[0007] 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

[0008] 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.

[0008a] In one aspect, the present disclosure refers to use of a pharmaceutical composition comprising recombinant adeno-associated virus (rAAV) particles in the manufacture of a medicament for treating an ocular neovascular disease in an individual, wherein the medicament is for administration of a unit dose of about 1×10^{10} vector genomes (vg) to about 2×10^{11} vg of rAAV particles to one eye of the individual, wherein the medicament is to be administered by intravitreal injection (IVT) to the one eye of the individual, wherein the individual is a human, 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, and wherein the medicament is for use in combination with an implant containing a steroid for the one eye.

[0009] 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.

[0009a] In one aspect, the present disclosure refers to use of a pharmaceutical composition comprising 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 medicament is for administration of a unit dose of about 1×10^{10} vector genomes (vg) to about 2×10^{11} vg of rAAV particles to one eye of the individual, wherein the medicament is to be administered by intravitreal injection (IVT) to the one eye of the individual, wherein the individual is a human, 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, and wherein the medicament is for use in combination with an implant containing a steroid in the one eye.

[00010] 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.

[00011] 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.

[00012] 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.

[00013] 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 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. In some examples, the administering the unit dose of rAAV particles to the contralateral eye is at least about 2 weeks after administering the unit dose of rAAV particles to the one eye. In some examples, 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.

[00014] In some examples that may be combined with any of the preceding examples, the nucleic acid comprises the nucleic acid sequence of SEQ ID NO: 40 or a sequence having at least 85% identity thereto.

[00015] In some examples that may be combined with any of the preceding examples, the polypeptide comprises the amino acid sequence of SEQ ID NO: 35. In some examples that may be combined with any of the preceding examples, the polypeptide comprises the amino acid sequence of SEQ ID NO: 41. In some examples, the polypeptide is aflibercept.

[00016] In some examples that may be combined with any of the preceding examples, the nucleic acid further comprises a first enhancer region, a promoter region, a 5'UTR region, a second enhancer region, and a polyadenylation site. In some examples, the nucleic acid comprises, in the 5’ to 3’ order: (a) a first enhancer region;

(b) a promoter region; (c) a 5'UTR region; (d) 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; (e) a second enhancer region; and (f) a polyadenylation site; and flanked by AAV2 inverted terminal repeats (ITRs). In some examples, 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. In some examples, the promoter region comprises a CMV sequence comprising the sequence of SEQ ID NO: 23 or a sequence having at least 85% identity thereto. In some examples, the nucleic acid encoding a polypeptide comprises the nucleic acid sequence of SEQ ID NO: 40 or a sequence having at least 85% identity thereto. In some examples, the polypeptide comprises the amino acid sequence of SEQ ID NO: 35 or a sequence having at least 85% identity thereto. In some examples, the polypeptide comprises the amino acid sequence of SEQ ID NO: 41 or a sequence having at least 85% identity thereto. In some examples, the polypeptide is aflibercept. In some examples, 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. In some examples, 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. In some examples, 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. In some examples, the nucleic acid further comprises (a) a first enhancer region comprising a CMV sequence comprising the sequence of SEQ ID NO: 22 or a sequence having at least 85% identity thereto; (b) a promoter region, comprising a CMV sequence comprising the sequence of SEQ ID NO: 23 or a sequence having at least 85% identity thereto; (c) a 5'UTR region comprising, 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; (d) a second enhancer region comprising a full EES sequence comprising the sequence of SEQ ID NO: 26 or a sequence having at least 85% identity thereto; and (e) a HGH polyadenylation site comprising the sequence of SEQ ID NO: 27 or

a sequence having at least 85% identity thereto. In some examples, the nucleic acid comprises AAV ITRs flanking the elements.

[00017] In some examples that may be combined with any of the preceding examples, the nucleic acid comprises the sequence of SEQ ID NO: 39 or a sequence having at least 85% identity thereto.

[00018] In some examples that may be combined with any of the preceding examples, 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. In some examples, the rAAV particles comprise an AAV2 VP1 capsid protein comprising a GH loop that comprises an amino acid sequence having any of at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 38.

[00019] In some examples that may be combined with any of the preceding examples, the rAAV particles comprise an AAV2 VP1 capsid protein comprising the amino acid sequence of SEQ ID NO: 37 or an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 37. In some examples, the rAAV particles comprise an AAV2 VP1 capsid protein comprising an amino acid sequence having any of at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO: 37.

[00020] In some examples that may be combined with any of the preceding examples, the AAV2 capsid protein comprises, or consists of, 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. In some examples, the AAV2 capsid protein comprises the amino acid sequence LALGETTRPA (SEQ ID NO: 1) 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 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. In some examples, the AAV2 capsid protein comprises the amino acid sequence LALGETTRPA (SEQ ID NO: 1) 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 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.

[00021] In some examples that may be combined with any of the preceding examples, the administration of the unit dose of rAAV particles to the one eye and/or the contralateral eye is by intravitreal administration.

[00022] In some examples that may be combined with any of the preceding examples, the unit dose of rAAV particles is in a pharmaceutical formulation. In some examples, the pharmaceutical formulation comprises the rAAV particles, sodium chloride, sodium phosphate and a surfactant. In some examples, the pharmaceutical formulation comprises about 150 to about 200 mM sodium chloride, about 1 to about 10 mM monobasic sodium phosphate, about 1 to about 10 mM dibasic sodium phosphate, about 0.0005% (w/v) to about 0.005% (w/v) poloxamer 188, and about 6×10^{13} to about 6×10^{10} vector genomes (vg) per mL (vg/mL) of the rAAV particles, wherein the pharmaceutical formulation has a pH of about 7.0 to about 7.5. In some examples, the pharmaceutical formulation comprises about 180 mM sodium chloride, about 5 mM monobasic sodium phosphate, about 5 mM dibasic sodium phosphate, about 6×10^{12} vg/mL of the rAAV particles, and about 0.001% (w/v) poloxamer 188, wherein the pharmaceutical formulation has a pH of about 7.3. In some examples, the pharmaceutical formulation comprises about 180 mM sodium chloride, about 5 mM monobasic sodium phosphate, about 5 mM dibasic sodium phosphate, about 2×10^{12} vg/mL of the rAAV particles, and about 0.001% (w/v) poloxamer 188, wherein the pharmaceutical formulation has a pH of about 7.3. In some examples, the pharmaceutical formulation comprises about 180 mM sodium chloride, about 5 mM monobasic sodium phosphate, about 5 mM dibasic sodium phosphate, about 6×10^{11} vg/mL of the rAAV particles, and about 0.001% (w/v) poloxamer 188, wherein the pharmaceutical formulation has a pH of about 7.3.

[00023] In some examples that may be combined with any of the preceding examples, the unit dose of rAAV particles comprises a volume of about 25 µL to about 250 µL. In some examples, the unit dose of rAAV particles comprises a volume of about 100µL. In some examples, the unit dose of rAAV particles comprises a volume of about 30µL. In some examples that may be combined with any of the preceding examples, the unit dose of rAAV particles administered to the one eye and/or to the

contralateral eye comprises a volume of about 25 μL to about 250 μL. In some examples, the unit dose of rAAV particles administered to the one eye and/or to the contralateral eye comprises a volume of about 100 μL. In some examples, the unit dose of rAAV particles administered to the one eye and/or to the contralateral eye comprises a volume of about 50 μL. In some examples, the unit dose of rAAV particles administered to the one eye and/or to the contralateral eye comprises a volume of about 30 μL.

[00024] In some examples that may be combined with any of the preceding examples, the individual received prior treatment for the ocular neovascular disease with an anti-VEGF agent. In some examples, 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. In some examples, the individual has not received prior treatment for the ocular neovascular disease with an anti-VEGF agent. In some examples, the anti-VEGF agent is aflibercept.

[00025] In some examples that may be combined with any of the preceding examples, 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.

[00026] In some examples that may be combined with any of the preceding examples, the unit dose of rAAV particles is administered in combination with steroid treatment. In some examples, the steroid treatment is a corticosteroid treatment. In some examples, the steroid treatment is a systemic steroid treatment. In some examples, the steroid treatment is an oral steroid treatment. In some examples, the steroid treatment is a prednisone treatment. In some examples, the oral prednisone treatment comprises administering prednisone at a dose of about 60 mg per day for a total of 6 days starting at 3 days before administration of the unit dose of rAAV particles to the one eye and/or to the contralateral eye, followed by administering prednisone at a dose of about 40 mg per day for a total of 3 days, followed by administering prednisone at a dose of about 20 mg per day for a total of 2 days, and followed by administering prednisone at a dose of about 10 mg per day for a total of 2 days. In some examples, the steroid

treatment is a topical steroid treatment. In some examples, the steroid treatment is a difluprednate treatment. In some examples, the steroid is administered before, during and/or after administration of the unit dose of rAAV particles. In some examples, the steroid is administered before, during and/or after administration of the unit dose of rAAV particles to the one eye and/or to the contralateral eye.

[00027] In some examples that may be combined with any of the preceding examples, the steroid treatment is a topical steroid treatment and the topical steroid treatment is a daily steroid treatment for up to about 4 weeks, up to about 6 weeks, or up to about 8 weeks from administering the unit dose of rAAV particles. In some examples, the topical steroid treatment comprises about four administrations of topical steroid on about week 1, about three administrations of topical steroid on about week 2, about two administrations of topical steroid on about week 3, and about one administration of topical steroid on about week 4; timing starting with and following administration of the unit dose of rAAV particles. In some examples, the topical steroid treatment comprises about four administrations of topical steroid per day for about 3 weeks after administration of the unit dose of rAAV particles, followed by about 3 administrations of topical steroid per day for about 1 week, followed by about 2 administrations of topical steroid per day for about 1 week, and followed by about 1 administration of topical steroid per day for about 1 week. 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 at about one week prior to administration of the unit dose of rAAV particles. 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 at about the administration of the unit dose of rAAV particles. 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 at about one week prior to administration of the unit dose of 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.

[00028] In some examples, the ocular neovascular disease is wet age-related macular degeneration (wAMD).

[00029] In some examples that may be combined with any of the preceding examples, the administering the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in maintenance or a decrease of retinal thickness compared to the retinal thickness prior to administration of the unit dose of rAAV particles. In some examples, the maintenance or the decrease of retinal thickness compared to the retinal thickness prior to administration of the unit dose of rAAV particles is present at about 30 weeks, about 34 weeks, about 44 weeks, about 6 months, about 1 year, about 1.5 years, about 2 years, about 3 years, about 5 years, about 10 years, or more after administration of the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual. In some examples, the administering the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in a decrease in retinal thickness compared to the retinal thickness prior to administration of the unit dose of rAAV particles. In some examples, the decrease in retinal thickness is at least about 10% compared to the retinal thickness prior to administration of the unit dose of rAAV particles. In some examples, retinal thickness is central subfield thickness (CST) or central retinal thickness (CRT).

[00030] In some examples that may be combined with any of the preceding examples, the administering the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in maintenance or a decrease in macular volume compared to the macular volume prior to administration of the unit dose of rAAV particles. In some examples, the maintenance or the decrease in macular volume compared to the macular volume prior to administration of the unit dose of rAAV particles is present at about 30 weeks, about 34 weeks, about 44 weeks, about 6 months, about 1 year, about 1.5 years, about 2 years, about 3 years, about 5 years, about 10 years, or more after administration of the unit dose of rAAV particles to the one eye and/or to the contralateral

eye of the individual. In some examples, the administering the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in a decrease in macular volume compared to the macular volume prior to administration of the unit dose of rAAV particles. In some examples, the decrease in macular volume is at least about 10% compared to the macular volume prior to administration of the unit dose of rAAV particles.

[00031] In some examples that may be combined with any of the preceding examples, the administering the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in maintenance or an improvement of visual acuity compared to the visual acuity prior to administration of the unit dose of rAAV particles. In some examples, the maintenance or the improvement of visual acuity compared to the visual acuity prior to administration of the unit dose of rAAV particles is present at about 30 weeks, about 34 weeks, about 44 weeks, about 6 months, about 1 year, about 1.5 years, about 2 years, about 3 years, about 5 years, about 10 years, or more after administration of the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual. In some examples, the administering the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in an improvement of visual acuity compared to the visual acuity prior to administration of the unit dose of rAAV particles. In some examples, visual acuity is best corrected visual acuity (BCVA).

[00032] In some examples that may be combined with any of the preceding examples, administration of a single unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual provides a therapeutic benefit (e.g., treatment of an ocular neovascular disease, reduction of retinal fluid, maintenance or a decrease of retinal thickness, maintenance or a decrease in macular volume, and/or maintenance or an improvement of visual acuity). In some examples, administration of a single unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual provides a therapeutic benefit that is present at about 30 weeks or more, about 34 weeks or more, about 44 weeks or more, about 6 months or more, about 1 year or more, about 1.5 years or more, or about 2 years, about 3 years, about 5 years, about 10 years, or more after administration of the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual.

[00033] In some examples that may be combined with any of the preceding examples, 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 at least about 50% of the individuals in the plurality not requiring an anti-VEGF rescue treatment. In some examples, at least about 50% of the individuals in the plurality do not require an anti-VEGF rescue treatment for at least about 20 weeks, at least about 36 weeks, at least about 52 weeks, at least about 56 weeks, or more after administration of the unit dose of rAAV particles.

[00034] In some examples that may be combined with any of the preceding examples, administration of a single unit dose of rAAV particles to the one eye and/or to the contralateral eye of a plurality of individuals results in at least about 67% of the individuals in the plurality not requiring an anti-VEGF rescue treatment. In some examples, at least about 67% of the individuals in the plurality do not require an anti-VEGF rescue treatment for at least about 20 weeks, at least about 36 weeks, at least about 52 weeks, at least about 60 weeks, at least about 64 weeks, or at least about 66 weeks after administration of the unit dose of rAAV particles.

[00035] In some examples that may be combined with any of the preceding examples, 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 at least about 78% of the individuals in the plurality not requiring an anti-VEGF rescue treatment. In some examples, at least about 78% of the individuals in the plurality do not require an anti-VEGF rescue treatment for at least about 20 weeks, at least about 36 weeks, or more after administration of the unit dose of rAAV particles.

[00036] In some examples that may be combined with any of the preceding examples, 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 100% of the individuals in the plurality not requiring an anti-VEGF rescue treatment. In some examples, 100% of the individuals in the plurality do not require an anti-VEGF rescue treatment for at least about 64 weeks, at least about 68 weeks, at least about 72 weeks, at least about 76 weeks, at least about 80 weeks, at least about 84 weeks, or more after administration of the unit dose of rAAV particles.

[00037] In some examples that may be combined with any of the preceding examples, 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 a reduction in the annualized anti-VEGF injection rate of at least about 80%, at least about 85%, at least about 87%, at least about 90%, at least about 95%, at least about 99%, or 100% compared to the annualized anti-VEGF injection rate prior to administration of the unit dose of rAAV particles.

[00038] In some examples, the ocular neovascular disease is diabetic macular edema (DME). In some examples, the administering 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). In some examples, the administering the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in a 2-step improvement in Diabetic Retinopathy Severity Scale (DRSS). In some examples, the administering the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in a 3-step improvement in Diabetic Retinopathy Severity Scale (DRSS).

[00039] In an example, methods for treating an ocular neovascular disease in an individual are provided. The methods comprise administering a unit dose of about 2×10^{11} vector genomes (vg) or less of recombinant adeno-associated virus (rAAV) particles to one eye of an individual, wherein the individual is 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 claim 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. In various examples of the methods, retinal fluid in the eye of an individual with an ocular neovascular disease is reduced.

[00040] In an example, methods for reducing retinal fluid in an eye of an individual with an ocular neovascular disease are provided. The methods comprise administering a unit dose of rAAV particles to one eye of the individual, wherein the individual is 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. In examples of the methods, the individual has received at least one treatment of an anti-VEGF agent in about 12 weeks prior to administration of the unit dose of rAAV particles. In examples of various methods, the amount or presence of retinal fluid in the one eye of the individual is refactory to prior treatment with an anti-VEGF agent. In further examples of the methods, the anti-VEGF agent is aflibercept. In examples of any of the above methods, 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 examples of any of the above methods, the retinal fluid is subretinal fluid (SRF) or intraretinal fluid (IRF).

[00041] Methods for treating an ocular neovascular disease in an individual are provided. The methods comprise (a) administering an anti-VEGF agent to one eye of the individual and (b) administering a unit dose of about 6 x 1011 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 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 AAV 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. Examples of the methods comprise administering the unit dose of rAAV particles to the one eye of the individual about 1 week or about 7 days after the administration of the anti-VEGF agent. Examples of the methods comprise 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 examples of the methods, the anti-VEGF agent comprises aflibercept. In examples of the method, the aflibercept is administered at a dose of about 2 mg by intravitreal injection.

[00042] In examples of the above methods, the unit dose of rAAV particles is between about 6×10^{10} to about 6×10^{11} vector genomes per eye (vg/eye). In examples of the above methods, 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 of the above methods, the unit dose of rAAV particles is about 2×10^{11} vector genomes per eye (vg/eye). In other examples of the above

methods, the unit dose of rAAV particles is about 6 x 10^{11} vector genomes per eye (vg/eye).

[00043] In examples of any of the above methods, the individual has one or more symptoms of an ocular neovascular disease in the contralateral eye. Various examples of the above methods further comprise administering a unit dose of rAAV particle to the contralateral eye of the individual. 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. In some examples, administering the unit dose of rAAV particle 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 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. In some examples, administering the unit dose of rAAV particles to the contralateral eye is at least about 2 weeks after administering the unit dose of rAAV particles to the one eye. In some examples of the above methods, 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.

[00044] In examples of any of the above methods, the nucleic acid comprises the nucleic acid sequence of SEQ ID NO:40 or a sequence having at least 85% identity thereto. In examples of the above methods, the polypeptide comprises the amino acid sequence of SEQ ID NO:35. In examples of any of the above methods, the polypeptide comprises the amino acid sequence of SEQ ID NO:41. In examples of any of the methods, the polypeptide is aflibercept. In examples of the methods, the nucleic acid further comprises a first enhancer region, a promoter region, a 5'UTR region, a second enhancer region and a polyadenylation site. In examples of the methods, the nucleic acid comprises, in the 5' to 3' order: (a) a first enhancer region (b) a promoter region; (c) a 5' UTR region; (d) 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; (e) a second enhancer region; and (f) a polyadenylation site, and flanked by AAV2 inverted terminal repeats (ITRs). In some examples, 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. In some examples, the promoter region comprises a CMV sequence comprising the sequence of SEQ ID NO:23 or a sequence having at least 85% identity thereto. In some examples of the methods, the nucleic acid encoding a polypeptide comprises the nucleic acid sequence of SEQ ID NO:40 or a sequence having at least 85% identity thereto. In various examples, the polypeptide comprises the amino acid sequence of SEQ ID NO:35 or a sequence having at least 95% identity thereto. In various examples, the polypeptide comprises the amino acid sequence of SEQ ID NO:41 or a sequence having at least 95% identity thereto. In some examples, the polypeptide is aflibercept. In various examples, 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. In some examples of the methods, 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. In certain examples of the methods, 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.

[00045] In an example of the methods, the nucleic acid further comprises (a) a first enhancer region comprising a CMV sequence comprising the sequence set forth in SEQ ID NO:22 or a sequence having at least 85% identity thereto; (b) a promoter region, comprising a CMV sequence comprising the sequence of SEQ ID NO:23 or a sequence having at least 85% identity thereto, (c) a 5' UTR comprising 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 leat 85% identity thereto, (d) a second enhancer region comprising a full EES sequence comprising the sequence of SEQ ID NO:26 or a sequence having at least 85% identity thereto, and (e) a HGH polyadenylation site comprising the sequence of SEQ ID NO:27 or a sequence having at least 85% identity thereto.

[00046] In examples of any of the methods, the nucleic acid comprises the sequence of SEQ ID NO:39 or a sequence having at least 85% identity thereto.

[00047] In examples of any of the above methods, the AAV2 capsid protein comprises the amino acid sequence LGETTRPA (SEQ ID NO:1) 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 sequence of SEQ ID NO:13. In examples of any of the above methods, the AAV2 capsid protein comprises the amino acid sequence LALGETTRPA (SEQ ID NO:1) 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 sequence of SEQ ID NO:13.

[00048] In examples of any of the above methods, 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.

[00049] Examples of any of the above methods, wherein the administration of the unit dose of rAAV particles to the one eye and/or the contralateral eye is by intravitreal administration are provided.

[00050] In examples of any of the above methods, the unit dose of rAAV particles is in a pharmaceutical formulation. In some examples, the pharmaceutical formulation comprises the rAAV particles, sodium chloride, sodium phosphate and a surfactant. In an example of the above methods, the pharmaceutical composition comprises about 150 to about 200 mM sodium chloride, about 1 to about 10 mM monobasic sodium phosphate, about 1 to about 10 mM dibasic sodium phosphate, about 0.0005% (w/v) to about 0.0005% (w/v) poloxamer 188 and about 6 x 10^{13} to about 6 x 10^{10} vector genomes (vg) per mL (vg/ml) of the rAAV particles wherein the pharmaceutical formulation has a pH of about 7.0 to about 7.5. In some examples, the pharmaceutical composition comprises about 180 mM sodium chloride, about 5 mM monobasic sodium phosphate, about 5 mM dibasic sodium phosphate, about 6 x 10^{12} vg/ml of the rAAV particles and about 0.001% (w/v) poloxamer 188, wherein the pharmaceutical formulation has a pH of about 7.3. In some examples, the pharmaceutical composition comprises about 180 mM sodium chloride, about 5 mM monobasic sodium phosphate, about 5 mM dibasic sodium phosphate, about 6 x 10^{11} vg/ml of the rAAV particles and about 0.001% (w/v) poloxamer 188, wherein the pharmaceutical formulation has a pH of about 7.3.

[00051] In examples of any of the above methods, the unit dose of rAAV particles administered to the one eye and or to the contralateral eye is in a volume of about 25 µl to about 250 µl. In some examples, the unit dose of rAAV particles administered to one eye and/or to the contralateral eye comprises a volume of about 100 µl. In some examples, the

unit dose of rAAV particles administered to one eye and/or to the contralateral eye comprises a volume of about 30 µl.

[00052] In examples of the above methods, the individual received prior treatment for the ocular neovascular disease with an anti-VEGF agent. In some examples, 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.

[00053] In examples of some of the above methods, the individual has not received prior treatment for the ocular neovascular disease with an anti-VEGF agent.

[00054] In examples of any one of the above methods, the anti-VEGF agent is aflibercept.

[00055] In examples of any one of the above methods, 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, ischemia retinopathy, diabetic retinal edema or any combination thereof.

[00056] In examples of the above methods, the unit dose of rAAV particles is administered in combination with steroid treatment. In certain examples, the steroid treatment is a corticosteroid treatment. In some examples, the steroid treatment is a systemic steroid treatment. In various examples, the steroid treatment is an oral steroid treatment. In some examples, the steroid treatment is a prednisone treatment. In certain examples of the methods, the steroid treatment is a topical steroid treatment. In examples of the methods, the steroid treatment is a difluprednate treatment. In examples of the above methods, the steroid is administered before, during and/or after administration of the unit dose of rAAV particles to the one eye and/or to the contralateral eye.

[00057] In examples of some methods, the steroid treatment is a topical steroid treatment and the topical steroid treatment is a daily steroid treatment for up to about 4 weeks, up to about 6 weeks, or up to about 8 weeks from administering the unit dose of rAAV particles. In some examples of the above method, the topical steroid treatment comprises about four administrations of a topical steroid per day on about week 1, about three administrations of topical steroid per day on about week 2, about two administrations of topical steroid per day on about week 3, and about one administration per day of topical steroid on about week 4;

timing starting with and following administration of the unit dose of rAAV particles. In some examples of the methods, the topical steroid treatment comprises about four administrations of topical steroid per day for about three weeks after administration of the unit dose of rAAV particles, followed by about 3 administrations of topical steroid per day for about 1 week, followed by about 2 administrations of topical steroid per day for about 1 week and followed by about 1 administration of topical steroid per day for about 1 week. In some examples of the methods, 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, followed by about one administration of topical steroid per day for about one week; timing starting at about one week prior to administration of the unit dose of rAAV particles.

[00058] In some examples of the methods, the methods further comprise administering a topical steroid treatment. In examples of the methods, the topical steroid treatment is a difluprednate treatment. In examples of the above methods, 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, followed by about one administration of topical steroid per day for about one week; timing starting with and following administration of an anti-VEGF agent. In examples of the above methods, the topical steroid comprises difluprednate 0.05% at a dose of about 1 µg to about 3 µg. In some examples of the above methods, the topical steroid comprises difluprednate 0.05% at a dose of about 2.5µg.

[00059] In examples of any of the above methods administering the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in maintenance of or a decrease of retinal thickness compared to the retinal thickness prior to administration of the unit dose of rAAV particles. In some examples, the administering the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in a decrease in retinal thickness compared to the retinal thickness prior to administration of the unit dose of rAAV particles. In certain examples of the methods, the decrease in retinal thickness is at least about 10% compared to the retinal thickness prior

to administration of the unit dose of rAAV particles. In examples of certain methods, the retinal thickness is central subfield thickness (CST) or central retinal thickness (CRT).

[00060] In examples of any of the above methods, administering the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in maintenance or a decrease in macular volume compared to the macular volume prior to administration of the unit dose of rAAV particles. In an example of the methods, administering the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in a decrease in macular volume compared to the macular volume prior to administration of the unit dose of rAAV particles. In example of the methods, the decrease in macular volume is at least about 10% compared to the macular volume prior to administration of the unit dose of rAAV particles.

[00061] In examples of any of the above methods, the administering the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in maintenance or an improvement of visual acuity compared to the visual acuity prior to administration of the unit dose of rAAV particles. In some examples of the methods, administering the unit dose of rAAV particles to the one eye and/or to the contralateral eye of the individual results in an improvement of visual acuity compared to the visual acuity prior to administration of the unit dose of rAAV particles. In examples of the methods, visual acuity is best corrected visual acuity (BCVA).

[00062] In examples of any of the above methods, 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 at least about 50% of the individuals in the plurality not requiring an anti-VEGF rescue treatment. In some examples of the methods, at least about 50% of the individuals in the plurality do not require an anti-VEGF rescue treatment for at least about 20 weeks, at least about 36 weeks, at least about 52 weeks, at least about 56 weeks or more after administration of the unit dose of rAAV particles.

[00063] In examples of any of the above methods, 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 at least about 67% of the individuals in the plurality not requiring an anti-VEGF rescue treatment. In some examples of the methods, at least about 67% of the individuals in the plurality do not require an anti-VEGF rescue treatment for at least about 20 weeks, at least

about 36 weeks, at least about 52 weeks, at least about 60 weeks, at least about 64 weeks or at least about 66 weeks after administration of the unit dose of rAAV particles.

[00064] In examples of the above methods, 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 at least about 78% of the individuals in the plurality not requiring an anti-VEGF rescue treatment. In various examples at least about 78% of the individuals in the plurality do not require an anti-VEGF rescue treatment for at least about 20 weeks, at least about 36 weeks or mor after administration of the unit dose of rAAV particles.

[00065] In examples of the above methods, 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 100% of the individuals in the plurality not requiring an anti-VEGF rescue treatment. In examples of the methods, 100% of the individuals in the plurality do not require an anti-VEGF rescue treatment for at least about 64 weeks, at least about 68 weeks, at least about 72 weeks, at least about 76 weeks, at least about 80 weeks, at least about 84 weeks or more after administration of the unit dose of rAAV particles.

[00066] Examples of any of the above methods provide administration of the unit dose of rAAV particles to the one eye and/or to the contralateral eye of a plurality of individuals that results in a reduction in the annualized anti-VEFG injection rate of at least about 80%, at least about 85%, at least about 87%, at least about 90%, at least about 95% at least about 99% or 100% compared to the annualized anti-VEGF injection rate prior to administration of the unit dose of rAAV particles.

[00067] In examples of various methods, the ocular neovascular disease is wet age-related macular degeneration (AMD).

[00068] In examples of various methods, the ocular neovascular disease is diabetic macular edema (DME). In various examples, administering 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 Score (DRSS).

[00069] Examples of the application provide a unit dose of about 6 x 1011 vector genomes (vg) or less of recombinant adeno-associated virus (rAAV) particles for use in a method for treating an ocular neovascular disease in an individual, the method comprising administering the unit dose to one eye of the individual, wherein the individual is a human and wherein the rAAV particle 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.

[00069a] In one aspect, the present disclosure refers to use of a unit dose of about 1×10^{10} vector genomes (vg) to about 2×10^{11} 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 medicament is to be administered by intravitreal injection (IVT) to one eye of the individual, wherein the individual is a human, 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, and wherein the medicament is for use in combination with an implant containing a steroid in the one eye.

[00070] An example of the application provides a unit dose of rAAV particles for use in a method of reducing retinal fluid in an eye of an individual with an ocular neovascular disease, the method comprising administering the unit dose to one eye of the individual, wherein the individual is 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. Examples of the above unit doses for use in an indicated method wherein the method further comprises administering an anti-VEGF agent to one eye of the individual before administration of the unit dose.

INCORPORATION BY REFERENCE

[00071] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

BRIEF DESCRIPTION OF THE DRAWINGS

[00072] **Figure 1** provides a summary of collection eyes utilized In Life Humor Collections at the indicated time points (30 days, 60 days and 98 days) in the aqueous humor (AH) or vitreous humor (VH). The eye or eyes from which the collection was made is indicated. “OD” signifies the ocular dexter or right eye. “OS” signifies the ocular sinister or left eye. “OU” signifies oculus uterque or both eyes. The subject animal identifier and group number are also indicated.

[00073] **Figure 2** provides a table summarizing aflibercept levels obtained in the Vitreous Humor at the indicated time points and in the indicated eye or eyes of the subject. BLOQ signifies “below the level of quantitation”. Dosing is indicated in vg/eye. Eyes were treated with either 3E10 or 1E11 viral genomes (vg)/treated eye. Subject animals are identified.