pH of from about 5.0 to about 8.0;

the average number of particles detected in the composition after being stored at a temperature of about 2.0 °C to about 8.0 °C for at least about twelve weeks does not exceed about 50 particles/mL, where the particles have a diameter > about 10 μm as measured by

the microscopic method particle count test described in (788) Particulate Matter in Injections, Revised Bulletin, Official October 1, 2011, The United States Pharmacopeial Convention; and

the composition is suitable for intravitreal injection.

39. The composition of claim 38, wherein the composition comprises an aqueous carrier, sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, or a combination thereof.

40. The composition of claim 38, wherein the pH is about 7.5.

41. The composition of claim 38, wherein the composition is buffered with hydrochloric acid.

42. The composition of claim 38, wherein the composition is buffered with sodium hydroxide.

43. The composition of claim 38, wherein the average number of particles detected in the composition after being stored at a temperature of about 2.0 °C to about 8.0 °C for at least about twelve weeks does not exceed 5 particles/mL, where the particles have a diameter > 25 μm as measured by the microscopic method particle count test described in (788) Particulate Matter in Injections, Revised Bulletin, Official October 1, 2011, The United States Pharmacopeial Convention.

44. The composition of claim 38, wherein the average number of particles detected in the composition after being stored at a temperature of about 2.0 °C to about 8.0 °C for at least about twelve weeks does not exceed 2 particles/mL, where the particles have a diameter > 50 μm as measured by the microscopic method particle count test described in (788) Particulate Matter in Injections, Revised Bulletin, Official October 1, 2011, The United States Pharmacopeial Convention.

45. The composition of claim 39, wherein the composition comprises:

a) about 3% w/v of Antagonist A or another pharmaceutically acceptable salt thereof;

b) about 95.9% w/v of an aqueous carrier;

c) about 0.9% w/v sodium chloride;

d) about 0.03% w/v monobasic sodium phosphate monohydrate; and

e) about 0.2% w/v dibasic sodium phosphate heptahydrate.

46. The composition of claim 38, wherein the composition comprises about 0.003-5.0 mg of Antagonist A or another pharmaceutically acceptable salt thereof.

47. The composition of claim 46, wherein the composition is suitable for a single intravitreal administration.

48. The composition of claim 45, wherein the composition comprises about 0.03-3.0 mg of Antagonist A or another pharmaceutically acceptable salt thereof.

49. The composition of claim 48, wherein the composition is suitable for a single intravitreal administration.

50. The composition of claim 47 or 49, wherein the intravitreal administration is via a 27-30 gauge needle.

51. A composition comprising:

a) Antagonist A or another pharmaceutically acceptable salt thereof; and

b) a pharmaceutically acceptable excipient, buffering agent, aqueous carrier, or combination thereof, wherein

the composition has a pH of from about 5.0 to about 8.0;

at least about 50% of the Antagonist A or another pharmaceutically acceptable salt thereof shows no sign of decomposition or modification resulting in the formation of a new chemical entity when stored at a temperature of from about 2.0 °C to about 8.0 °C for at least about 12 weeks; and

the composition is suitable for intravitreal injection.

52. The composition of claim 51, wherein the composition comprises an aqueous carrier, sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, or a combination thereof.

53. The composition of claim 51, wherein the pH is about 7.5.

54. The composition of claim 51, wherein the composition is buffered with hydrochloric acid.

55. The composition of claim 51, wherein the composition is buffered with sodium hydroxide.

56. The composition of claim 51, wherein at least about 70% of the Antagonist A or another pharmaceutically acceptable salt shows no sign of decomposition or modification resulting in the formation of a new chemical entity when stored at a temperature of from about 2.0 °C to about 8.0 °C for at least about 12 weeks.

57. The composition of claim 51, wherein at least about 90% of the Antagonist A or another pharmaceutically acceptable salt shows no sign of decomposition or modification resulting

in the formation of a new chemical entity when stored at a temperature of from about 2.0 °C to about 8.0 °C for at least about 12 weeks.

58. The composition of claim 52, wherein the composition comprises:

a) about 3% w/v of Antagonist A or a pharmaceutically acceptable salt thereof;

b) about 95.9% w/v of an aqueous carrier;

c) about 0.9% w/v sodium chloride;

d) about 0.03% w/v monobasic sodium phosphate monohydrate; and

e) about 0.2% w/v dibasic sodium phosphate heptahydrate.

59. The composition of claim 51, wherein the composition comprises about 0.003-5.0 mg of Antagonist A or another pharmaceutically acceptable salt thereof.

60. The composition of claim 59, wherein the composition is suitable for a single intravitreal administration.

61. The composition of claim 59, wherein the composition comprises about 0.03-3.0 mg of Antagonist A or another pharmaceutically acceptable salt thereof.

62. The composition of claim 61, wherein the composition is suitable for a single intravitreal administration.

63. The composition of claim 60 or 62, wherein the intravitreal administration is via a 27-30 gauge needle.

64. A composition comprising:

a) about 3% w/v of Antagonist A or another pharmaceutically acceptable salt thereof;

b) about 0.9% w/v sodium chloride;

c) about 0.03% w/v monobasic sodium phosphate monohydrate;

e) about 0.2% w/v dibasic sodium phosphate heptahydrate; and

f) an aqueous carrier.

65. The composition of claim 64, wherein the composition has a pH of from about 5.0 to about 8.0.

66. The composition of claim 64, wherein the composition has a pH of about 7.5.

67. The composition of claim 64, wherein the composition comprises about 95.9% w/v of the pharmaceutically acceptable aqueous carrier.

68. The composition of claim 64, wherein the composition comprises about 0.003-5.0 mg of Antagonist A or another pharmaceutically acceptable salt thereof.

69. The composition of claim 64, wherein the composition comprises about 0.03-3.0 mg of Antagonist A or another pharmaceutically acceptable salt thereof.

70. The composition of claim 64, wherein the composition is suitable for intravitreal administration.

71. The composition of claim 70, wherein the composition is suitable for a single intravitreal administration.

72. The composition of claim 70 or 71, wherein the intravitreal administration is via a 27-30 gauge needle.

73. The composition of any one of claims 38, 51 and 64, wherein the concentration of Antagonist A or the other pharmaceutically acceptable salt in the composition is from about 5 mg/mL to about 50 mg/mL.

74. The composition of claim 73, wherein the concentration of Antagonist A or the other pharmaceutically acceptable salt thereof is about 30 mg/mL.

75. The composition of any one of claims 38, 51 and 64, wherein the dosage of Antagonist A in the composition is about 1.5 mg in a volume of 0.03 mL to 0.15 mL.

76. The composition of any one of claims 38, 51 and 64, wherein the composition is contained in a single undivided container.

77. The composition of any one of claims 38, 51 and 64, wherein the composition is in a unit dosage form.

78. A composition comprising:

a) Antagonist A or another pharmaceutically acceptable salt thereof; and

b) a pharmaceutically acceptable excipient, buffering agent, aqueous carrier, or combination thereof, wherein

the composition has a pH of from about 5.0 to about 8.0;

the average number of particles detected in the composition after being stored at a temperature of about 2.0 °C to about 8.0 °C for at least about twelve weeks does not exceed about 50 particles/mL, where the particles have a diameter > about 10 μm as measured by the light obscuration particle count test described in (788) Particulate Matter in Injections, Revised Bulletin, Official October 1, 2011, The United States Pharmacopeial Convention; and

the composition is suitable for intravitreal injection.

79. The composition of claim 78, wherein the composition comprises an aqueous carrier, sodium chloride, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, or a combination thereof.

80. The composition of claim 78, wherein the pH is about 7.5.

81. The composition of claim 78, wherein the composition is buffered with hydrochloric acid.

82. The composition of claim 78, wherein the composition is buffered with sodium hydroxide.

83. The composition of claim 78, wherein the average number of particles detected in the composition after being stored at a temperature of about 2.0 °C to about 8.0 °C for at least about twelve weeks does not exceed 5 particles/mL, where the particles have a diameter > 25 μm as measured by the light obscuration particle count test described in (788) Particulate Matter in Injections, Revised Bulletin, Official October 1, 2011, The United States Pharmacopeial Convention.

84. The composition of claim 78, wherein the average number of particles detected in the composition after being stored at a temperature of about 2.0 °C to about 8.0 °C for at least about twelve weeks does not exceed 2 particles/mL, where the particles have a diameter > 50 μm as measured by the light obscuration particle count test described in (788) Particulate Matter in Injections, Revised Bulletin, Official October 1, 2011, The United States Pharmacopeial Convention.

85. The composition of claim 79, wherein the composition comprises:

a) about 3% w/v of Antagonist A or another pharmaceutically acceptable salt thereof;

b) about 95.9% w/v of an aqueous carrier;

c) about 0.9% w/v sodium chloride;

d) about 0.03% w/v monobasic sodium phosphate monohydrate; and

e) about 0.2% w/v dibasic sodium phosphate heptahydrate.

86. The composition of claim 78, wherein the composition comprises about 0.003-5.0 mg of Antagonist A or another pharmaceutically acceptable salt thereof.

87. The composition of claim 86, wherein the composition is suitable for a single intravitreal administration.

88. The composition of claim 85, wherein the composition comprises about 0.03-3.0 mg of Antagonist A or another pharmaceutically acceptable salt thereof.

89. The composition of claim 88, wherein the composition is suitable for a single intravitreal administration.

90. The composition of claim 87 or 89, wherein the intravitreal administration is via a 27-30 gauge needle.

91. The composition of claim 78, wherein the concentration of Antagonist A or the other pharmaceutically acceptable salt in the composition is from about 5 mg/mL to about 50 mg/mL.

92. The composition of claim 91, wherein the concentration of Antagonist A or the other pharmaceutically acceptable salt thereof is about 30 mg/mL.

93. The composition of claim 78, wherein the dosage of Antagonist A in the composition is about 1.5 mg in a volume of 0.03 mL to 0.15 mL.

94. The composition of claim 78, wherein the composition is contained in a single undivided container.

95. The composition of claim 78, wherein the composition is in a unit dosage form.