

vessel growth, or proliferative DR (PDR), with new abnormal blood vessel growth within the retina or choroid. Diabetic macular edema (DME) is a complication of DR, and is another example of an ocular disease affecting the macula. DME affects up to 10% of people with diabetes and is caused by fluid accumulation in the macula. DME is the most frequent cause of sight loss in people with DR. Available therapies for treating DME include laser and anti-vascular endothelial growth factor (anti-VEGF) drugs such as aflibercept.

[0006] Aflibercept is a recombinant fusion protein that acts as a decoy receptor for vascular endothelial growth factor subtypes A and B (VEGF-A and VEGF-B) and placental growth factor (PGF). By binding to these ligands, aflibercept is able to prevent them from binding to vascular endothelial growth factor receptors (VEGFR), VEGFR-1 and VEGFR-2, to suppress neovascularization and decrease vascular permeability. Aflibercept consists of domain 2 of VEGFR-1 and domain 3 of VEGFR-2 fused with the Fc fragment of IgG1.

[0007] Current standard of care anti-VEGF agents such as aflibercept need to be re-administered via intravitreal (IVT) injection every 4 to 8 weeks to achieve optimal therapeutic outcomes and maintain visual acuity. Compliance with such a regimen is burdensome to patients, their caregivers, and the healthcare system, and most patients fall out of compliance with the optimal regimen over time, which is correlated with vision loss (Khanani AM, *et al.*). In addition, there are complications including endophthalmitis, retinal detachments, traumatic cataract, and elevated intraocular pressure (IOP); the risks of these complications are likely to increase with repeated IVT injections (Falavarjani *et al.*, (2013) Eye (Lond), 27(7):787-794).

[0008] Therefore, there is a need in the art for therapies for ocular neovascular diseases such as wAMD, DR, or DME that are effective, reduce the risk of adverse effects, and are amenable to high long-term patient compliance.

SUMMARY

[0009] In one example, provided herein is a method for treating an ocular neovascular disease in an individual, the method comprising administering a unit dose of about 6×10^{11} vector genomes (vg) or less of recombinant adeno-associated virus (rAAV) particles to one eye of the individual, wherein the individual is a human, and wherein the rAAV particles comprise: (a) a nucleic acid encoding a polypeptide comprising an amino acid sequence with at least about 95% identity to the amino acid sequence of SEQ ID NO: 35 and flanked by AAV2 inverted terminal repeats (ITRs), and (b) an AAV2 capsid protein comprising, or consisting of, an amino acid sequence LGETTRP (SEQ ID NO: 14) inserted between positions 587 and 588 of the capsid protein, wherein the amino acid residue numbering corresponds to an AAV2 VP1 capsid protein. In some examples, the method comprises reducing retinal fluid in an eye of the individual.

[0009a] In one aspect, the present disclosure refers to use of a unit dose of 1×10^{10} to 2×10^{11} vector genomes (vg) of recombinant adeno-associated virus (rAAV) particles in the manufacture of a medicament for treating an ocular neovascular disease in an individual, wherein the unit dose is to be administered to one eye of the individual, wherein the individual is a human, and wherein the rAAV particles comprise: a) a nucleic acid encoding a polypeptide comprising an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO: 35 and flanked by AAV2 inverted terminal repeats (ITRs), and b) an AAV2 capsid protein comprising an amino acid sequence LGETTRP (SEQ ID NO: 14) inserted between positions 587 and 588 of the capsid protein, wherein the amino acid residue numbering corresponds to an AAV2 VP1 capsid protein comprising the amino acid sequence of SEQ ID NO: 13,

wherein the unit dose of rAAV particles is to be administered in combination with a difluprednate treatment.

[0010] In another example, provided herein is a method for reducing retinal fluid in an eye of an individual with an ocular neovascular disease, the method comprising administering a unit dose of rAAV particles to one eye of the individual, wherein the individual is a human, and wherein the rAAV particles

comprise: (a) a nucleic acid encoding a polypeptide comprising an amino acid sequence with at least about 95% identity to the amino acid sequence of SEQ ID NO: 35 and flanked by AAV2 inverted terminal repeats (ITRs), and (b) an AAV2 capsid protein comprising, or consisting of, an amino acid sequence LGETTRP (SEQ ID NO: 14) inserted between positions 587 and 588 of the capsid protein, wherein the amino acid residue numbering corresponds to an AAV2 VP1 capsid protein. In some examples, the individual has received at least one treatment of an anti-VEGF agent in about last 12 weeks prior to administration of the unit dose of rAAV particles. In some examples, the amount or presence of retinal fluid in the one eye of the individual is refractory to prior treatment with an anti-VEGF agent. In some examples, the anti-VEGF agent is aflibercept. In some examples, the retinal fluid in the one eye is reduced by at least about 60%. In some examples, the retinal fluid in the one eye is reduced by about 80% compared to the level of retinal fluid in the one eye of the individual prior to administration of the rAAV to the individual. In some examples, the retinal fluid is subretinal fluid (SRF) or intraretinal fluid (IRF). In some examples, the unit dose of rAAV particles is about 6×10^{11} vector genomes per eye (vg/eye) or less.

[0010a] In one example, the present disclosure refers to use of a unit dose of rAAV particles in the manufacture of a medicament for reducing retinal fluid in an eye of an individual with an ocular neovascular disease, wherein the unit dose of rAAV particles is to be administered to one eye of the individual, wherein the individual is a human, and wherein the rAAV particles comprise: a) a nucleic acid encoding a polypeptide comprising an amino acid sequence with at least about 95% identity to the amino acid sequence of SEQ ID NO: 35 and flanked by AAV2 inverted terminal repeats (ITRs), and b) an AAV2 capsid protein comprising an amino acid sequence LGETTRP (SEQ ID NO: 14) inserted between positions 587 and 588 of the capsid protein, wherein the amino acid residue numbering corresponds to an AAV2 VP1 capsid protein.

[0011] In another example, provided herein is a method for treating an ocular neovascular disease in an individual, the method comprising: (a) administering an anti-VEGF agent to one eye of the individual; and (b) administering a unit dose of about 6×10^{11} vector genomes (vg) or less of recombinant adeno-associated virus (rAAV) particles to the one eye of the individual after administration of the anti-VEGF agent, wherein the individual is a human, and wherein the rAAV particles comprise: (i) a nucleic acid encoding a polypeptide comprising an amino acid sequence with at least about 95% identity to the amino acid sequence of SEQ ID NO: 35 and flanked by AAV2 inverted terminal repeats (ITRs), and (ii) an AAV2 capsid protein comprising an amino acid sequence LGETTRP (SEQ ID NO: 14) inserted between positions 587 and 588 of the capsid protein, wherein the amino acid residue numbering corresponds to an AAV2 VP1 capsid protein. In some examples, the method comprises administering the unit dose of rAAV particles to the one eye of the individual about 1 week or about 7 days after administration of the anti-VEGF agent. In some examples, the method comprises administering the unit dose of rAAV particles to the one eye of the individual about 1 week to about 2 weeks after administration of the anti-VEGF agent. In some examples, the method comprises administering the unit dose of rAAV particles to the one eye of the individual about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, or about 15 days after administration of the anti-VEGF agent. In some examples, the method comprises administering the anti-VEGF agent to the one eye of the individual on Day 1, and administering the unit dose of rAAV particles to the one eye of the individual on Day 8. In some examples, the anti-VEGF agent comprises aflibercept. In some examples, the aflibercept is administered at a dose of about 2 mg by intravitreal injection. In some examples, the method further comprises administering a topical steroid treatment. In some examples, the topical steroid treatment is a difluprednate treatment. In some examples, the topical steroid treatment comprises about four

administrations of topical steroid per day for about four weeks, followed by about three administrations of topical steroid per day for about one week, followed by about two administrations of topical steroid per day for about one week, and followed by about one administration of topical steroid per day for about one week; timing starting with and following administration of the anti-VEGF agent. In some examples, the topical steroid treatment comprises about four administrations of topical steroid per day for about one month, followed by about three administrations of topical steroid per day for about one month, followed by about two administrations of topical steroid per day for about one month, and followed by about one administration of topical steroid per day for about one month; timing starting with and following administration of the anti-VEGF agent. In some examples, the topical steroid treatment comprises about four administrations of topical steroid per day for about one month, followed by about three administrations of topical steroid per day for about one month, followed by about two administrations of topical steroid per day for about one month, and followed by about one administration of topical steroid per day for about one month; timing starting with and following administration of the rAAV particles. In some examples, the topical steroid comprises difluprednate 0.05% at a dose of about 1µg to about 3 µg. In some examples, the topical steroid comprises difluprednate 0.05% at a dose of about 2.5µg.

[0011a] In one example, the present disclosure refers to use of a unit dose of about 6×10^{11} vector genomes (vg) or less of recombinant adeno-associated virus (rAAV) particles in the manufacture of a medicament for treating an ocular neovascular disease in an individual, wherein the unit dose of rAAV particles is to be administered in combination with an anti-VEGF agent, and wherein the unit dose of rAAV particles is to be administered to one eye of the individual after administration of the anti-VEGF agent to the one eye, wherein the individual is a human, and wherein the rAAV particles comprise: (i) a nucleic acid encoding a polypeptide comprising an amino acid sequence with at least about 95% identity to the amino acid sequence of SEQ ID NO: 35 and flanked by AAV2 inverted terminal repeats (ITRs), and (ii) an AAV2 capsid protein comprising an amino acid sequence LGETTRP (SEQ ID NO: 14) inserted between positions 587 and 588 of the capsid protein, wherein the amino acid residue numbering corresponds to an AAV2 VP1 capsid protein.

[0012] In some examples that may be combined with any of the preceding examples, the unit dose of rAAV particles is about 6×10^{10} to about 2×10^{11} vector genomes per eye (vg/eye). In some examples, the unit dose of rAAV particles is about 2×10^{11} or about 6×10^{10} vector genomes per eye (vg/eye). In some examples that may be combined with any of the preceding examples, the unit dose of rAAV particles is between about 6×10^{10} to about 6×10^{11} vector genomes per eye (vg/eye). In some examples that may be combined with any of the preceding examples, the unit dose of rAAV particles is between about 6×10^{10} to about 2×10^{11} vector genomes per eye (vg/eye). In some examples that may be combined with any of the preceding examples, the unit dose of rAAV particles is between about 2×10^{11} to about 6×10^{11} vector genomes per eye (vg/eye). In some examples, the unit dose of rAAV particles is about 2×10^{11} or about 6×10^{10} vector genomes per eye (vg/eye). In some examples, the unit dose of rAAV particles is about 2×10^{11} vg/eye. In some examples, the unit dose of rAAV particles is about 6×10^{11} vg/eye.

[0013] In some examples that may be combined with any of the preceding examples, the individual has one or more symptoms of an ocular neovascular disease in the contralateral eye.

[0014] In some examples that may be combined with any of the preceding examples, the methods provided herein further comprise administering a unit dose of rAAV particles to the contralateral eye of the individual. In some examples, the administering the unit dose of rAAV particles to the contralateral eye is up to about 2 weeks after administering the unit dose of rAAV particles to the one eye. In some examples, the administering the unit dose of rAAV particles to the contralateral eye is on the same day as the administering the unit dose of rAAV particles to the one eye; or the administering the unit dose of rAAV particles to the contralateral eye is between about 1 day to about 14 days after administering the unit dose of rAAV particles to the one eye. In some examples, the unit dose of

Claims

1. Use of a unit dose of 1×10^{10} to 2×10^{11} vector genomes (vg) of recombinant adeno-associated virus (rAAV) particles in the manufacture of a medicament for treating an ocular neovascular disease in an individual, wherein the unit dose is to be administered to one eye of the individual, wherein the individual is a human, and wherein the rAAV particles comprise:
 - a) a nucleic acid encoding a polypeptide comprising an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO: 35 and flanked by AAV2 inverted terminal repeats (ITRs), and
 - b) an AAV2 capsid protein comprising an amino acid sequence LGETTRP (SEQ ID NO: 14) inserted between positions 587 and 588 of the capsid protein, wherein the amino acid residue numbering corresponds to an AAV2 VP1 capsid protein comprising the amino acid sequence of SEQ ID NO: 13,wherein the unit dose of rAAV particles is to be administered in combination with a difluprednate treatment.
2. The use of claim 1, wherein retinal fluid in the one eye of the individual with an ocular neovascular disease is reduced.
3. The use of claim 2, wherein:

the retinal fluid in the one eye is reduced by at least 60%;

the retinal fluid in the one eye is reduced by about 80% compared to the level of retinal fluid in the one eye of the individual prior to administration of the rAAV particles to the individual; and/or

the retinal fluid is subretinal fluid (SRF) or intraretinal fluid (IRF).
4. The use of any one of claims 1-3, wherein the unit dose of rAAV particles is to be administered in combination with an anti-VEGF agent.
5. The use of claim 4, wherein:
 - (a) the unit dose of rAAV particles is to be administered to the one eye of the individual 1 week after administration of the anti-VEGF agent, and/or the anti-VEGF agent is to be administered to the one eye of the individual on Day 1, and the unit dose of rAAV particles is to be administered to the one eye of the individual on Day 8; and/or
 - (b) the anti-VEGF agent comprises aflibercept, optionally wherein the aflibercept is to be administered at a dose of 2 mg by intravitreal injection.
6. The use of any one of claims 1-5, wherein the unit dose of rAAV particles is:
 - (a) between 6×10^{10} to 2×10^{11} vector genomes per eye (vg/eye); or

(b) 6×10^{10} or 2×10^{11} vector genomes per eye (vg/eye).

7. The use of any one of claims 1-6, wherein the individual has one or more symptoms of an ocular neovascular disease in the contralateral eye.

8. The use of any one of claims 1-7, wherein the unit dose of rAAV particles is to be further administered to a contralateral eye of the individual.

9. The use of claim 8, wherein:

(a) the unit dose of rAAV particles is to be administered to the contralateral eye up to 2 weeks after administration of the unit dose of rAAV particles to the one eye, optionally wherein:

(i) the unit dose of rAAV particles is to be administered to the contralateral eye on the same day as the unit dose of rAAV particles administered to the one eye, or the unit dose of rAAV particles is to be administered to the contralateral eye between 1 day to 14 days after administration of the unit dose of rAAV particles to the one eye, and/or

(ii) the unit dose of rAAV particles administered to the contralateral eye of the individual comprises the same or less vector genomes per eye (vg/eye) than the unit dose of rAAV particles administered to the one eye of the individual; or

(b) the unit dose of rAAV particles is to be administered to the contralateral eye at least 2 weeks after administration of the unit dose of rAAV particles to the one eye, optionally wherein the unit dose of rAAV particles administered to the contralateral eye of the individual comprises more vector genomes per eye (vg/eye) than the unit dose of rAAV particles administered to the one eye of the individual.

10. The use of any one of claims 1-9, wherein:

the nucleic acid comprises the nucleic acid sequence of SEQ ID NO: 40 or a sequence having at least 85% identity thereto;

the polypeptide comprises the amino acid sequence of SEQ ID NO: 35 or SEQ ID NO: 41; and/or

the polypeptide is aflibercept.

11. The use of any one of claims 1-9, wherein:

(a) the nucleic acid further comprises a first enhancer region, a promoter region, a 5'UTR region, a second enhancer region, and a polyadenylation site; optionally wherein the first enhancer region comprises a CMV sequence comprising the sequence of SEQ ID NO: 22 or a sequence having at least 85% identity thereto, the promoter region comprises a CMV sequence comprising the sequence of SEQ ID NO: 23 or a sequence having at least 85% identity thereto, the 5'UTR region comprises, in 5' to 3' order, a TPL sequence comprising the sequence of SEQ ID NO: 24 or a

sequence having at least 85% identity thereto and an eMLP sequence comprising the sequence of SEQ ID NO: 25 or a sequence having at least 85% identity thereto, the second enhancer region comprises a full EES sequence comprising the sequence of SEQ ID NO: 26 or a sequence having at least 85% identity thereto, and the polyadenylation site comprises an HGH polyadenylation site comprising the sequence of SEQ ID NO: 27 or a sequence having at least 85% identity thereto;

(b) the nucleic acid comprises, in the 5' to 3' order:

(i) a first enhancer region, optionally wherein the first enhancer region comprises a CMV sequence comprising the sequence of SEQ ID NO: 22 or a sequence having at least 85% identity thereto,

(ii) a promoter region, optionally wherein the promoter region comprises a CMV sequence comprising the sequence of SEQ ID NO: 23 or a sequence having at least 85% identity thereto,

(iii) a 5'UTR region, optionally wherein the 5'UTR region comprises, in 5' to 3' order, a TPL sequence comprising the sequence of SEQ ID NO: 24 or a sequence having at least 85% identity thereto and an eMLP sequence comprising the sequence of SEQ ID NO: 25 or a sequence having at least 85% identity thereto,

(iv) a nucleic acid encoding a polypeptide comprising an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO: 35, optionally wherein the nucleic acid encoding the polypeptide comprises the nucleic acid sequence of SEQ ID NO: 40 or a sequence having at least 85% identity thereto, and further optionally wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 35, the amino acid sequence of SEQ ID NO: 41 or a sequence having at least 95% identity thereto, or is aflibercept,

(v) a second enhancer region, optionally wherein the second enhancer region comprises a full EES sequence comprising the sequence of SEQ ID NO: 26 or a sequence having at least 85% identity thereto, and

(vi) a polyadenylation site, optionally wherein the polyadenylation site comprises a HGH polyadenylation site comprising the sequence of SEQ ID NO: 27 or a sequence having at least 85% identity thereto,

and flanked by AAV2 inverted terminal repeats (ITRs); and/or

(c) the nucleic acid comprises the sequence of SEQ ID NO: 39 or a sequence having at least 85% identity thereto.

12. The use of any one of claims 1-11, wherein:

the AAV2 capsid protein comprises the amino acid sequence LGETTRP (SEQ ID NO: 14) inserted between positions 587 and 588 of the AAV2 VP1 comprising the sequence of SEQ ID NO: 13; or

the AAV2 capsid protein comprises the amino acid sequence LALGETTRPA (SEQ ID NO: 1) inserted between positions 587 and 588 of the AAV2 VP1 comprising the sequence of SEQ ID NO: 13.

13. The use of any one of claims 1-12, wherein the rAAV particles comprise an AAV2 VP1 capsid protein comprising a GH loop that comprises the amino acid sequence of SEQ ID NO: 38 or an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 38.

14. The use of any one of claims 1-13, wherein the unit dose of rAAV particles:

(a) is to be administered to the one eye and/or the contralateral eye by intravitreal administration; and/or

(b) is in a pharmaceutical formulation, optionally wherein the pharmaceutical formulation comprises the rAAV particles, sodium chloride, sodium phosphate and a surfactant, and further optionally wherein the pharmaceutical formulation comprises:

(i) 150 to 200 mM sodium chloride, 1 to 10 mM monobasic sodium phosphate, 1 to 10 mM dibasic sodium phosphate, 0.0005% (w/v) to 0.005% (w/v) poloxamer 188, and 6×10^{13} to 6×10^{10} vector genomes (vg) per mL (vg/mL) of the rAAV particles, wherein the pharmaceutical formulation has a pH of 7.0 to 7.5,

(ii) 180 mM sodium chloride, 5 mM monobasic sodium phosphate, 5 mM dibasic sodium phosphate, 6×10^{12} vg/mL of the rAAV particles, and 0.001% (w/v) poloxamer 188, wherein the pharmaceutical formulation has a pH of 7.3,

(iii) 180 mM sodium chloride, 5 mM monobasic sodium phosphate, 5 mM dibasic sodium phosphate, 2×10^{12} vg/mL of the rAAV particles, and 0.001% (w/v) poloxamer 188, wherein the pharmaceutical formulation has a pH of 7.3, or

(iv) 180 mM sodium chloride, 5 mM monobasic sodium phosphate, 5 mM dibasic sodium phosphate, 6×10^{11} vg/mL of the rAAV particles, and 0.001% (w/v) poloxamer 188, wherein the pharmaceutical formulation has a pH of 7.3.

15. The use of any one of claims 1-14, wherein the unit dose of rAAV particles administered to the one eye and/or to the contralateral eye is in a volume of 25 μ L to 250 μ L, 100 μ L, or 30 μ L.

16. The use of any one of claims 1-15, wherein:

(a) the individual received prior treatment for the ocular neovascular disease with an anti-VEGF agent, optionally wherein the individual has received 1 or 2 injections of an anti-VEGF agent

in the one eye and/or in the contralateral eye prior to administration of the rAAV particles in the one eye and/or in the contralateral eye; or

(b) the individual has not received prior treatment for the ocular neovascular disease with an anti-VEGF agent,

optionally wherein the anti-VEGF agent is aflibercept.

17. The use of any one of claims 1-16, wherein the ocular neovascular disease is wet age-related macular degeneration (AMD), retinal neovascularization, choroidal neovascularization diabetic retinopathy, proliferative diabetic retinopathy, retinal vein occlusion, central retinal vein occlusion, branched retinal vein occlusion, diabetic macular edema, diabetic retinal ischemia, ischemic retinopathy, diabetic retinal edema, or any combination thereof.

18. The use of any one of claims 1-3 or 6-17, wherein
the difluprednate treatment is to be administered before, during and/or after administration of the unit dose of rAAV particles to the one eye and/or to the contralateral eye.

19. The use of claim 18, wherein:

(a) the difluprednate treatment is a daily difluprednate treatment for up to 4 weeks, up to 6 weeks, or up to 8 weeks from administration of the unit dose of rAAV particles;

(b) the difluprednate treatment comprises four administrations of difluprednate per day on week 1, three administrations of difluprednate per day on week 2, two administrations of difluprednate per day on week 3, and one administration per day of difluprednate on week 4; timing starting with and following administration of the unit dose of rAAV particles;

(c) the difluprednate treatment comprises four administrations of difluprednate per day for 3 weeks after administration of the unit dose of rAAV particles, followed by 3 administrations of difluprednate per day for 1 week, followed by 2 administrations of difluprednate per day for 1 week, and followed by 1 administration of difluprednate per day for 1 week; or

(d) the difluprednate treatment comprises four administrations of difluprednate per day for four weeks, followed by three administrations of difluprednate per day for one week, followed by two administrations of difluprednate per day for one week, and followed by one administration of difluprednate per day for one week, timing starting at one week prior to administration of the unit dose of rAAV particles,

optionally wherein the difluprednate treatment comprises difluprednate 0.05% at a dose of 1 µg to 3 µg, or at a dose of 2.5 µg.

20. The use of any one of claims 4-17, wherein

the difluprednate treatment comprises four administrations of difluprednate per day for four weeks, followed by three administrations of difluprednate per day for one week, followed by two administrations of difluprednate per day for one week, and followed by one administration of difluprednate per day for one week, timing starting with and following administration of the anti-VEGF agent,

optionally wherein the difluprednate treatment comprises difluprednate 0.05% at a dose of 1 µg to 3 µg, or at a dose of 2.5 µg.

21. The use of any one of claims 1-20, wherein:

(a) administration of the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in:

(i) maintenance or a decrease of retinal thickness compared to the retinal thickness prior to administration of the unit dose of rAAV particles, a decrease in retinal thickness compared to the retinal thickness prior to administration of the unit dose of rAAV particles, or a decrease in retinal thickness of at least 10% compared to the retinal thickness prior to administration of the unit dose of rAAV particles, optionally wherein retinal thickness is central subfield thickness (CST) or central retinal thickness (CRT),

(ii) maintenance or a decrease in macular volume compared to the macular volume prior to administration of the unit dose of rAAV particles, a decrease in macular volume compared to the macular volume prior to administration of the unit dose of rAAV particles, or a decrease in macular volume of at least 10% compared to the macular volume prior to administration of the unit dose of rAAV particles, and/or

(iii) maintenance or an improvement of visual acuity compared to the visual acuity prior to administration of the unit dose of rAAV particles, or an improvement of visual acuity compared to the visual acuity prior to administration of the unit dose of rAAV particles, optionally wherein visual acuity is best corrected visual acuity (BCVA); and/or

(b) administration of the unit dose of rAAV particles to the one eye and/or to the contralateral eye of a plurality of individuals results in:

(i) at least 50% of the individuals in the plurality not requiring an anti-VEGF rescue treatment, optionally wherein at least 50% of the individuals in the plurality do not require an anti-VEGF rescue treatment for at least 20 weeks, at least 36 weeks, at least 52 weeks, at least 56 weeks, or more after administration of the unit dose of rAAV particles,

(ii) at least 67% of the individuals in the plurality not requiring an anti-VEGF rescue treatment, optionally wherein at least 67% of the individuals in the plurality do not require an anti-VEGF rescue treatment for at least 20 weeks, at least 36 weeks, at least 52 weeks, at least 60 weeks, at least 64 weeks, or at least 66 weeks after administration of the unit dose of rAAV particles,

(iii) at least 78% of the individuals in the plurality not requiring an anti-VEGF rescue treatment, optionally wherein at least 78% of the individuals in the plurality do not require an anti-VEGF rescue treatment for at least 20 weeks, at least 36 weeks, or more after administration of the unit dose of rAAV particles,

(iv) 100% of the individuals in the plurality not requiring an anti-VEGF rescue treatment, optionally wherein 100% of the individuals in the plurality do not require an anti-VEGF rescue treatment for at least 64 weeks, at least 68 weeks, at least 72 weeks, at least 76 weeks, at least 80 weeks, at least 84 weeks, or more after administration of the unit dose of rAAV particles, and/or

(v) a reduction in the annualized anti-VEGF injection rate of at least 80%, at least 85%, at least 87%, at least 90%, at least 95%, at least 99%, or 100% compared to the annualized anti-VEGF injection rate prior to administration of the unit dose of rAAV particles.

22. The use of any one of claims 1-3, 6-19, or 21, wherein the ocular neovascular disease is wet age-related macular degeneration (AMD).

23. The use of any one of claims 1, 2, 4-17, 20, or 21, wherein the ocular neovascular disease is diabetic macular edema (DME), optionally wherein administration of the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in a 2-step or in a 3-step improvement in Diabetic Retinopathy Severity Scale (DRSS).