Extended, High Dose VEGF Antagonist Regimens for Treatment of Angiogenic Eye Disorders

CROSS- REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. provisional patent application no. 63/523,019, filed June 23, 2023; U.S. provisional patent application no. 63/523,335, filed June 26, 2023; U.S. provisional patent application no. 63/531,758, filed August 9, 2023; U.S. provisional patent application no. 63/540,308, filed September 25, 2023; U.S. provisional patent application no. 63/546,476, filed October 30, 2023; U.S. provisional patent application no. 63/601,198, filed November 20, 2023; U.S. provisional patent application no. 63/604,484, filed November 30, 2023; U.S. provisional patent application no. 63/606,507, filed December 5, 2023; U.S. provisional patent application no. 63/606,887, filed December 6, 2023; U.S. provisional patent application no. 63/608,138, filed December 8, 2023; U.S. provisional patent application no. 63/622,675, filed January 19, 2024; U.S. provisional patent application no. 63/625,146, filed January 25, 2024; U.S. provisional patent application no. 63/552,571, filed February 12, 2024; U.S. provisional patent application no. 63/556,308, filed February 21, 2024; U.S. provisional patent application no. 63/566,163, filed March 15, 2024; each of which is herein incorporated by reference in its entirety.

REFERENCE TO A SEQUENCE LISTING

[0002] This application incorporates by reference a computer readable Sequence Listing in ST.26 XML format, titled 11554WO01_Sequence, created on June 21, 2024, and containing 5,467 bytes.

FIELD OF THE INVENTION

[0003] The field of the present invention relates to methods for treating or preventing angiogenic eye disorders by administering a VEGF antagonist.

BACKGROUND OF THE INVENTION

[0004] The PHOTON clinical trial in DR/DME and the PULSAR clinical trial in wAMD are double-masked, active-controlled pivotal trials conducted in multiple centers globally. In both trials, patients were randomized into 3 treatment groups to receive either: aflibercept 8 mg every 12 weeks, aflibercept 8 mg every 16 weeks, or EYLEA every 8 weeks.

[0005] Patients treated with aflibercept 8 mg in both trials had 3 initial monthly doses, and patients treated with EYLEA received 5 initial monthly doses in PHOTON and 3 in PULSAR. In the first year, patients in the aflibercept 8 mg groups could have their dosing intervals shortened to as frequent as every 8-weeks if protocol-defined criteria for disease progression were observed. Intervals could not be extended until the second year of the study. Patients in both EYLEA groups (the control group for both PHOTON and PULSAR) maintained a fixed 8-week dosing regimen throughout their participation in the trials.

SUMMARY OF THE INVENTION

[0006] The present invention provides methods for treating or preventing an angiogenic eye disorder (*e.g.*, age-related macular degeneration (neovascular (nAMD)), macular edema (ME), macular edema following retinal vein occlusion (ME-RVO), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, diabetic retinopathies (DR) (*e.g.*, non-proliferative diabetic retinopathy (*e.g.*, characterized by a Diabetic Retinopathy Severity Scale (DRSS) level of about 47 or 53) or proliferative diabetic retinopathy; *e.g.*, in a subject that does not suffer from DME), and/or Diabetic retinopathy in a subject who has diabetic macular edema (DME)) comprising administering to an eye of the subject (preferably by intravitreal injection) one or more doses (*e.g.*, of $\geq$8 mg ($\pm$0.8 mg)) of aflibercept such that the clearance of free aflibercept from the ocular compartment is about 0.367-0.457 mL/day (*e.g.*, 0.41 mL/day) after an intravitreal injection of aflibercept and the time for the amount for free aflibercept to reach the lower limit of quantitation (LLOQ) in the ocular compartment of a subject after said intravitreal injection of aflibercept is about 15 weeks; and the time for free aflibercept to reach the lower limit of quantitation (LLOQ) in the plasma (*e.g.*, about 0.0156 mg/L) of a subject after said intravitreal injection of aflibercept is about 3.5 weeks; for example, wherein the aflibercept is administered in an aqueous pharmaceutical formulation wherein the aflibercept has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8°C. In an embodiment of the invention, the aqueous pharmaceutical formulation comprises an aqueous pharmaceutical formulation comprising: at least about 100 mg/ml of a VEGF receptor fusion protein comprising two polypeptides that each comprises an

immunoglobin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2, and a multimerizing component; about 10-100 mM L-arginine; sucrose; a histidine-based buffer; and a surfactant; wherein the formulation has a pH of about 5.0 to about 6.8; wherein the VEGF receptor fusion protein has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8°C. In an embodiment of the invention, the method comprises administering a single initial dose of about 8 mg (±0.8 mg) or more of aflibercept, followed by one or more secondary doses of about 8 mg (±0.8 mg) or more of the aflibercept, followed by one or more tertiary doses of about 8 mg (±0.8 mg) or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 (preferably 4) weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 8, 12, 16, 20, 8-24, 12-24, 16-24, 20-24 or 24 weeks after the immediately preceding dose.

[0007] The present invention provides a method for slowing the clearance of free aflibercept from the ocular compartment after an intravitreal injection relative to the rate of clearance of aflibercept from the ocular compartment after an intravitreal injection of $\leq$ 4 mg aflibercept comprising intravitreally injecting into an eye of a subject in need thereof, a single initial dose of about 8 mg (±0.8 mg) or more of aflibercept, followed by one or more secondary doses of about 8 mg (±0.8 mg) or more of the aflibercept, followed by one or more tertiary doses of about 8 mg (±0.8 mg) or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose. In an embodiment of the invention, the clearance of free aflibercept from the ocular compartment is about 34% slower than that from the ocular compartment after an intravitreal injection of $\leq$ 4 mg aflibercept, *e.g.*, wherein the clearance of free aflibercept from the ocular compartment is about 0.367-0.457 mL/day or 0.41 mL/day after an intravitreal injection of $\geq$ 8 mg (±0.8 mg) aflibercept.

[0008] The present invention also provides a method for increasing the time for the amount of free aflibercept to reach the lower limit of quantitation (LLOQ) in the ocular compartment of a subject after an intravitreal injection of aflibercept relative to the time to reach LLOQ of the amount of free aflibercept in the ocular compartment of a subject after an intravitreal injection of about 2 mg aflibercept, *e.g.*, increasing by greater than 1.3 weeks, for example, by about 6 weeks-to more than 10 weeks, for example, to about 15 weeks, comprising intravitreally injecting into an eye of a subject in need thereof, a single initial dose of about 8 mg (±0.8 mg) or more of aflibercept, followed by one or more secondary doses of about 8 mg (±0.8 mg) or more of the aflibercept, followed by one or more tertiary doses of about 8 mg (±0.8 mg) or more of the

aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 8-24, 12-24, 16-24, 20-24 or 24 weeks after the immediately preceding dose.

[0009] The present invention also provides a method for increasing the time for free aflibercept to reach the lower limit of quantitation (LLOQ) in the plasma (*e.g.*, about 0.0156 mg/L) of a subject after an intravitreal injection of aflibercept relative to the time to reach LLOQ of free aflibercept in the plasma of a subject after an intravitreal injection of about 2 mg aflibercept, *e.g.*, increased by more than 1.5 weeks, for example by about 2 weeks-to about 3.5 weeks, comprising intravitreally injecting into an eye of a subject in need thereof, a single initial dose of about 8 mg (±0.8 mg) or more of aflibercept, followed by one or more secondary doses of about 8 mg (±0.8 mg) or more of the aflibercept, followed by one or more tertiary doses of about 8 mg (±0.8 mg) or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose. In an embodiment of the invention, the ≥8 mg (±0.8 mg) aflibercept is administered in an aqueous pharmaceutical formulation including aflibercept which includes one or more of histidine-based buffer, arginine (*e.g.*, L-arginine, for example, L-arginine HCl), a sugar or polyol such as sucrose and having a pH of about 5.8. In an embodiment of the invention, the aflibercept has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8°C; for example, wherein the ≥8 mg (±0.8 mg) aflibercept is in an aqueous pharmaceutical formulation comprising an aqueous pharmaceutical formulation comprising: at least about 100 mg/ml of a VEGF receptor fusion protein comprising two polypeptides that each comprises an immunoglobin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2, and a multimerizing component; about 10-100 mM L-arginine; sucrose; a histidine-based buffer; and a surfactant; wherein the formulation has a pH of about 5.0 to about 6.8; wherein the VEGF receptor fusion protein has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8°C.

[00010] The present invention provides a method for treating or preventing an angiogenic eye disorder (e.g.,age-related macular degeneration (neovascular (nAMD)), macular edema (ME), macular edema following retinal vein occlusion (ME-RVO), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma,

post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, diabetic retinopathies (DR) (*e.g.*, non-proliferative diabetic retinopathy (*e.g.*, characterized by a Diabetic Retinopathy Severity Scale (DRSS) level of about 47 or 53) or proliferative diabetic retinopathy; *e.g.*, in a subject that does not suffer from DME), and/or Diabetic retinopathy in a subject who has diabetic macular edema (DME)) in a subject in need thereof, for improving best corrected visual acuity (BCVA) in a subject in need thereof with nAMD, DR and/or DME; or for promoting retinal drying in a subject with nAMD, DR and/or DME in need thereof; comprising administering to an eye of the subject (preferably by intravitreal injection), one or more doses of about 8 mg (±0.8 mg) or more of VEGF receptor fusion protein, preferably aflibercept, once every 24 weeks. In an embodiment of the invention, the method comprises administering to an eye of the subject, a single initial dose of about 8 mg (±0.8 mg) or more of a VEGF receptor fusion protein, preferably aflibercept, followed by one or more secondary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 (preferably 4) weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 8-24, 12-24, 16-24, 20-24 or 24 weeks after the immediately preceding dose.

[00011] The present invention includes a method for treating or preventing an angiogenic eye disorder (e.g.,age-related macular degeneration (neovascular (nAMD)), macular edema (ME), macular edema following retinal vein occlusion (ME-RVO), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, diabetic retinopathies (DR) (*e.g.*, non-proliferative diabetic retinopathy (*e.g.*, characterized by a Diabetic Retinopathy Severity Scale (DRSS) level of about 47 or 53) or proliferative diabetic retinopathy; *e.g.*, in a subject that does not suffer from DME), and/or Diabetic retinopathy in a subject who has diabetic macular edema (DME)) in a subject in need thereof, comprising administering to an eye of the subject (preferably by intravitreal injection), a single initial dose of about 8 mg (±0.8 mg) or more of a VEGF receptor fusion protein, preferably aflibercept, followed by one or more secondary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein, followed by one or more

tertiary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 (preferably 4) weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 8-24, 12-24, 16-24, 20-24 or 24 weeks after the immediately preceding dose.

[00012] In an embodiment of the invention, the method for treating or preventing an angiogenic eye disorder (e.g.,age-related macular degeneration (neovascular (nAMD)), macular edema (ME), macular edema following retinal vein occlusion (ME-RVO), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, diabetic retinopathies (DR) (*e.g.*, non-proliferative diabetic retinopathy (*e.g.*, characterized by a Diabetic Retinopathy Severity Scale (DRSS) level of about 47 or 53) or proliferative diabetic retinopathy; *e.g.*, in a subject that does not suffer from DME), and/or Diabetic retinopathy in a subject who has diabetic macular edema (DME)) in a subject comprises comprising administering, to a subject in need thereof (preferably by intravitreal injection), ≥8 mg (±0.8 mg) VEGF receptor fusion protein, preferably aflibercept, (*e.g.*, in a volume of 0.07 mL or 70 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days, monthly) for the first three doses, followed by ≥8 mg (±0.8 mg) VEGF receptor fusion protein (*e.g.*, in a volume of 0.07 mL) via intravitreal injection once every 8-24, 12-24, 16-24, 20-24 or 24 weeks (6 months, +/- 7 days).

[00013] The present invention also provides a method for treating or preventing an angiogenic eye disorder (e.g.,age-related macular degeneration (neovascular (nAMD)), macular edema (ME), macular edema following retinal vein occlusion (ME-RVO), retinal vein occlusion (RVO), central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), diabetic macular edema (DME), choroidal neovascularization (CNV), iris neovascularization, neovascular glaucoma, post-surgical fibrosis in glaucoma, proliferative vitreoretinopathy (PVR), optic disc neovascularization, corneal neovascularization, retinal neovascularization, vitreal neovascularization, pannus, pterygium, vascular retinopathy, diabetic retinopathies (DR) (*e.g.*, non-proliferative diabetic retinopathy (*e.g.*, characterized by a Diabetic Retinopathy Severity Scale (DRSS) level of about 47 or 53) or proliferative diabetic retinopathy; *e.g.*, in a subject that does not suffer from DME), and/or Diabetic retinopathy in a subject who has diabetic macular edema (DME)), in a subject in need thereof: (1) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein, then the method comprises, after 1 month, administering

to the subject the initial ≥8 mg (±0.8 mg) dose of VEGF receptor fusion protein and, 1 month thereafter, the 1st ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and, 1 month thereafter, the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (2) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein, then the method comprises, after 1 month, administering to the subject the first ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein and, 1 month thereafter, the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, one or more ≥ 8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (3) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein, then the method comprises, after 1 month, administering to the subject the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein and then, every 24 weeks thereafter, one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (4) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein, then the method comprises, after 1 month, administering to the subject the 1st ≥8 mg (±0.8 mg) maintenance dose of VEGF receptor fusion protein and all further ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein every 24 weeks according to the HDq24 dosing regimen; (5) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month, then the method comprises, after another 1 month, administering to the subject the initial ≥8 mg (±0.8 mg) dose of VEGF receptor fusion protein and, 1 month thereafter, the 1st ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and 1 month thereafter, the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, one or more ≥ 8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (6) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month, then the method comprises, after another 1 month, administering to the subject a first ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein and, 1 month thereafter, the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (7) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month, then the method comprises, after another 1 month,

administering to the subject the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein and then, every 24 weeks thereafter, one or more ≥ 8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (8) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month, then the method comprises, after another 1 month, administering to the subject the 1st ≥8 mg (±0.8 mg) maintenance dose of VEGF receptor fusion protein and all further ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein every 24 weeks according to the HDq24 dosing regimen; (9) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and a 2nd 2 mg secondary dose of VEGF receptor fusion protein after another 1 month, then the method comprises, after another 1 month, administering to the subject the initial ≥8 mg (±0.8 mg) dose of VEGF receptor fusion protein and, 1 month thereafter, the 1st ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and 1 month thereafter, the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (10) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and a 2nd 2 mg secondary dose of VEGF receptor fusion protein after another 1 month, then the method comprises, after another 1 month, administering to the subject the first ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein and, 1 month thereafter, the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (11) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and a 2nd 2 mg secondary dose of VEGF receptor fusion protein after another 1 month, then the method comprises, after another 1 month, administering to the subject the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein and then, every 24 weeks thereafter, one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (12) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and a 2nd 2 mg secondary dose of VEGF receptor fusion protein after another 1 month, then the method comprises, after 2 months, administering to the subject the 1st ≥8 mg (±0.8 mg) maintenance dose of VEGF receptor fusion protein and, all further ≥8 mg (±0.8 mg)

maintenance doses of VEGF receptor fusion protein every 24 weeks according to the HDq24 dosing regimen; (13) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and a 2nd 2 mg secondary dose of VEGF receptor fusion protein after another 1 month and a 3rd 2 mg secondary dose of VEGF receptor fusion protein after 1 month, then the method comprises, after 1 month, administering to the subject the initial ≥8 mg (±0.8 mg) dose of VEGF receptor fusion protein and 1 month thereafter, the 1st ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and 1 month thereafter, the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (14) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and a 2nd 2 mg secondary dose of VEGF receptor fusion protein after another 1 month and a 3rd 2 mg secondary dose of VEGF receptor fusion protein after 1 month, then the method comprises, after 1 month, administering to the subject the first ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein and 1 month thereafter, the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (15) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and a 2nd 2 mg secondary dose of VEGF receptor fusion protein after another 1 month and a 3rd 2 mg secondary dose of VEGF receptor fusion protein after 1 month, then the method comprises, after 1 month, administering to the subject the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein and then, every 24 weeks thereafter, one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (16) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and a 2nd 2 mg secondary dose of VEGF receptor fusion protein after another 1 month and a 3rd 2 mg secondary dose of VEGF receptor fusion protein after 1 month, then the method comprises, after 2 months, administering to the subject the 1st ≥8 mg (±0.8 mg) maintenance dose of VEGF receptor fusion protein and all further ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein every 24 weeks according to the HDq24 dosing regimen; (17) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and a 2nd 2 mg secondary dose of VEGF

receptor fusion protein after another 1 month and a 3rd 2 mg secondary dose of VEGF receptor fusion protein after 1 month; and a 4th 2 mg secondary dose of VEGF receptor fusion protein after 1 month; thereafter, then the method comprises, after 2 months, administering to the subject the initial ≥8 mg (±0.8 mg) dose of VEGF receptor fusion protein and, 1 month thereafter, the 1st ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and 1 month thereafter, the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (18) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and a 2nd 2 mg secondary dose of VEGF receptor fusion protein after another 1 month and a 3rd 2 mg secondary dose of VEGF receptor fusion protein after 1 month; and a 4th 2 mg secondary dose of VEGF receptor fusion protein after 1 month; thereafter, then the method comprises, after 2 months, administering to the subject the first ≥ 8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein and, 1 month thereafter, the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (19) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and a 2nd 2 mg secondary dose of VEGF receptor fusion protein after another 1 month and a 3rd 2 mg secondary dose of VEGF receptor fusion protein after 1 month, and a 4th 2 mg secondary dose of VEGF receptor fusion protein after 1 month; thereafter, then the method comprises, after 2 months, administering to the subject the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein and, 24 weeks thereafter, one or more 24 weekly ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (20) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and a 2nd 2 mg secondary dose of VEGF receptor fusion protein after another 1 month and a 3rd 2 mg secondary dose of VEGF receptor fusion protein after 1 month, and a 4th 2 mg secondary dose of VEGF receptor fusion protein after 1 month, thereafter, then the method comprises, after 2 months, administering to the subject the 1st ≥8 mg (±0.8 mg) maintenance dose of VEGF receptor fusion protein and, all further ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein every 24 weeks according to the HDq24 dosing regimen; (21) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and

a 2nd 2 mg secondary dose of VEGF receptor fusion protein after another 1 month and a 3rd 2 mg secondary dose of VEGF receptor fusion protein after 1 month, and a 4th 2 mg secondary dose of VEGF receptor fusion protein after 1 month; and one or more 2 mg maintenance doses every 8 weeks thereafter, then the method comprises, 2 months after the last VEGF receptor fusion protein maintenance dose, administering to the subject the initial ≥8 mg (±0.8 mg) dose of VEGF receptor fusion protein and, 1 month thereafter, the 1st ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and 1 month thereafter, the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (22) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and a 2nd 2 mg secondary dose of VEGF receptor fusion protein after another 1 month and a 3rd 2 mg secondary dose of VEGF receptor fusion protein after 1 month; and a 4th 2 mg secondary dose of VEGF receptor fusion protein after 1 month; and one or more 2 mg maintenance doses every 8 weeks thereafter, then the method comprises, 2 months after the last VEGF receptor fusion protein maintenance dose administering to the subject the first 8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein and, 1 month thereafter, the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; (23) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and a 2nd 2 mg secondary dose of VEGF receptor fusion protein after another 1 month and a 3rd 2 mg secondary dose of VEGF receptor fusion protein after 1 month; and a 4th 2 mg secondary dose of VEGF receptor fusion protein after 1 month; and one or more 2 mg maintenance doses every 8 weeks thereafter, then the method comprises, 2 months after the last VEGF receptor fusion protein maintenance dose, administering to the subject the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein and, 24 weeks thereafter, one or more 24 weekly ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; or (24) wherein the subject has received an initial 2 mg dose of VEGF receptor fusion protein and a 1st 2 mg secondary dose of VEGF receptor fusion protein after 1 month and a 2nd 2 mg secondary dose of VEGF receptor fusion protein after another 1 month and a 3rd 2 mg secondary dose of VEGF receptor fusion protein after 1 month; and a 4th 2 mg secondary dose of VEGF receptor fusion protein after 1 month; and one or more 2 mg maintenance doses every 8 weeks thereafter, then the method comprises, 2 months after the

last VEGF receptor fusion protein maintenance dose, administering to the subject the 1st ≥8 mg (±0.8 mg) maintenance dose of VEGF receptor fusion protein and, all further ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein every 24 weeks according to the HDq24 dosing regimen; wherein, said HDq24 dosing regimen comprises: a single initial dose of about ≥8 mg (±0.8 mg) or more of VEGF receptor fusion protein, followed by one or more secondary doses of about ≥8 mg (±0.8 mg) or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about ≥8 mg (±0.8 mg) or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose.

[00014] The present invention also provides a method for treating or preventing neovascular age related macular degeneration (nAMD), diabetic retinopathy and/or diabetic macular edema, in a subject in need thereof who has been on a dosing regimen for treating or preventing said disorder wherein: (a) the subject has received an initial ≥8 mg (±0.8 mg) dose of VEGF receptor fusion protein then the method comprises, after 1 month, administering to the subject the first ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein and 1 month thereafter, administering the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, administering one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; or (b) the subject has received an initial ≥8 mg (±0.8 mg) dose of VEGF receptor fusion protein & 1st ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein after 1 month, then the method comprises, after another 1 month, administering to the subject the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen; or (c) the subject has received an initial ≥8 mg (±0.8 mg) dose of VEGF receptor fusion protein & 1st ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein after 1 month & the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein after another month, then the method comprises, after 24 weeks administering to the subject the 1st ≥8 mg (±0.8 mg) maintenance dose of VEGF receptor fusion protein and all further ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein every 24 weeks according to the HDq24 dosing regimen; or (d) the subject has received an initial ≥8 mg (±0.8 mg) dose of VEGF receptor fusion protein & a 1st ≥ 8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein after 1 month & the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein after another month, then every 24 weeks thereafter, the subject has

received one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein; and, then the method comprises, after 24 weeks from the last maintenance dose of VEGF receptor fusion protein, administering to the subject one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein and all further ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein every 24 weeks according to the HDq24 dosing regimen; wherein, said HDq24 dosing regimen comprises: a single initial dose of about ≥8 mg (±0.8 mg) or more of VEGF receptor fusion protein, followed by one or more secondary doses of about ≥8 mg (±0.8 mg) or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about ≥8 mg (±0.8 mg) or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose.

[00015] The present invention provides a method for treating or preventing neovascular age related macular degeneration (nAMD), diabetic retinopathy or diabetic macular edema, in a subject in need thereof, comprising administering to an eye of the subject (preferably, by intravitreal injection), a single initial dose of about 8 mg (±0.8 mg) or more of a VEGF receptor fusion protein, preferably aflibercept, followed by one or more secondary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 8, 12 or 16 or 20 weeks after the immediately preceding dose; further comprising, when a 8, 12, 16 or 20 week tertiary dose is due, evaluating the patient for suitability to lengthen the teritary dose interval, and if, in the judgment of a treating physician based on the patient's visual acuity and/or central retinal thickness, lengthening the tertiary dose interval is appropriate, increasing the tertiary dose interval by an increment of 4 weeks, for example, wherein the interval is lengthened up to about 24 weeks, *e.g.*, after one or more 4 week increases in the interval.

[00016] The present invention also provides a method for treating or preventing an angiogenic eye disorder (preferably nAMD, DR and/or DME), in a subject in need thereof who has been on a dosing regimen for treating or preventing the disorder calling for a single initial dose of about 2 mg of VEGF receptor fusion protein, preferably aflibercept, followed by one or more secondary doses of about 2 mg of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 2 mg of the VEGF receptor fusion protein; wherein each secondary dose is administered about 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 8 weeks after the immediately preceding dose; and wherein the

subject is at any phase of the 2 mg VEGF receptor fusion protein dosing regimen, comprising administering to an eye of the subject (preferably by intravitreal injection), an 8 mg (±0.8 mg) dose of VEGF receptor fusion protein, evaluating the subject in about 4 or 8 or 10 or 12 weeks after said administering and, if, in the judgment of the treating physician dosing every 24 weeks is appropriate, then continuing to dose the subject every 24 weeks with ≥8 mg (±0.8 mg) VEGF receptor fusion protein.

[00017] In an embodiment of the invention, a subject in a method of the present invention has been on a dosing regimen for treating or preventing neovascular age related macular degeneration, diabetic retinopathy and/or diabetic macular edema of a single initial dose of about 2 mg of a VEGF receptor fusion protein, preferably aflibercept, followed by 2, 3 or 4 secondary doses of about 2 mg of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 2 mg of the VEGF receptor fusion protein; wherein each secondary dose is administered about 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 8 weeks after the immediately preceding dose.

[00018] The present invention also provides a method for treating or preventing neovascular age related macular degeneration, diabetic retinopathy or diabetic macular edema, in a subject in need thereof, comprising administering to an eye of the subject (preferably by intravitreal injection), a single initial dose of about 8 mg (±0.8 mg) or more of a VEGF receptor fusion protein, preferably aflibercept, followed by one or more secondary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 (preferably 4) weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 12 or 16 weeks after the immediately preceding dose; further comprising, after receiving one or more of said tertiary doses about 12 or 16 after the immediately preceding dose, lengthening the tertiary dose interval from 12, 16 or 20 to 24 weeks, after the immediately preceding dose. For example, in an embodiment of the invention, during said treatment, the subject exhibits (a) <5 letter loss in BCVA; and/or (b) central retinal thickness (CRT) <300 or 320 μm. In an embodiment of the invention, the method further comprises evaluating BVCA and/or CRT in the subject and, if the subject exhibits (a) <5 letter loss in BCVA; and/or (b) CRT <300 or 320 μm, lengthening the tertiary dose interval.

[00019] The present invention also provides a method treating or preventing neovascular age related macular degeneration, diabetic retinopathy and/or diabetic macular edema, in a subject in need thereof, comprising administering to an eye of the subject (preferably by intravitreal injection), a single initial dose of about ≥8 mg (±0.8 mg) or more of a VEGF receptor fusion

protein, preferably aflibercept, followed by one or more secondary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 (preferably 4) weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose; further comprising, after receiving one or more of said tertiary doses about 24 weeks after the immediately preceding dose, shortening the tertiary dose interval from 24 to 12, 16 or 20. In an embodiment of the invention, during said treatment, the subject exhibits (a) > 10 letter loss in BCVA relative to baseline; and/or (b) > 50 µm increase in CRT relative to baseline. For example, in an embodiment of the invention, the method further comprises evaluating BVCA and/or CRT in the subject and, if the subject exhibits (a) > 10 letter loss in BCVA relative to baseline; and/or (b) > 50 µm increase in CRT relative to baseline, shortening the tertiary dose interval.

[00020] In an embodiment of the invention, if

(a) greater than 5 letters are lost in BCVA (ETDRS), relative to the BCVA observed at about 12 weeks after treatment initiation;

(b) a greater than 25 micrometers increase in CRT is observed relative to the CRT observed at about 12 weeks after treatment initiation; and/or

(c) there is a new onset foveal neovascularization or foveal hemorrhage;

e.g., at week 16 or week 20 after treatment initiation, then, the interval between tertiary doses is decreased from 24 to 12, 16 or 20 weeks; or

(a) greater than 5 letters are lost in BCVA (ETDRS), relative to the BCVA observed at about 12 weeks after treatment initiation;

(b) a greater than 25 micrometers increase in CRT is observed relative to the CRT observed at about 12 weeks after treatment initiation; and/or

(c) there is a new onset foveal neovascularization or foveal hemorrhage;

e.g., at week 24 after treatment initiation, then, the interval between tertiary doses is decreased from 24 to 12, 16 or 20 weeks.

[00021] The present invention provides a method for treating or preventing neovascular age related macular degeneration, diabetic retinopathy and/or diabetic macular edema, in a subject in need thereof, comprising administering to an eye of the subject (preferably by intravitreal injection), 3 doses of about ≥8 mg (±0.8 mg) VEGF receptor fusion protein, preferably aflibercept, in a formulation that comprises about 114.3 mg/ml VEGF receptor fusion protein at

an interval of once every 4 weeks; wherein after said 3 doses, administering one or more doses of the VEGF receptor fusion protein at an interval which is lengthened up to 24 weeks.

[00022] The present invention includes a method for treating or preventing neovascular age related macular degeneration, diabetic retinopathy and/or diabetic macular edema, in a subject in need thereof, comprising administering to an eye of the subject (preferably by intravitreal injection), a single initial dose of about 8 mg (±0.8 mg) or more of VEGF receptor fusion protein, preferably aflibercept, followed by 2 secondary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein, wherein each secondary dose is administered about 2 to 4 (preferably 4) weeks after the immediately preceding dose; followed by one or more tertiary doses every 12, 16, 20 or 24 weeks and, after said doses, a) determining if the subject meets at least one criterion for reducing or lengthening one or more tertiary dose intervals by 2 weeks, 3 weeks, 4 weeks or 2-4 weeks between tertiary doses of the VEGF receptor fusion protein; and b) if said determination is made, administering further doses of the VEGF receptor fusion protein at said reduced or lengthened intervals between doses wherein criteria for lengthening the interval include: 1. <5 letter loss in BCVA; and/or 2. CRT <300 or 320 micrometers; and, wherein criteria for reducing the interval include: 1. >10 letter loss in BCVA; 2. persistent or worsening DME; and/or 3. >50 micrometers increase in CRT. In an embodiment of the invention, wherein criteria for lengthening the interval include both: 1. <5 letter loss in BCVA from week 12; and 2. CRT <300 or 320 micrometers as measured by SD-OCT; and/or wherein criteria for reducing the interval include both: 1. >10 letter loss in BCVA, *e.g.*, from week 12 in association with persistent or worsening DME; and 2. >50 micrometers increase in CRT, *e.g.*, from week 12. In an embodiment of the invention, if said criteria are met, said interval is lengthened to 24 weeks.

[00023] The present invention provides a method for treating or preventing neovascular age related macular degeneration, diabetic retinopathy and/or diabetic macular edema, in a subject in need thereof that has been pre-treated with one or more 2 mg doses of VEGF receptor fusion protein, preferably aflibercept, comprising administering to an eye of the subject (preferably by intravitreal injection), a single initial dose of about 8 mg (±0.8 mg) or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 (preferably 4) weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose.

[00024] In an embodiment of the invention, subjects having certain exclusion criteria are excluded from treatment or are not excluded from treatment if exclusion criteria are not met. For example, a subject having any one or more of ocular or periocular infection; active intraocular inflammation; and/or hypersensitivity; is excluded from administration of VEGF receptor fusion protein to the eye. In an embodiment of the invention, a method of the present invention further comprises a step of evaluating the subject for: ocular or periocular infection; active intraocular inflammation; and/or hypersensitivity; and excluding the subject from said administration if any one or more if found in the subject.

[00025] In an embodiment of the invention, subjects are monitored for adverse events, such as conjunctival hemorrhage, cataract, vitreous detachment, vitreous floaters, corneal epithelium defect and/or increased intraocular pressure. If such AEs are identified, the identified AE may be treated and/or such treatment or prevention may be ceased.

[00026] In an embodiment of the invention, a method includes preparation prior to administration of a VEGF receptor fusion protein, preferably aflibercept. For example, wherein the method comprises, prior to each administration, providing or having available- one single-dose glass vial having a protective plastic cap and a stopper containing an aqueous formulation comprising ≥8 mg (±0.8 mg) VEGF receptor fusion protein in about 70 microliters; a filter needle, *e.g.*, one 18-gauge x 1½-inch, 5-micron, filter needle that includes a tip and a bevel; an invention needle, *e.g.*, one 30-gauge x ½-inch injection needle; and a syringe, *e.g.*, one 1-mL Luer lock syringe having a graduation line marking for 70 microliters of volume; packaged together; then (1) visually inspecting the aqueous formulation in the vial and, if particulates, cloudiness, or discoloration are visible, then using another vial of aqueous formulation containing the VEGF receptor fusion protein; (2) removing the protective plastic cap from the vial; and (3) cleaning the top of the vial with an alcohol wipe; then using aseptic technique: (4) removing the 18-gauge x 1½-inch, 5-micron, filter needle and the 1 mL syringe from their packaging; (5) attaching the filter needle to the syringe by twisting it onto the Luer lock syringe tip; (6) pushing the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or a bottom edge of the vial; (7) withdrawing all of the VEGF receptor fusion protein vial contents into the syringe, keeping the vial in an upright position, slightly inclined, while ensuring the bevel of the filter needle is submerged into the liquid; (8) continuing to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the formulation; (9) drawing the plunger rod sufficiently back when emptying the vial in order to completely empty the filter needle; (10) removing the filter needle from the syringe and disposing of the filter needle; (11) removing the 30-gauge x ½-inch injection needle

from its packaging and attaching the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip; (12) holding the syringe with the needle pointing up, and checking the syringe for bubbles, wherein if there are bubbles, gently tapping the syringe with a finger until the bubbles rise to the top; and (13) slowly depressing the plunger so that the plunger tip aligns with the graduation line that marks 70 microliters on the syringe. In an embodiment of the invention, injection of VEGF receptor fusion protein is performed under controlled aseptic conditions, which comprise surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) and anesthesia and a topical broad–spectrum microbicide are administered prior to the injection.

[00027] In an embodiment of the invention, the subject has been receiving a dosing regimen for treating or preventing neovascular age related macular degeneration, diabetic retinopathy and/or diabetic macular edema calling for: a single initial dose of about 2 mg of VEGF receptor fusion protein, followed by 2, 3 or 4 secondary doses of about 2 mg of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 2 mg of the VEGF receptor fusion protein; wherein each secondary dose is administered about 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 8 weeks after the immediately preceding dose; wherein the subject is at any phase (initial dose, secondary dose or tertiary dose) of the 2 mg VEGF receptor fusion protein dosing regimen.

[00028] In an embodiment of the invention, 24 weeks is 6 months, 168 days or twice per year, one or more secondary doses is 2 secondary doses; 2 to 4 weeks is about 4 weeks; 12-20 weeks is about 12 weeks; 12-20 weeks is about 16 weeks; 12-20 weeks is about 20 weeks; 12-20 weeks is about 12-16 weeks; 8–16 weeks is about 12 weeks; 8–16 weeks is about 16 weeks; 8–16 weeks is about 12-16 weeks; 2 to 4 weeks is about 4 weeks and one or more secondary doses is 2 secondary doses; 12-20 weeks is about 12 weeks and one or more secondary doses is 2 secondary doses; 12-20 weeks is about 16 weeks and one or more secondary doses is 2 secondary doses; 12-20 weeks is about 20 weeks and one or more secondary doses is 2 secondary doses; 12-20 weeks is about 12-16 weeks and one or more secondary doses is 2 secondary doses; 2 to 4 weeks is about 4 weeks and one or more secondary doses is 2 secondary doses and the VEGF receptor fusion protein is aflibercept; 12-20 weeks is about 12 weeks and one or more secondary doses is 2 secondary doses and the VEGF receptor fusion protein is aflibercept; 12-20 weeks is about 16 weeks and one or more secondary doses is 2 secondary doses and the VEGF receptor fusion protein is aflibercept; 12-20 weeks is about 20 weeks and one or more secondary doses is 2 secondary doses and the VEGF receptor fusion protein is aflibercept; and/or 12-20 weeks is about 12-16 weeks and one

or more secondary doses is 2 secondary doses and the VEGF receptor fusion protein is aflibercept.

[00029] In an embodiment of the invention, the VEGF receptor fusion protein: comprises amino acids 27-457 of the amino acid sequence set forth in SEQ ID NO: 2; is selected from the group consisting of: aflibercept and conbercept; comprises two polypeptides that comprise (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO: 2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO: 2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO: 2; comprises two polypeptides that comprise an immunoglobin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component; comprises two polypeptides that comprise an immunoglobin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2, an Ig domain 4 of VEGFR2 and a multimerizing component; or comprises two VEGFR1R2-FcΔC1(a) polypeptides encoded by the nucleic acid sequence of SEQ ID NO: 1. In an embodiment of the invention, the VEGF receptor fusion protein comprises or consists of amino acids 27-457 of the amino acid sequence set forth in SEQ ID NO: 2. Preferably, the VEGF receptor fusion protein is aflibercept.

[00030] In an embodiment of the invention, the VEGF receptor fusion protein is in an aqueous pharmaceutical formulation selected from the group consisting of A-KKKK. In an embodiment of the invention, the VEGF receptor fusion protein, preferably aflibercept, is in an aqueous pharmaceutical formulation comprising about 114.3 mg/ml VEGF receptor fusion protein, preferably aflibercept.

[00031] In an embodiment of the invention, the VEGF receptor fusion protein, preferably aflibercept, is administered to both eyes of the subject.

[00032] In an embodiment of the invention, the VEGF receptor fusion protein, preferably aflibercept, is administered from a syringe or pre-filled syringe, *e.g.*, which is glass or plastic, and/or sterile; *e.g.*, with a 30 gauge × ½-inch sterile injection needle.

[00033] In an embodiment of the invention, a subject has previously received one or more doses of 2 mg VEGF receptor fusion protein, *e.g.*, Eylea. One or more further doses than specifically mentioned may be administered to a subject.

[00034] In an embodiment of the invention, a subject who has received 2 mg of VEGF receptor fusion protein, preferably aflibercept, has received the protein in an aqueous pharmaceutical formulation comprising 40 mg/ml VEGF receptor fusion protein, 10 mM sodium phosphate, 40 mM NaCl, 0.03% polysorbate 20 and 5% sucrose, with a pH of 6.2.

[00035] In an embodiment of the invention, the ≥8 mg (±0.8 mg) VEGF receptor fusion protein, preferably aflibercept, is in an aqueous pharmaceutical formulation including ≥100 mg/ml VEGF

receptor fusion protein, histidine-based buffer and arginine (preferably L-arginine); *e.g.*, comprising a sugar or polyol (*e.g.*, sucrose). In an embodiment of the invention, the formulation has a pH of about 5.8. For example, the formulation may include about 103-126 mg/ml of the VEGF receptor fusion protein, histidine-based buffer and arginine; in an embodiment of the invention, including about 114.3 mg/ml of the VEGF receptor fusion protein, histidine-based buffer and arginine.

[00036] In an embodiment of the invention, the ≥8 mg (±0.8 mg) of VEGF receptor fusion protein, preferably aflibercept, is administered in a volume of about 100 μl or less, about 75 μl or less; about 70 μl or less; or about 50 μl; 51 μl; 52 μl; 53 μl; 54 μl; 55 μl; 56 μl; 57 μl; 58 μl; 59 μl; 60 μl; 61 μl; 62 μl; 63 μl; 64 μl; 65 μl; 66 μl; 67 μl; 68 μl; 69 μl; 70 μl; 71 μl; 72 μl; 73 μl; 74 μl; 75 μl; 76 μl; 77 μl; 78 μl; 79 μl; 80 μl; 81 μl; 82 μl; 83 μl; 84 μl; 85 μl; 86 μl; 87 μl; 88 μl; 89 μl; 90 μl; 91 μl; 92 μl; 93 μl; 94 μl; 95 μl; 96 μl; 97 μl; 98 μl; 99 μl; or 100 μl; *e.g.*, in a volume of about 70 ± 4 or 5 microliters.

[00037] In an embodiment of the invention, the methods herein include the step of administering the VEGF receptor fusion protein, preferably aflibercept, to both eyes of the subject, *e.g.*, intravitreally.

[00038] In an embodiment of the invention, the subject achieves and/or maintains one or more of, an improvement in Diabetic Retinopathy Severity Scale (DRSS); an improvement in best corrected visual acuity; a dry retina; a gain in best corrected visual acuity; a BCVA of at least 69 letters; a foveal center without fluid; a decrease in central retinal thickness (CRT); no vascular leakage as measured by fluorescein angiography (FA); an improvement from pre-treatment baseline in National Eye Institute Visual Function Questionnaire (NEI-VFQ) total score; a retina without fluid (total fluid, intraretinal fluid [IRF] and/or subretinal fluid [SRF]) at the foveal center and in center subfield; maintenance of a fluid-free retina (total fluid, IRF and/or SRF at foveal center and in the center subfield); a lack of macular edema; a retina free of fluid on spectral domain optical coherence tomography (SD-OCT); Does not deviate from the HDq12 or HDq16 or HDq20 treatment regimen once started; Non-inferior BVCA compared to that of aflibercept which is intravitreally dosed at 2 mg approximately every 4 weeks for the first 3, 4 or 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months; Increase in BCVA (according to ETDRS letter score) of about 7, 8 or 9 letters by week 60 from start of treatment, wherein the baseline BCVA is about 61, 62 or 63; BCVA (according to ETDRS letter score) of at least about 69 letters by week 48 or 60 from start of treatment; Does not lose 5, 10, 15 or 69 letters or more BCVA after week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; Improvement in BCVA (according to ETDRS letter score) by week 12, 24, 36, 48, 60, 72, 84, 90

or 96 from start of treatment; Improvement in BVCA by week 4, week 8, week 12, week 16, week 20, week 24, week 28, week 32, week 36, week 40, week 44, or week 48 from start of treatment; Between weeks 48 and 60, a BCVA score (according to ETDRS letter score) of about 69, 70, 71, 72 or 73; Between weeks 36 and 48, a change in BCVA score (according to ETDRS letter score) from initiation of treatment of about 7, 8 or 9 wherein the BCVA at any point between week 36 to 48 is about 60 or 70; Between weeks 48 and 60, a change in BCVA score (according to ETDRS letter score) from initiation of treatment of about 7, 8 or 9, wherein the BCVA at any point between week 48 to 60 is about 69, 70, 71, 72 or 73; Increase in BCVA as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart or Snellen equivalent by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 or 48 weeks from start of treatment by ≥4 letters, ≥5 letters, ≥6 letters, ≥7 letters, ≥8 letters, > 9 letters or > 10 letters; Does not lose 5, 10 or 15 letters by week 48 or 60 from start of treatment (according to ETDRS letter score); Gains at least 5, 10 or 15 letter by week 48 or 60 from start of treatment (according to ETDRS letter score); Improvement in BCVA, by 4 weeks after initiation of treatment, of about 4 or 5 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 4 or 5 letters (ETDRS or Snellen equivalent) when on HDq16 regimen; Improvement in BCVA, by 8 weeks after initiation of treatment, of about 6 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 5 or 6 letters (ETDRS or Snellen equivalent) when on HDq16 regimen; Improvement in BCVA, by 12 weeks after initiation of treatment, of about 6 or 7 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 6 letters (ETDRS or Snellen equivalent) when on HDq16 regimen; Improvement in BCVA, by 16 weeks after initiation of treatment, of about 6 or 7 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of 7 letters (ETDRS or Snellen equivalent) when on HDq16 regimen; Improvement in BCVA, by 20 weeks after initiation of treatment, of about 6 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 6 letters (ETDRS or Snellen equivalent) when on HDq16 regimen; Improvement in BCVA, by 24 weeks after initiation of treatment, of about 7 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 5 or 6 letters (ETDRS or Snellen equivalent) when on HDq16 regimen; Improvement in BCVA, by 28 weeks after initiation of treatment, of about 7 or 8 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on HDq16 regimen; Improvement in BCVA, by 32 weeks after initiation of treatment, of about 7 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on HDq16 regimen; Improvement in BCVA, by 36 weeks after initiation of treatment, of 8 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 6 or 7 letters

(ETDRS or Snellen equivalent) when on HDq16 regimen; Improvement in BCVA, by 40 weeks after initiation of treatment, of about 8 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 6 or 7 letters (ETDRS or Snellen equivalent) when on HDq16 regimen; Improvement in BCVA, by 44 weeks after initiation of treatment, of about 8 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on HDq16 regimen; Improvement in BCVA, by 48 weeks after initiation of treatment, of about 8 or 9 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on HDq16 regimen; An improvement in BCVA by about week 8 after initiation of treatment which is maintained thereafter during the treatment regimen to at least week 48; A BCVA by 4 weeks after initiation of treatment of about 68 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 66 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 8 weeks after initiation of treatment of about 70 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 67 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 12 weeks after initiation of treatment of about 70 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 68 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 16 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 69 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 20 weeks after initiation of treatment of about 70 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 68 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 24 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 67 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 28 weeks after initiation of treatment of about 72 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 32 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 36 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 68 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 40 weeks after initiation of treatment of about 72 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 69 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 44 weeks after initiation of treatment of about 72 letters

(ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 48 weeks after initiation of treatment of about 73 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA improvement, by week 48 following treatment initiation, of about 9 or 10 letters (ETDRS or Snellen equivalent) when baseline BCVA is about <73 ETDRS letters when on HDq12 regimen; A BCVA improvement, by week 48 following treatment initiation, of about 5 or 6 letters (ETDRS or Snellen equivalent) when baseline BCVA is about >73 ETDRS letters when on HDq12 regimen; A BCVA improvement, by week 48 following treatment initiation, of about 8 or 9 letters (ETDRS or Snellen equivalent) when baseline BCVA is about <73 ETDRS letters when on HDq16 regimen; A BCVA improvement, by week 48 following treatment initiation, of about 4 or 5 letters (ETDRS or Snellen equivalent) when baseline BCVA is about >73 ETDRS letters when on HDq16 regimen; A BCVA improvement, by week 48 following treatment initiation, of about 7 or 8 letters (ETDRS or Snellen equivalent) when baseline CRT is about < about 400 micrometers when on HDq12 regimen; A BCVA improvement, by week 48 following treatment initiation, of about 9 or 10 letters (ETDRS or Snellen equivalent) when baseline CRT is about >400 micrometers when on HDq12 regimen; A BCVA improvement, by week 48 following treatment initiation, of about 5 or 6 letters (ETDRS or Snellen equivalent) when baseline CRT is about < about 400 micrometers when on HDq16 regimen; A BCVA improvement, by week 48 following treatment initiation, of about 9 or 10 letters (ETDRS or Snellen equivalent) when baseline CRT is about > about 400 micrometers when on HDq16 regimen; Gain of >5, >10 or ≥15 letters BCVA (according to ETDRS letter score) by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; ≥ 2 or >3 step improvement in Diabetic Retinopathy Severity Scale (DRSS), by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; ≥ 2 step improvement in diabetic retinopathy severity scale (DRSS) by week 4, week 8, week 12, 16, 20, 24, 28, 32, 36, 40, 44 or 48 weeks from start of treatment; Retina without fluid (total fluid, intraretinal fluid [IRF] and/or subretinal fluid [SRF]) at the foveal center and in center subfield by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment as measured by optical coherence tomography (OCT); No vascular leakage as measured by fluorescein angiography (FA) by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; Maintenance of a fluid-free retina (total fluid, IRF and/or SRF at foveal center and in the center subfield) by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; Reduction in total area of fluorescein leakage within ETDRS grid (mm2) at week 48 or 60 by about 12, 13 or 14 mm^2 or more as measured by fluorescein angiography; Retina free of fluid on spectral domain

optical coherence tomography (SD-OCT) by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; Retina without fluid (total fluid, intraretinal fluid [IRF] and/or subretinal fluid [SRF]) at the foveal center by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 or 48 weeks from start of treatment; Dry retina by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; Foveal center without fluid by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment as measured by optical coherence tomography (OCT); A change in central retinal thickness, by 4 weeks after initiation of treatment of about -118 or -118.3 micrometers when on the HDq12 regimen; or of about -124 or -125 or -124.9 or -125.5 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 8 weeks after initiation of treatment of about -137 or -137.4 micrometers when on the HDq12 regimen; or of about -139 or -140 or -139.6 or -140.3 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 12 weeks after initiation of treatment of about -150 or -150.1 micrometers when on the HDq12 regimen; or of about -152 or -153 or -152.7 or -153.4 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 16 weeks after initiation of treatment of about -139 or -139.4 micrometers when on the HDq12 regimen; or of about -145 or -146 or -145.5 or -146.4 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 20 weeks after initiation of treatment of about -117 or -117.1 micrometers when on the HDq12 regimen; or of about -112 or -113 or -112.5 or -113.3 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 24 weeks after initiation of treatment of about -158 or -158.1 micrometers when on the HDq12 regimen; or of about -103 or -104 or -103.8 or -104.3 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 28 weeks after initiation of treatment of about -146 or -147 or -146.7 micrometers when on the HDq12 regimen; or of about -162 or -162.3 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 32 weeks after initiation of treatment of about -132 micrometers when on the HDq12 regimen; or of about -145 or -146 or -145.8 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 36 weeks after initiation of treatment of about -168 or -168.1 micrometers when on the HDq12 regimen; or of about -124 or -125 or -124.7 or -125.2 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 40 weeks after initiation of treatment of about -163 micrometers when on the HDq12 regimen; or of about -122 or -123 or -122.5 or -123.1 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 44 weeks after initiation of treatment of about -147 or -148 or -147.4 micrometers when on the HDq12 regimen; or of about -164 or -164.1 or -164.3 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 48 weeks after initiation of treatment of about -171 or -172 or -171.7 micrometers when on the HDq12

regimen; or of about -148 or -149 or -148.3 or -149.4 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 60 weeks after initiation of treatment of about -181.95 or -176.24 micrometers when on the HDq12 regimen; or of about -166.26 or -167.18 micrometers when on the HDq16 regimen; A reduction in central retinal thickness by week 4, 5, 6, 7 or 8 after initiation of treatment which is maintained within about ±17, ±18 or ±19 micrometers thereafter during the treatment regimen to at least week 48 from initiation of treatment; Decrease in central retinal thickness by about 100, 125, 150, 175 or 200 micrometers by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; Reduction in central retinal thickness of about 148-182 micrometers by about week 48 or 60 from start of treatment as measured by optical coherence tomography (OCT)) wherein the baseline CRT is about 449, 450, 455 or 460 micrometers; Decrease in central retinal thickness (CRT) by at least about 100, 125, 130, 135, 140, 145, 149, 150, 155, 160, 165, 170, 171, 172, 173, 174 or 175 micrometers by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 or 48 from start of treatment; at about 0.1667 days after the first dose, free aflibercept concentration in plasma of about 0.149 (±0.249) mg/l; wherein, at baseline, free aflibercept concentration in plasma was not detectable wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 0.3333 days after the first dose, free aflibercept in plasma of about 0.205 (±0.250) mg/l; wherein, at baseline, free aflibercept in plasma not detectable wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 1 days after the first dose, free aflibercept in plasma of about 0.266 (±0.211) mg/l wherein, at baseline, free aflibercept in plasma not detectable wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 2 days after the first dose, free aflibercept in plasma of about 0.218 (±0.145) mg/l wherein, at baseline, free aflibercept in plasma not detectable wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 4 days after the first dose, free aflibercept in plasma of about 0.140 (±0.0741) mg/l wherein, at baseline, free aflibercept in plasma not detectable wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 7 days after the first dose, free aflibercept in plasma of about 0.0767 (±0.0436) mg/l wherein, at baseline, free aflibercept in plasma not detectable, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 14 days after the first dose, free aflibercept in plasma of about 0.0309 (±0.0241) mg/l wherein at baseline free aflibercept in plasma not detectable wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 21 days after the first dose, free aflibercept in plasma of about 0.0171 (±0.0171) mg/l wherein, at baseline, free aflibercept in plasma not detectable wherein the subject has not received intravitreal aflibercept

treatment for at least 12 weeks; At about 28 days after the first dose, free aflibercept in plasma of about 0.00730 (±0.0113) mg/l wherein, at baseline, free aflibercept in plasma not detectable wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 0.1667 days after the first dose, adjusted bound aflibercept in plasma of about 0.00698 (±0.0276) mg/l wherein, at baseline, there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 0.3333 days after the first dose, adjusted bound aflibercept in plasma of about 0.00731 (±0.0279) mg/l wherein, at baseline, there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 1 days after the first dose, adjusted bound aflibercept in plasma of about 0.0678 (±0.0486) mg/l wherein, at baseline, there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 2 days after the first dose, adjusted bound aflibercept in plasma of about 0.138 (±0.0618) mg/l wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 4 days after the first dose, adjusted bound aflibercept in plasma of about 0.259 (±0.126) mg/l wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 7 days after the first dose, adjusted bound aflibercept in plasma of about 0.346 (±0.151) mg/l wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 14 days after the first dose, adjusted bound aflibercept in plasma of about 0.374 (±0.110) mg/l wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 21 days after the first dose, adjusted bound aflibercept in plasma of about 0.343 (±0.128) mg/l wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; At about 28 days after the first dose, adjusted bound aflibercept in plasma of about 0.269 (±0.149) mg/l wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; the maximum concentration of free aflibercept in the plasma is reached about 0.965 days after the first dose; Reaches a maximum concentration of about 0.310 mg/l (±0.263) free aflibercept in the plasma; Free aflibercept in the plasma of from about 0 to about 1.08 mg/L; Free aflibercept maximum concentration in the plasma (mg/l) per dose (mg) of aflibercept of

about 0.0388 (±0.0328) mg/l/mg; The maximum concentration of adjusted bound aflibercept in the plasma is reached about 14 days after the first dose; Reaches a maximum concentration of about 0.387 mg/l (±0.135) adjusted bound aflibercept in the plasma; Adjusted bound aflibercept concentration in the plasma of from about 0.137 to about 0.774 mg/L; Adjusted bound aflibercept in the plasma maximum (mg/l) per dose (mg) of aflibercept of about 0.0483 (±0.0168) mg/l/mg; Does not have anti-drug antibodies against aflibercept after 48 or 60 weeks of treatment; Improvement from pre-treatment baseline in National Eye Institute Visual Function Questionnaire (NEI-VFQ) total score; and/or Lack of macular edema. For example, in an embodiment of the invention, a dry retina lacks intraretinal fluid and/or subretinal fluid; or retinal drying is characterized by no intraretinal fluid (IRF) and no subretinal fluid (SRF) in the eye of the subject, after the subject has received three monthly doses of the VEGF receptor fusion protein, preferably aflibercept.

[00039] In an embodiment of the invention, the subject achieves and/or maintains one or more of: Improvement in BCVA, by 64 weeks after initiation of treatment, of about 9 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or of about 8 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; Improvement in BCVA, by 68 weeks after initiation of treatment, of about 8 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or of about 8 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; Improvement in BCVA, by 72 weeks after initiation of treatment, of about 8 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or of about 6 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; Improvement in BCVA, by 76 weeks after initiation of treatment, of about 8 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or of about 7 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; Improvement in BCVA, by 80 weeks after initiation of treatment, of about 8 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or of about 8 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; Improvement in BCVA, by 84 weeks after initiation of treatment, of about 8 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or of about 8 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; Improvement in BCVA, by 88 weeks after initiation of treatment, of about 9 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or of about 7 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; Improvement in BCVA, by 92 weeks after initiation of treatment, of about 9 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or of about 7 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; Improvement in BCVA, by 96 weeks after initiation of treatment, of about 9 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or of

about 8 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 64 weeks after initiation of treatment of about 73 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 68 weeks after initiation of treatment of about 72 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 69 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 72 weeks after initiation of treatment of about 73 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 68 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 76 weeks after initiation of treatment of about 73 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 68 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 80 weeks after initiation of treatment of about 72 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 69 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 84 weeks after initiation of treatment of about 72 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 88 weeks after initiation of treatment of about 73 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 69 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 92 weeks after initiation of treatment of about 73 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 69 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A BCVA by 96 weeks after initiation of treatment of about 73 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 69 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; A change in central retinal thickness, by 64 weeks after initiation of treatment of about -173.4 micrometers or about -173 micrometers when on the HDq12 regimen; or of about -164.3 micrometers or about -164 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 68 weeks after initiation of treatment of about -159.4 micrometers or about -159 micrometers when on the HDq12 regimen; or of about -153.9 micrometers or about -154 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 72 weeks after initiation of treatment of about -166.6 micrometers or about -167 micrometers when on the HDq12 regimen; or of about -134.2 micrometers or about -134 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 76 weeks after initiation of treatment of about -181.1 micrometers or about -181 micrometers when on the HDq12 regimen; or of about -160.8 micrometers or about -161 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 80 weeks after initiation of treatment of about

-168.9 micrometers or about -169 micrometers when on the HDq12 regimen; or of about -164 micrometers or about -164 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 84 weeks after initiation of treatment of about -177.5 micrometers or about -178 micrometers when on the HDq12 regimen; or of about -150.2 micrometers or about -150 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 88 weeks after initiation of treatment of about -171.2 micrometers or about -171 micrometers when on the HDq12 regimen; or of about -144.3 micrometers or about -144 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 92 weeks after initiation of treatment of about -166.7 micrometers or about -167 micrometers when on the HDq12 regimen; or of about -155.5 micrometers or about -156 micrometers when on the HDq16 regimen; A change in central retinal thickness, by 96 weeks after initiation of treatment of about -185.3 micrometers or about -185 micrometers when on the HDq12 regimen; or of about -155 micrometers or about -155 micrometers when on the HDq16 regimen; A central retinal thickness by 64 weeks after initiation of treatment of about 279.4 micrometers when on the HDq12 regimen or of about 289.6 micrometers when on the HDq16 regimen; A central retinal thickness by 68 weeks after initiation of treatment of about 294.5 micrometers when on the HDq12 regimen or of about 305.3 micrometers when on the HDq16 regimen; A central retinal thickness by 72 weeks after initiation of treatment of about 284.2 micrometers when on the HDq12 regimen or of about 327.2 micrometers when on the HDq16 regimen; A central retinal thickness by 76 weeks after initiation of treatment of about 270.6 micrometers when on the HDq12 regimen or of about 302 micrometers when on the HDq16 regimen; A central retinal thickness by 80 weeks after initiation of treatment of about 284.6 micrometers when on the HDq12 regimen or of about 293.5 micrometers when on the HDq16 regimen; A central retinal thickness by 84 weeks after initiation of treatment of about 274.7 micrometers when on the HDq12 regimen or of about 310.8 micrometers when on the HDq16 regimen; A central retinal thickness by 88 weeks after initiation of treatment of about 283.7 micrometers when on the HDq12 regimen or of about 312.3 micrometers when on the HDq16 regimen; A central retinal thickness by 92 weeks after initiation of treatment of about 285.7 micrometers when on the HDq12 regimen or of about 301.8 micrometers when on the HDq16 regimen; and/or A central retinal thickness by 96 weeks after initiation of treatment of about 267.5 micrometers when on the HDq12 regimen or of about 304.2 micrometers when on the HDq16 regimen.

[00040] In an embodiment of the invention, reference to 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56 or 60 weeks from start of treatment is about 48 weeks or 60 weeks from start of treatment.

[00041] In an embodiment of the invention, 1 initial dose, 2 secondary doses and 3 tertiary doses of VEGF receptor fusion protein, preferably aflibercept, are administered to the subject in the first year; 1 initial dose, 2 secondary doses and 2 tertiary doses of VEGF receptor fusion protein, *e.g.*, aflibercept, are administered to the subject in the first year; or 1 initial dose, 2 secondary doses and 3 tertiary doses of VEGF receptor fusion protein, *e.g.*, aflibercept, are administered to the subject in the first year followed by 2 -4 tertiary doses in the second year.

[00042] In an embodiment of the invention, the interval between doses are adjusted (increased/maintained/reduced) based on visual and/or anatomic outcomes, *e.g.*, according to criteria as set forth in Figure 3 and/or Figure 4.

[00043] The present invention also provides a kit comprising a container comprising VEGF receptor fusion protein, preferably aflibercept; and Instruction for use of VEGF receptor fusion protein, wherein the container is a vial or a pre-filled syringe, wherein the container comprises ≥ 100 mg/mL VEGF receptor fusion protein, wherein the container comprises ≥ 114.3 mg/mL VEGF receptor fusion protein, wherein the instruction comprises instruction for the administration of aflibercept to DR, DME and/or nAMD patients, wherein the instruction comprises instruction that aflibercept ≥8 mg (±0.8 mg) treatment is initiated with 1 injection per month (about every 4 weeks) for 3 consecutive doses, wherein the instruction comprises instruction that after the initial 3 consecutive doses the injection interval may be lengthened up to every 24 weeks, and wherein the instruction comprises instruction that the treatment interval may be adjusted based on the physician's judgement of visual and/or anatomic outcomes.

[00044] The present invention provides aflibercept for use in the treatment or prevention of an angiogenic eye disorder, neovascular age related macular degeneration, diabetic retinopathy and/or diabetic macular edema in a subject in need thereof comprising administering to an eye of the subject (preferably by intravitreal injection), one or more doses of aflibercept at an interval and quantity whereby the clearance of free aflibercept from the ocular compartment is about 0.367-0.457 mL/day after an intravitreal injection of aflibercept, the time for the amount for free aflibercept to reach the lower limit of quantitation (LLOQ) in the ocular compartment of a subject after said intravitreal injection of aflibercept is about 15 weeks; and the time for free aflibercept to reach the lower limit of quantitation (LLOQ) in the plasma of the subject after said intravitreal injection of aflibercept is about 3.5 weeks.

[00045] The present invention provides aflibercept for use in a method for slowing the clearance of free aflibercept from the ocular compartment after an intravitreal injection relative to the rate of clearance of aflibercept from the ocular compartment after an intravitreal injection of

< 4 mg aflibercept wherein the method comprises intravitreally injecting into an eye of a subject in need thereof, a single initial dose of about 8 mg (±0.8 mg) or more of aflibercept, followed by one or more secondary doses of about 8 mg (±0.8 mg) or more of the aflibercept, followed by one or more tertiary doses of about 8 mg (±0.8 mg) or more of the aflibercept;
wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose.

[00046] The present invention provides aflibercept for use a method for increasing the time for the amount of free aflibercept to reach the lower limit of quantitation (LLOQ) in the ocular compartment of a subject after an intravitreal injection of aflibercept relative to the time to reach LLOQ of the amount of free aflibercept in the ocular compartment of a subject after an intravitreal injection of about 2 mg aflibercept,
wherein the method comprises intravitreally injecting into an eye of a subject in need thereof, a single initial dose of about 8 mg (±0.8 mg) or more of aflibercept, followed by
one or more secondary doses of about 8 mg (±0.8 mg) or more of the aflibercept, followed by one or more tertiary doses of about 8 mg (±0.8 mg) or more of the aflibercept;
wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose.

[00047] The present invention provides aflibercept for use in a method for increasing the time for free aflibercept to reach the lower limit of quantitation (LLOQ) in the plasma of a subject after an intravitreal injection of aflibercept relative to the time to reach LLOQ of free aflibercept in the plasma of a subject after an intravitreal injection of about 2 mg aflibercept, wherein the method comprises intravitreally injecting into an eye of a subject in need thereof, a single initial dose of about 8 mg (±0.8 mg) or more of aflibercept, followed by one or more secondary doses of about 8 mg (±0.8 mg) or more of the aflibercept, followed by one or more tertiary doses of about 8 mg (±0.8 mg) or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose.

[00048] The present invention provides a VEGF receptor fusion protein for use in a method
- for treating or preventing an angiogenic eye disorder, nAMD, diabetic retinopathy (DR) and/or diabetic macular edema (DME), in a subject in need thereof,

- for improving best corrected visual acuity in a subject in need thereof with an angiogenic eye disorder, nAMD, DR and/or DME; or
- for promoting retinal drying in a subject with DR and/or DME in need thereof;
wherein the method comprises administering to an eye of the subject, one or more doses of about 8 mg (±0.8 mg) or more of VEGF receptor fusion protein once every 24 weeks.

[00049] The present invention provides aflibercept for use in the treatment or prevention of an angiogenic eye disorder, neovascular age related macular degeneration, diabetic retinopathy and/or diabetic macular edema, in a subject in need thereof, wherein the treatment or prevention comprises initiating the treatment with 1 injection of 8 mg (±0.8 mg) aflibercept per month (every 4 weeks) for three consecutive doses followed by one or more injection once every 24 weeks, wherein the concentration of aflibercept of each said dose is 114.3 mg/mL or wherein the application volume of each said dose is 70 µL. In an embodiment of the invention the treatment interval between two subsequent administrations of 8 mg (±0.8 mg) aflibercept is adjusted (increased/maintained/reduced) based on visual and/or anatomic outcomes such as but not limited to letter gain or letter loss in BCVA; increase or reduction in CRT; presence or absence of subretinal fluid; or presence or absence of hemorraghe or persistent or worsening DME. In an embodiment of the invention the treatment interval is reduced by 2-4 weeks, 2 weeks, 3 weeks or by 4 weeks compared to the previous treatment interval in case said subject has been identified as one with meeting at least one of the following criteria for reduction of the treatment interval: > 5 letter or > 10 letter loss in BCVA; CRT of >300 or 320 µm; > 50 µm increase in CRT; or 2. persistent or worsening DME. In an embodiment of the invention the treatment interval is extended by 2-4 weeks, 2 weeks, 3 weeks or by 4 weeks compared to the previous treatment interval in case said subject has been identified as one with meeting at least one of the following criteria for extending the treatment interval: < 5 letter < 10 letter loss in BCVA; CRT <300 or 320 µm; > 50 µm decrease in CRT; absence of subretinal fluid; or absence of hemorraghe.

[00050] The present invention provides a VEGF receptor fusion protein for use in the treatment or prevention of an angiogenic eye disorder or diabetic macular edema, in a subject in need thereof wherein the method comprises administering 8 mg (±0.8 mg) VEGF receptor fusion protein (*e.g.*, in a volume of 0.07 mL or 70 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days, monthly) for the first three doses, followed by 8 mg (±0.8 mg) VEGF receptor fusion protein (*e.g.*, in a volume of 0.07 mL) via intravitreal injection once every 24 weeks (+/- 7 days).

[00051] The present invention provides a VEGF receptor fusion protein for use in the treatment or prevention of diabetic retinopathy (DR), in a subject in need thereof , wherein the method comprises administering 8 mg (±0.8 mg) VEGF receptor fusion protein (*e.g.*, in a volume of 0.07 mL or 70 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days, monthly) for the first three doses, followed by 8 mg (±0.8 mg) VEGF receptor fusion protein (*e.g.*, in a volume of 0.07 mL) via intravitreal injection once every 24 weeks (+/- 7 days).

[00052] The present invention provides a VEGF receptor fusion protein for use in the treatment or prevention of neovascular age related macular degeneration, in a subject in need thereof , wherein the method comprises administering 8 mg (±0.8 mg) VEGF receptor fusion protein (*e.g.*, in a volume of 0.07 mL or 70 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days, monthly) for the first three doses, followed by 8 mg (±0.8 mg) VEGF receptor fusion protein (*e.g.*, in a volume of 0.07 mL) via intravitreal injection once every 24 weeks (+/- 7 days).

[00053] The present invention provides aflibercept for use in the treatment or prevention of an angiogenic eye disorder, neovascular age related macular degeneration, diabetic macular edema or diabetic retinopathy, in a subject in need thereof, comprising administering to an eye of the subject (preferably by intravitreal injection), a single initial dose ≥8 mg (±0.8 mg) aflibercept, followed by one or more tertiary doses of about ≥8 mg (±0.8 mg) of aflibercept; wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose. In an embodiment of the invention, the subject is not a treatment naïve subject, or the subject was pre-treated with a VEGF antagonist or preferably the subject was pre-treated with ≥8 mg (±0.8 mg) aflibercept or with 2 mg aflibercept.

[00054] The present invention provides aflibercept for use in the treatment or prevention of an angiogenic eye disorder, neovascular age related macular degeneration, diabetic macular edema or diabetic retinopathy, in a subject which was pre-treated with 2 mg aflibercept, comprising administering to an eye of the subject (preferably by intravitreal injection), a single initial dose of about ≥8 mg (±0.8 mg) aflibercept, followed by one or more secondary doses of about ≥8 mg (±0.8 mg) of aflibercept, followed by one or more tertiary doses of about ≥8 mg (±0.8 mg) aflibercept, wherein each secondary dose is administered about 4 weeks after the immediately preceding dose and wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose. In an embodiment of the invention, the administration of one or more doses of ≥8 mg (±0.8 mg) aflibercept to an eye of the subject is according to HDq24 or treat and extent dosing regimen.

[00055] The present invention provides a VEGF receptor fusion protein for use in the treatment or prevetion of an angiogenic eye disorder, nAMD, diabetic retinopathy and/or diabetic macular edema, in a subject in need thereof who has been on a dosing regimen for treating or preventing said disorder wherein:

(a) the subject has received an initial ≥8 mg (±0.8 mg) dose of VEGF receptor fusion protein then the method comprises, after 1 month, administering to the subject the first ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein and 1 month thereafter, administering the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, administering one or more 8 mg maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen;

or

(b) the subject has received an initial 8 mg dose of VEGF receptor fusion protein & 1st ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein after 1 month, then the method comprises, after another 1 month, administering to the subject the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein; and then, every 24 weeks thereafter, one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein according to the HDq24 dosing regimen;

or

(c) the subject has received an initial 8 mg dose of VEGF receptor fusion protein & 1st 8 mg secondary dose of VEGF receptor fusion protein after 1 month & the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein after another month, then the method comprises, after 24 weeks administering to the subject the 1st ≥8 mg (±0.8 mg) maintenance dose of VEGF receptor fusion protein and all further ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein every 24 weeks according to the HDq24 dosing regimen;

or

(d) the subject has received an initial ≥8 mg dose of VEGF receptor fusion protein & a 1st ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein after 1 month & the 2nd ≥8 mg (±0.8 mg) secondary dose of VEGF receptor fusion protein after another month, then every 24 weeks thereafter, the subject has received one or more ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein; and, then the method comprises, after 24 weeks from the last maintenance dose of VEGF receptor fusion protein, administering to the subject one or more ≥8 mg maintenance doses of VEGF receptor fusion protein and all further ≥8 mg (±0.8 mg) maintenance doses of VEGF receptor fusion protein every 24 weeks according to the HDq24 dosing regimen;

wherein,
said HDq24 dosing regimen comprises:
a single initial dose (preferably by intravitreal injection) of about ≥8 mg (±0.8 mg) or more of VEGF receptor fusion protein, followed by
one or more secondary doses (preferably by intravitreal injection) of about ≥8 mg (±0.8 mg) or more of the VEGF receptor fusion protein, followed by
one or more tertiary doses (preferably by intravitreal injection) of about ≥8 mg (±0.8 mg) or more of the VEGF receptor fusion protein;
wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose.

[00056] The present invention provides a VEGF receptor fusion protein for use in the treatment or prevention of an angiogenic eye disorder, in a subject in need thereof who has been on a dosing regimen for treating or preventing the disorder calling for a single initial dose of about 2 mg of VEGF receptor fusion protein, followed by one or more secondary doses of about 2 mg of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 2 mg of the VEGF receptor fusion protein; wherein each secondary dose is administered about 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 8 weeks after the immediately preceding dose; and wherein the subject is at any phase of the 2 mg VEGF receptor fusion protein dosing regimen,comprising administering to an eye of the subject (preferably by intravitreal injection), an ≥8 mg(±0.8 mg) dose of VEGF receptor fusion protein, evaluating the subject in about 4 or 8 or 10 or 12 weeks after said administering and, if, in the judgment of the treating physician dosing every 24 weeks is appropriate, then continuing to dose the subject every 24 weeks with ≥8 mg (±0.8 mg) VEGF receptor fusion protein.

[00057] The present invention provides a VEGF receptor fusion protein for use in the treatment and prevention of an angiogenic eye disorder, nAMD, diabetic retinopathy or diabetic macular edema, in a subject in need thereof, wherein the treatment or prevention comprises administering to an eye of the subject, a single initial dose of about ≥8 mg (±0.8 mg) or more of a VEGF receptor fusion protein, followed by one or more secondary doses, preferably 2 doses, of about ≥8 mg(±0.8 mg) or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about ≥8 mg (±0.8 mg) or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 12, 16 or 20 weeks after the immediately

preceding dose; further comprising, after receiving one or more of said tertiary doses about 12, 16 or 20 after the immediately preceding dose, lengthening the tertiary dose interval from

- 12 weeks to 24 weeks;
- 26 weeks to 24 weeks; or
- 20 weeks to 24 weeks,

after the immediately preceding dose.

[00058] The present invention provides a VEGF receptor fusion protein for use in the treatment and prevention of an angiogenic eye disorder, diabetic retinopathy and/or diabetic macular edema, in a subject in need thereof, comprising administering to an eye of the subject (preferably by intravitreal injection), a single initial dose of about 8 mg(±0.8 mg) or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg(±0.8 mg) or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg(±0.8 mg) or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose; further comprising, after receiving one or more of said tertiary doses about 24 weeks after the immediately preceding dose, shortening the tertiary dose interval from

- 24 weeks to 8 weeks;
- 24 weeks to 12 weeks;
- 24 weeks to 16 weeks, or
- 24 weeks to 20 weeks.

[00059] The present invention provides a VEGF receptor fusion protein for use in the treatment and prevention of an angiogenic eye disorder, nAMD, diabetic retinopathy and/or diabetic macular edema, in a subject in need thereof, comprising administering to an eye of the subject (preferably by intravitreal injection), 3 doses of about 8 mg(±0.8 mg) VEGF receptor fusion protein in a formulation that comprises about 114.3 mg/ml VEGF receptor fusion protein at an interval of once every 4 weeks; wherein after said 3 doses, administering one or more doses of the VEGF receptor fusion protein at an interval which is lengthened up to 24 weeks.

[00060] The present invention provides a VEGF receptor fusion protein for use in the treatment and prevention of an angiogenic eye disorder, neovascular age related macular degeneration, diabetic retinopathy and/or diabetic macular edema, in a subject in need thereof, comprising administering to an eye of the subject (preferably by intravitreal injection), a single initial dose of about 8 mg (±0.8 mg) or more of VEGF receptor fusion protein, followed by 2 secondary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein,

followed by one or more tertiary doses of about 8 mg (±0.8 mg) or more of VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose and wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose; and, after said doses,

a) determining if the subject meets at least one criterion for reducing or lengthening one or more intervals by 2 weeks, 3 weeks, 4 weeks or 2-4 weeks between doses of the VEGF receptor fusion protein; and

b) if said determination is made, administering further doses of the VEGF receptor fusion protein at said reduced or lengthened intervals between doses

wherein criteria for lengthening the interval include:

1. <5 letter loss in BCVA; and/or
2. CRT <300 or 320 micrometers;

and, wherein criteria for reducing the interval include:

1. >10 letter loss in BCVA;
2. persistent or worsening DME; and/or
3. >50 micrometers increase in CRT.

[00061] The present invention provides a VEGF receptor fusion protein for use in the treatment and prevention of an angiogenic eye disorder, nAMD, diabetic retinopathy and/or diabetic macular edema, in a subject in need thereof that has been pre-treated with one or more 2 mg doses of VEGF receptor fusion protein, comprising administering to an eye of the subject (preferably by intravitreal injection), a single initial dose of about 8 mg (±0.8 mg) or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose.

[00062] The present invention provides a VEGF receptor fusion protein for use in the treatment and prevention of an angiogenic eye disorder, in a subject in need thereof, comprising administering to an eye of the subject (preferably by intravitreal injection), one or more doses of 8 mg (±0.8 mg) or more of VEGF receptor fusion protein about every 24 weeks.

[00063] A VEGF receptor fusion protein for use in the treatment and prevention of an angiogenic eye disorder wherein the treatment or prevention comprises, prior to each administration, providing

- one single-dose glass vial having a protective plastic cap and a stopper containing an aqueous formulation comprising 8 mg (±0.8 mg) or more VEGF receptor fusion protein in about 70 microliters;
- one 18-gauge x 1½-inch, 5-micron, filter needle that includes a tip and a bevel;

packaged together; then

(1) visually inspecting the aqueous formulation in the vial and, if particulates, cloudiness, or discoloration are visible, then using another vial of aqueous formulation containing the VEGF receptor fusion protein;

(2) removing the protective plastic cap from the vial; and

(3) cleaning the top of the vial with an alcohol wipe; then

using aseptic technique:

(4) removing the 18-gauge x 1½-inch, 5-micron, filter needle and the 1 mL syringe from their packaging;

(5) attaching the filter needle to the syringe by twisting it onto the Luer lock syringe tip;

(6) pushing the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or a bottom edge of the vial;

(7) withdrawing all of the VEGF receptor fusion protein vial contents into the syringe, keeping the vial in an upright position, slightly inclined, while ensuring the bevel of the filter needle is submerged into the liquid;

(8) continuing to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the formulation;

(9) drawing the plunger rod sufficiently back when emptying the vial in order to completely empty the filter needle;

(10) removing the filter needle from the syringe and disposing of the filter needle;

(11) removing the 30-gauge x ½-inch injection needle from its packaging and attaching the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip;

(12) holding the syringe with the needle pointing up, and checking the syringe for bubbles, wherein if there are bubbles, gently tapping the syringe with a finger until the bubbles rise to the top; and

(13) slowly depressing the plunger so that the plunger tip aligns with the graduation line that marks 70 microliters on the syringe.

[00064] The present invention provides a VEGF receptor fusion protein for use in the treatment and prevention of an angiogenic eye disorder, neovascular age related macular degeneration,

diabetic retinopathy and/or diabetic macular edema in a subject in need thereof, wherein the subject has been receiving a dosing regimen for treating or preventing diabetic retinopathy and/or diabetic macular edema calling for: a single initial dose of about 2 mg of VEGF receptor fusion protein, followed by 4 secondary doses of about 2 mg of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 2 mg of the VEGF receptor fusion protein; wherein each secondary dose is administered about 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 8 weeks after the immediately preceding dose;wherein the subject is at any phase (initial dose, secondary dose or tertiary dose) of the 2 mg VEGF receptor fusion protein dosing regimen.

[00065] The present invention provides a VEGF receptor fusion protein for use in the treatment and prevention of an angiogenic eye disorder, nAMD, diabetic retinopathy and/or diabetic macular edema in a subject in need thereof, wherein 8 mg (±0.8 mg) or more of a VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising about 103-126 mg/ml VEGF receptor fusion protein, histidine-based buffer and arginine.

[00066] The present invention provides a VEGF receptor fusion protein for use in the treatment and prevention of an angiogenic eye disorder, nAMD, diabetic retinopathy and/or diabetic macular edema in a subject in need thereof wherein ≥8 mg (±0.8 mg) of a VEGF receptor fusion protein is an aqueous pharmaceutical formulation comprising about 114.3 mg/ml VEGF receptor fusion protein, histidine-based buffer and arginine.

[00067] The present invention provides aflibercept for use in the treatment and prevention of an angiogenic eye disorder, nAMD, diabetic retinopathy and/or diabetic macular edema in a subject in need thereof wherein the ≥8 mg (±0.8 mg) aflibercept is in an aqueous pharmaceutical formulation wherein the aflibercept has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8°C.

[00068] The present invention provides a VEGF receptor fusion protein for use in the treatment and prevention of an angiogenic eye disorder, nAMD, diabetic retinopathy and/or diabetic macular edema in a subject in need thereof wherein the ≥8 mg (±0.8 mg) VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising:

at least about 100 mg/ml of a VEGF receptor fusion protein;

about 10-100 mM L-arginine;

sucrose;

a histidine-based buffer; and

a surfactant;

wherein the formulation has a pH of about 5.0 to about 6.8; wherein the VEGF receptor fusion protein has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8°C.

[00069] The present invention provides a VEGF receptor fusion protein for use in the treatment and prevention of diabetic retinopathy and/or diabetic macular edema in a subject in need thereof wherein ≥8 mg (±0.8 mg) of VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising

- ≥100 mg/ml VEGF receptor fusion protein, histidine-based buffer and L-arginine;
- 140 mg/ml aflibercept; 20 mM histidine-based buffer; 5 % sucrose; 0.03 % polysorbate 20; 10 mM L-arginine; pH 5.8;
- 150 ± 15 mg/ml aflibercept, 10 mM phosphate-based buffer, 8 ± 0.8% (w/v) sucrose, 0.02-0.04% (w/v) polysorbate 20 and 50 mM L-arginine, pH 5.9-6.5;
- 103-126 mg/ml aflibercept, 10 ± 1 mM histidine-based buffer, 5 ± 0.5% (w/v) sucrose, 0.02-0.04% (w/v) polysorbate 20, and 50 ± 5 mM L-arginine, pH 5.5-6.1;
- 140 mg/ml aflibercept, 10 mM histidine-based buffer, 2.5 % (w/v) sucrose, 2.0 % (w/v) proline, 0.03 % (w/v) polysorbate 20 and 50 mM L-arginine, pH 5.8;
- 114.3 mg/ml aflibercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20 and 50 mM L-arginine, pH 5.8;
- ≥100 mg/ml aflibercept, histidine-based buffer and L-arginine;
- ≥100 mg/ml aflibercept at about pH 5.8, wherein the formulation forms <3% HMW aggregates after incubation at 5°C for 2 months;
- About 114.3 mg/mL aflibercept; 10 mM – 50 mM histidine-based buffer, sugar, non-ionic surfactant, L-Arginine, pH 5.8;
- About 114.3 mg/mL aflibercept; 10 mM His/His-HCl-based buffer, 5% sucrose, 0.03% polysorbate-20, 50 mM L-Arginine, pH 5.8; or
- about 114.3 mg/mL aflibercept; arginine monohydrochloride; histidine; histidine hydrochloride, monohydrate; polysorbate 20; sucrose and water for injection.

[00070] The present invention provides a VEGF receptor fusion protein for use in the treatment and prevention of an angiogenic eye disorder, nAMD, diabetic retinopathy and/or diabetic macular edema in a subject in need thereof wherein the subject achieves and/or maintains one or more of,

- an improvement in Diabetic Retinopathy Severity Scale (DRSS), *e.g.*, by at least 2 or 3 steps;

- an improvement in best corrected visual acuity;
- a dry retina;
- a gain in best corrected visual acuity;
- a gain in best corrected visual acuity of at least 5, 10 or 15 letters
- a BCVA of at least 69 letters;
- a decrease in central retinal thickness (CRT);
- no vascular leakage as measured by fluorescein angiography (FA);
- an improvement from pre-treatment baseline in National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) total score;
- a retina without fluid (total fluid, intraretinal fluid [IRF] and/or subretinal fluid [SRF]) at the foveal center and in center subfield;
- maintenance of a fluid-free retina (total fluid, IRF and/or SRF at foveal center and in the center subfield);
- a lack of macular edema;
- a retina free of fluid on spectral domain optical coherence tomography (SD-OCT); and/or
- Does not deviate from the HDq12 or HDq16 treatment regimen once started.

[00071] The present invention provides a VEGF receptor fusion protein for use in the treatment and prevention of an angiogenic eye disorder, nAMD, diabetic retinopathy and/or diabetic macular edema in a subject in need thereof, wherein the subject achieves and/or maintains one or more of:

- Non-inferior BVCA compared to that of aflibercept which is intravitreally dosed at 2 mg approximately every 4 weeks for the first 3, 4 or 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months;
- Increase in BCVA (according to ETDRS letter score) of about 7, 8 or 9 letters by week 60 from start of treatment, wherein the baseline BCVA is about 61, 62 or 63;
- BCVA (according to ETDRS letter score) of at least about 69 letters by week 48 or 60 from start of treatment;
- Does not lose 5, 10, 15 or 69 letters or more BCVA after week 12, 24, 36, 49, 60, 72, 84 or 90 from start of treatment;
- Improvement in BCVA (according to ETDRS letter score) by week 12, 24, 36, 49, 60, 72, 84 or 90 from start of treatment;
- Improvement in BVCA by week 4, week 8, week 12, week 16, week 20, week 24, week 28, week 32, week 36, week 40, week 44, or week 48 from start of treatment;

• Between weeks 48 and 60, a BCVA score (according to ETDRS letter score) of about 69, 70, 71, 72 or 73;
• Between weeks 36 and 48, a change in BCVA score (according to ETDRS letter score) from initiation of treatment of about 7, 8 or 9 wherein the BCVA at any point between week 36 to 48 is about 60 or 70;
• Between weeks 48 and 60, a change in BCVA score (according to ETDRS letter score) from initiation of treatment of about 7, 8 or 9, wherein the BCVA at any point between week 48 to 60 is about 69, 70, 71, 72 or 73;
• Increase in BCVA as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart or Snellen equivalent by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 or 48 weeks from start of treatment by ≥4 letters, ≥5 letters, ≥6 letters, ≥7 letters, ≥8 letters, > 9 letters or > 10 letters;
• Does not lose 5, 10 or 15 letters by week 48 or 60 from start of treatment (according to ETDRS letter score);
• Gains at least 5, 10 or 15 letter by week 48 or 60 from start of treatment (according to ETDRS letter score);
• Improvement in BCVA, by 4 weeks after initiation of treatment, of about 4 or 5 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 4 or 5 letters (ETDRS or Snellen equivalent) when on HDq16 regimen;
• Improvement in BCVA, by 8 weeks after initiation of treatment, of about 6 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 5 or 6 letters (ETDRS or Snellen equivalent) when on HDq16 regimen;
• Improvement in BCVA, by 12 weeks after initiation of treatment, of about 6 or 7 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 6 letters (ETDRS or Snellen equivalent) when on HDq16 regimen;
• Improvement in BCVA, by 16 weeks after initiation of treatment, of about 6 or 7 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of 7 letters (ETDRS or Snellen equivalent) when on HDq16 regimen;
• Improvement in BCVA, by 20 weeks after initiation of treatment, of about 6 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 6 letters (ETDRS or Snellen equivalent) when on HDq16 regimen;
• Improvement in BCVA, by 24 weeks after initiation of treatment, of about 7 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 5 or 6 letters (ETDRS or Snellen equivalent) when on HDq16 regimen;

• Improvement in BCVA, by 28 weeks after initiation of treatment, of about 7 or 8 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on HDq16 regimen;
• Improvement in BCVA, by 32 weeks after initiation of treatment, of about 7 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on HDq16 regimen;
• Improvement in BCVA, by 36 weeks after initiation of treatment, of 8 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 6 or 7 letters (ETDRS or Snellen equivalent) when on HDq16 regimen;
• Improvement in BCVA, by 40 weeks after initiation of treatment, of about 8 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 6 or 7 letters (ETDRS or Snellen equivalent) when on HDq16 regimen;
• Improvement in BCVA, by 44 weeks after initiation of treatment, of about 8 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on HDq16 regimen;
• Improvement in BCVA, by 48 weeks after initiation of treatment, of about 8 or 9 letters (ETDRS or Snellen equivalent) when on HDq12 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on HDq16 regimen;
• An improvement in BCVA by about week 8 after initiation of treatment which is maintained thereafter during the treatment regimen to at least week 48;
• A BCVA by 4 weeks after initiation of treatment of about 68 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 66 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen;
• A BCVA by 8 weeks after initiation of treatment of about 70 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 67 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen;
• A BCVA by 12 weeks after initiation of treatment of about 70 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 68 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen;
• A BCVA by 16 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 69 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen;

• A BCVA by 20 weeks after initiation of treatment of about 70 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 68 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen;
• A BCVA by 24 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 67 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen;
• A BCVA by 28 weeks after initiation of treatment of about 72 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen;
• A BCVA by 32 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen;
• A BCVA by 36 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 68 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen;
• A BCVA by 40 weeks after initiation of treatment of about 72 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 69 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen;
• A BCVA by 44 weeks after initiation of treatment of about 72 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen;
• A BCVA by 48 weeks after initiation of treatment of about 73 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen;
A BCVA improvement, by week 48 following treatment initiation, of about 9 or 10 letters (ETDRS or Snellen equivalent) when baseline BCVA is about <73 ETDRS letters when on HDq12 regimen;
• A BCVA improvement, by week 48 following treatment initiation, of about 5 or 6 letters (ETDRS or Snellen equivalent) when baseline BCVA is about >73 ETDRS letters when on HDq12 regimen;
• A BCVA improvement, by week 48 following treatment initiation, of about 8 or 9 letters (ETDRS or Snellen equivalent) when baseline BCVA is about <73 ETDRS letters when on HDq16 regimen;

• A BCVA improvement, by week 48 following treatment initiation, of about 4 or 5 letters (ETDRS or Snellen equivalent) when baseline BCVA is about >73 ETDRS letters when on HDq16 regimen;
• A BCVA improvement, by week 48 following treatment initiation, of about 7 or 8 letters (ETDRS or Snellen equivalent) when baseline CRT is about < about 400 micrometers when on HDq12 regimen;
• A BCVA improvement, by week 48 following treatment initiation, of about 9 or 10 letters (ETDRS or Snellen equivalent) when baseline CRT is about >400 micrometers when on HDq12 regimen;
• A BCVA improvement, by week 48 following treatment initiation, of about 5 or 6 letters (ETDRS or Snellen equivalent) when baseline CRT is about < about 400 micrometers when on HDq16 regimen;
• A BCVA improvement, by week 48 following treatment initiation, of about 9 or 10 letters (ETDRS or Snellen equivalent) when baseline CRT is about > about 400 micrometers when on HDq16 regimen;
• Gain of >5, >10 or ≥15 letters BCVA (according to ETDRS letter score) by week 12, 24, 36, 49, 60, 72, 84 or 90 from start of treatment;
• ≥ 2 or >3 step improvement in Diabetic Retinopathy Severity Scale (DRSS), by week 12, 24, 36, 49, 60, 72, 84 or 90 from start of treatment;
• ≥ 2 step improvement in diabetic retinopathy severity scale (DRSS) by week 4, week 8, week 12, 16, 20, 24, 28, 32, 36, 40, 44 or 48 weeks from start of treatment;
• Retina without fluid (total fluid, intraretinal fluid [IRF] and/or subretinal fluid [SRF]) at the foveal center and in center subfield by week 12, 24, 36, 49, 60, 72, 84 or 90 from start of treatment as measured by optical coherence tomography (OCT);
• No vascular leakage as measured by fluorescein angiography (FA) by week 12, 24, 36, 49, 60, 72, 84 or 90 from start of treatment;
• Maintenance of a fluid-free retina (total fluid, IRF and/or SRF at foveal center and in the center subfield) by week 12, 24, 36, 49, 60, 72, 84 or 90 from start of treatment;
• Reduction in total area of fluorescein leakage within ETDRS grid (mm2) at week 48 or 60 by about 12, 13 or 14 mm2 or more as measured by fluorescein angiography;
• Retina free of fluid on spectral domain optical coherence tomography (SD-OCT) by week 12, 24, 36, 49, 60, 72, 84 or 90 from start of treatment;

• Retina without fluid (total fluid, intraretinal fluid [IRF] and/or subretinal fluid [SRF]) at the foveal center by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 or 48 weeks from start of treatment;
• Dry retina by week 12, 24, 36, 49, 60, 72, 84 or 90 from start of treatment;
• Foveal center without fluid by week 12, 24, 36, 49, 60, 72, 84 or 90 from start of treatment as measured by optical coherence tomography (OCT);
• A change in central retinal thickness, by 4 weeks after initiation of treatment of about -118 or -118.3 micrometers when on the HDq12 regimen; or of about -124 or -125 or -124.9 or -125.5 micrometers when on the HDq16 regimen;
• A change in central retinal thickness, by 8 weeks after initiation of treatment of about -137 or -137.4 micrometers when on the HDq12 regimen; or of about -139 or -140 or -139.6 or -140.3 micrometers when on the HDq16 regimen;
• A change in central retinal thickness, by 12 weeks after initiation of treatment of about -150 or -150.1 micrometers when on the HDq12 regimen; or of about -152 or -153 or -152.7 or -153.4 micrometers when on the HDq16 regimen;
• A change in central retinal thickness, by 16 weeks after initiation of treatment of about -139 or -139.4 micrometers when on the HDq12 regimen; or of about -145 or -146 or -145.5 or -146.4 micrometers when on the HDq16 regimen;
• A change in central retinal thickness, by 20 weeks after initiation of treatment of about -117 or -117.1 micrometers when on the HDq12 regimen; or of about -112 or -113 or -112.5 or -113.3 micrometers when on the HDq16 regimen;
• A change in central retinal thickness, by 24 weeks after initiation of treatment of about -158 or -158.1 micrometers when on the HDq12 regimen; or of about -103 or -104 or -103.8 or -104.3 micrometers when on the HDq16 regimen;
• A change in central retinal thickness, by 28 weeks after initiation of treatment of about -146 or -147 or -146.7 micrometers when on the HDq12 regimen; or of about -162 or -162.3 micrometers when on the HDq16 regimen;
• A change in central retinal thickness, by 32 weeks after initiation of treatment of about -132 micrometers when on the HDq12 regimen; or of about -145 or -146 or -145.8 micrometers when on the HDq16 regimen;
• A change in central retinal thickness, by 36 weeks after initiation of treatment of about -168 or -168.1 micrometers when on the HDq12 regimen; or of about -124 or -125 or -124.7 or -125.2 micrometers when on the HDq16 regimen;

• A change in central retinal thickness, by 40 weeks after initiation of treatment of about -163 micrometers when on the HDq12 regimen; or of about -122 or -123 or -122.5 or -123.1 micrometers when on the HDq16 regimen;
• A change in central retinal thickness, by 44 weeks after initiation of treatment of about -147 or -148 or -147.4 micrometers when on the HDq12 regimen; or of about -164 or -164.1 or -164.3 micrometers when on the HDq16 regimen;
• A change in central retinal thickness, by 48 weeks after initiation of treatment of about -171 or -172 or -171.7 micrometers when on the HDq12 regimen; or of about -148 or -149 or -148.3 or -149.4 micrometers when on the HDq16 regimen;
• A change in central retinal thickness, by 60 weeks after initiation of treatment of about -181.95 or -176.24 micrometers when on the HDq12 regimen; or of about -166.26 or -167.18 micrometers when on the HDq16 regimen;
• A change in central retinal thickness of about -118 or -119 or -118.3 micrometers, between initiation of treatment (week 0) and week 4 when on the HDq12 regimen;
• A change in central retinal thickness of about -19, -20 or -19.1 micrometers, between weeks 4 and 8 when on the HDq12 regimen;
• A change in central retinal thickness of about -12, -13 or -12.7 micrometers, between weeks 8 and 12 when on the HDq12 regimen;
• A change in central retinal thickness of about -40, or -41 micrometers, between weeks 20 and 24 when on the HDq12 regimen;
• A change in central retinal thickness of about -36, -37 or -36.1 micrometers, between weeks 32 and 36 when on the HDq12 regimen;
• A change in central retinal thickness of about -24, -25 or -24.3 micrometers, between weeks 44 and 48 when on the HDq12 regimen;
• A change in central retinal thickness of -4, -5 or -4.5 micrometers, between weeks 48 and 60 when on the HDq12 regimen;
• A change in central retinal thickness of about -124, -125 or -124.9 micrometers, between initiation of treatment (week 0) and week 4 when on the HDq16 regimen;
• A change in central retinal thickness of about –14, -15 or -14.7 micrometers, between weeks 4 and 8 when on the HDq16 regimen;
• A change in central retinal thickness of about -13, -14 or -13.1 micrometers, between weeks 8 and 12 when on the HDq16 regimen;
• A change in central retinal thickness of about -58, -59 or -58.5 micrometers, between weeks 24 and 28 when on the HDq16 regimen;

• A change in central retinal thickness of about -41, -42 or -41.6 micrometers, between weeks 40 and 44 when on the HDq16 regimen;
• A reduction in central retinal thickness by week 4, 5, 6, 7 or 8 after initiation of treatment which is maintained within about +17, +18 or +19 micrometers thereafter during the treatment regimen to at least week 48 from initiation of treatment;
• Decrease in central retinal thickness by about 100, 125, 150, 175 or 200 micrometers by week 12, 24, 36, 49, 60, 72, 84 or 90 from start of treatment;
• Reduction in central retinal thickness of about 148-182 micrometers by about week 48 or 60 from start of treatment as measured by optical coherence tomography (OCT)) wherein the baseline CRT is about 449, 450, 455 or 460 micrometers;
• Decrease in central retinal thickness (CRT) by at least about 100, 125, 130, 135, 140, 145, 149, 150, 155, 160, 165, 170, 171, 172, 173, 174 or 175 micrometers by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 or 48 from start of treatment;
• At about 0.1667 days after the first dose, free aflibercept in plasma of about 0.149 (±0.249) mg/l; wherein, at baseline, free aflibercept in was plasma not detectable wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
• At about 0.3333 days after the first dose, free aflibercept in plasma of about 0.205 (±0.250) mg/l; wherein, at baseline, free aflibercept in plasma not detectable wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
• At about 1 days after the first dose, free aflibercept in plasma of about 0.266 (±0.211) mg/l wherein, at baseline, free aflibercept in plasma not detectable wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
• At about 2 days after the first dose, free aflibercept in plasma of about 0.218 (±0.145) mg/l wherein, at baseline, free aflibercept in plasma not detectable wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
• At about 4 days after the first dose, free aflibercept in plasma of about 0.140 (±0.0741) mg/l wherein, at baseline, free aflibercept in plasma not detectable wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
• At about 7 days after the first dose, free aflibercept in plasma of about 0.0767 (±0.0436) mg/l wherein, at baseline, free aflibercept in plasma not detectable, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;

• At about 14 days after the first dose, free aflibercept in plasma of about 0.0309 (±0.0241) mg/l wherein at baseline free aflibercept in plasma not detectable wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
• At about 21 days after the first dose, free aflibercept in plasma of about 0.0171 (±0.0171) mg/l wherein, at baseline, free aflibercept in plasma not detectable wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
• At about 28 days after the first dose, free aflibercept in plasma of about 0.00730 (±0.0113) mg/l wherein, at baseline, free aflibercept in plasma not detectable wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
• At about 0.1667 days after the first dose, adjusted bound aflibercept in plasma of about 0.00698 (±0.0276) mg/l wherein, at baseline, there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
• At about 0.3333 days after the first dose, adjusted bound aflibercept in plasma of about 0.00731 (±0.0279) mg/l wherein, at baseline, there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
• At about 1 days after the first dose, adjusted bound aflibercept in plasma of about 0.0678 (±0.0486) mg/l wherein, at baseline, there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
• At about 2 days after the first dose, adjusted bound aflibercept in plasma of about 0.138 (±0.0618) mg/l wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
• At about 4 days after the first dose, adjusted bound aflibercept in plasma of about 0.259 (±0.126) mg/l wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
• At about 7 days after the first dose, adjusted bound aflibercept in plasma of about 0.346 (±0.151) mg/l wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;

- At about 14 days after the first dose, adjusted bound aflibercept in plasma of about 0.374 (±0.110) mg/l wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
- At about 21 days after the first dose, adjusted bound aflibercept in plasma of about 0.343 (±0.128) mg/l wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
- At about 28 days after the first dose, adjusted bound aflibercept in plasma of about 0.269 (±0.149) mg/l wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks;
- The maximum level of free aflibercept in the plasma is reached about 0.965 days after the first dose;
- Reaches a maximum level of about 0.310 mg/l (±0.263) free aflibercept in the plasma;
- Free aflibercept in the plasma of from about 0 to about 1.08 mg/L;
- Free aflibercept in the plasma maximum (mg/l) per dose (mg) of aflibercept of about 0.388 (±0.0328) mg/l/mg;
- The maximum level of adjusted bound aflibercept in the plasma is reached about 14 days after the first dose;
- Reaches a maximum level of about 0.387 mg/l (±0.135) adjusted bound aflibercept in the plasma;
- Adjusted bound aflibercept in the plasma of from about 0.137 to about 0.774 mg/L;
- Adjusted bound aflibercept in the plasma maximum (mg/l) per dose (mg) of aflibercept of about 0.483 (±0.0168) mg/l/mg;
- Does not have anti-drug antibodies against aflibercept after 48 or 60 weeks of treatment;
- Improvement from pre-treatment baseline in National Eye Institute Visual Function Questionnaire (NEI-VFQ) total score; and/or
- Lack of macular edema.

[00072] The present invention provides a VEGF receptor fusion protein for use in the treatment and prevention of neovascular age related macular degeneration, diabetic retinopathy and/or diabetic macular edema in a subject in need thereof wherein the interval between doses of ≥8

mg (±0.8 mg) VEGF receptor fusion protein is adjusted (increased/maintained/reduced) based on visual and/or anatomic outcomes.

[00073] The present invention provides a VEGF receptor fusion protein for use in the treatment and prevention of neovascular age related macular degeneration, diabetic retinopathy and/or diabetic macular edema in a subject in need thereof wherein the doses of ≥8 mg (±0.8 mg) VEGF receptor fusion protein are administered according to pro re nata (PRN), capped PRN or treat and extend (T&E) dosing regimen.

[00074] The present invention also provides a kit comprising i) a container comprising a VEGF receptor fusion protein, preferably aflibercept and ii) instruction for use of the VEGF fusion protein. In an embodiment of the invention, the container is a vial or a pre-filled syringe. The vial a type I glass vial containing a nominal fill volume of abut 0.26 mL solution for intravitreal injection. In an embodiment of the invention the container comprises the VEGF receptor fusion protein at a concentration of more or equal to 100 mg/mL or the container comprises aflibercept at a concentration of about 114.3 mg/mL. In an embodiment of the invention, the instruction for use comprising instruction for use of the VEGF fusion protein or aflibercept for the treatment of DME and /or AMD. In an embodiment of the invention, the instruction for use comprises the information that i) the container comprises ≥8 mg (±0.8 mg) (114.3 mg/mL) aflibercept solution for intravitreal injection, ii) each single-dose vial provides a usable amount to deliver a single dose of 70 microliters containing ≥8 mg (±0.8 mg) aflibercept to adult patients, iii) the recommended dose is ≥8 mg (±0.8 mg) aflibercept (equivalent to 70 microliters solution for injection), iv) ≥8 mg (±0.8 mg) aflibercept treatment is initiated with 1 injection per month (every 4 weeks) for 3 consecutive doses, v) injection intervals may then be extended up to every 16 weeks or 20 weeks, vi) the treatment interval may be adjusted based on the physician's judgement of visual and/or anatomic outcomes and /or vii) that ≥8 mg (±0.8 mg) aflibercept / 0.07 mL is provided as a sterile, aqueous solution containing arginine monohydrochloride; histidine; histidine hydrochloride, monohydrate; polysorbate 20; sucrose and water for injection.

BRIEF DESCRIPTION OF THE FIGURES

[00075] **Figure 1**: Summary of PHOTON clinical trial.

[00076] **Figure 2**: Key eligibility criteria (inclusion criteria and exclusion criteria) of PHOTON clinical trial.

[00077] **Figure 3**: Dosing schedule and dose regimen modification (DRM) criteria of PHOTON clinical trial (to week 48).

[00078] **Figure 4**: Criteria for dose regimen modifications of PHOTON clinical trial.

[00079] **Figure 5**: Patient disposition at week 48 in PHOTON clinical trial.

[00080] **Figure 6**: Baseline demographics of subjects in PHOTON clinical trial.

[00081] **Figure 7**: Baseline characteristics of the study eye of subjects in PHOTON clinical trial.

[00082] **Figure 8**: Mean number of injections through week 48 in PHOTON clinical trial.

[00083] **Figure 9**: Mean change in Best Corrected Visual Acuity (BCVA) through week 48 in PHOTON clinical trial. Least squares mean change from baseline at week 48 shown.

[00084] **Figure 10**: Percentage of subjects maintaining Q12 week and Q16 week intervals through week 48 in PHOTON clinical trial.

[00085] **Figure 11**: Key secondary endpoint (EP) of percentage of subjects with ≥2 step improvement in Diabetic Retinopathy Severity Scale (DRSS) at week 48 in PHOTON clinical trial.

[00086] **Figure 12**: Percentage of subjects without retinal fluid at foveal center at week 48 in PHOTON clinical trial.

[00087] **Figure 13**: Mean change from baseline in central retinal thickness through week 48 in PHOTON clinical trial. Various matched intervals are highlighted in three insets.

[00088] **Figures 14A, 14B and 14C**: Ocular serious Treatment Emergent Adverse Events (TEAEs) through week 48 in PHOTON clinical trial (Fig. 14A); Most Frequent Adverse Events (AEs) through week 48 (Fig. 14B); Non-Ocular Safety through week 48 (Fig. 14C).

[00089] **Figure 15**: Treatment emergent intraocular inflammation through week 48 in PHOTON clinical trial.

[00090] **Figure 16**: Mean change from baseline in intraocular pressure through week 48 in PHOTON clinical trial.

[00091] **Figure 17**: Percentage of subjects meeting intraocular pressure criteria in PHOTON clinical trial.

[00092] **Figure 18**: Non-Ocular Serious TEAEs ≥1% through week 48 in PHOTON clinical trial.

[00093] **Figure 19**: Treatment emergent Anti-Platelet Trialists' Collaboration (APTC) events through week 48 in PHOTON clinical trial.

[00094] **Figure 20**: Treatment emergent hypertension events though week 48 in PHOTON clinical trial.

[00095] **Figure 21**: Potentially Clinically Significant Values (PCSVs) for blood pressure through week 48 in PHOTON clinical trial.

[00096] **Figure 22**: Mean change from baseline in systolic blood pressure through week 48 in PHOTON clinical trial. Baseline to week 9 SBP and mean baseline SBP shown in insets.

[00097] **Figure 23**: Mean change from baseline in diastolic blood pressure through week 48 in PHOTON clinical trial. Baseline to week 9 DBP and mean baseline DBP shown in insets.

[00098] **Figure 24**: Deaths through week 48 in PHOTON clinical trial.

[00099] **Figure 25A and 25B**: (A)Mean Change from Baseline in BCVA Score (ETDRS Letters) in Study Eye through Week 60, OC (Full Analysis Set); (B) Least Square Mean Change from Baseline in BCVA Score (ETDRS Letters) in Study Eye through Week 60 (Full Analysis Set). Abbreviations: 2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. BCVA=best-corrected visual activity; ETDRS=Early Treatment of Diabetic Retinopathy Study; HD=high dose; OC=observed cases, SE=standard error. OC: Observations after an ICE defined for the primary estimand were excluded.

[000100]**Figure 26A and 26B**: (A) Mean Change from Baseline in Central Retinal Thickness (microns) by Visit through Week 60, OC (Full Analysis Set) (B) Least Square Mean Change from Baseline in Central Retinal Thickness (microns) by Visit through Week 60, OC (Full Analysis Set). Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. ICE=intercurrent events; OC=observed case; SE=standard error. OC= observations after an ICE defined for the primary estimand were excluded.

[000101]**Figure 27**: Mean (+SD) Concentrations (mg/l) of Free Aflibercept in Plasma by Nominal Time and Treatment in Participants with DME with Unilateral Treatment in the Dense PK Sampling sub-study (Study VGFTe-HD-DME-1934, Log-Scaled, [DPKS]). N=Number of subjects; SD=Standard deviation; DME=Diabetic macular edema; 2q8=2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12=High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses; HDq16=High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses; LLOQ=Lower limit of quantitation; D=Day; H=Hour Note: Table under the figure presents the number of subjects contributing to the statistics for the corresponding visits/timepoints and treatments. Concentrations below the LLOQ were set to LLOQ/2. HDq12+HDq16 = combined data from treatment groups HDq12 and HDq16. Patients in the dense PK sub-study only received aflibercept injections unilaterally.

[000102]**Figure 28**: Mean (±SD) Concentrations (mg/l) of Adjusted Bound Aflibercept in Plasma by Nominal Time and Treatment in Participants with DME with Unilateral Treatment in the Dense PK Sampling sub-study (Study VGFTe-HD-DME-1934, Log-Scaled, [DPKS]). N=Number of subjects; SD=Standard deviation; DME=Diabetic macular edema; 2q8=2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12=High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses; HDq16=High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses; LLOQ=Lower limit of quantitation; D=Day; H=Hour. Note: Table under the figure presents the number of subjects contributing to the statistics for the corresponding visits/timepoints and treatments. Concentrations below the LLOQ were set to LLOQ/2. Adjusted bound aflibercept = 0.717*bound aflibercept. HDq12+HDq16 = combined data from treatment groups HDq12 and HDq16. Patients in the dense PK sub-study only received aflibercept injections unilaterally.

[000103]**Figure 29**: Mean (±SD) Concentrations (mg/l) of Free Aflibercept in Plasma by Nominal Time and Treatment Group in Participants with DME in the Sparse PK Sampling Study (Study VGFTe-HD-DME-1934, Log-Scaled, [PKAS]). N=Number of subjects; SD=Standard deviation; DME=Diabetic macular edema; 2q8=2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12=High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses; HDq16=High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses; LLOQ=Lower limit of quantitation; PKAS=Pharmacokinetics analysis set. Note: Table under the figure presents the number of subjects contributing to the statistics for the corresponding visits/timepoints and treatment groups. Concentrations below the LLOQ were set to LLOQ/2. Post-dose samples and samples collected during the dense PK sub-study (from post dose on Day 0 through Day 21) were excluded.

[000104]**Figure 30**: Mean (±SD) Concentrations (mg/l) of Adjusted Bound Aflibercept in Plasma by Nominal Time and Treatment Group in Participants with DME in the Sparse PK Sampling Study (Study VGFTe-HD-DME-1934, Log-Scaled, [PKAS]); N=Number of subjects; SD=Standard deviation; DME=Diabetic macular edema; 2q8=2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12=High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses; HDq16=High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses; LLOQ =¾Lower limit of quantitation. Note: Table under the figure presents the number of subjects contributing to the statistics for the corresponding visits/timepoints and treatment groups. Concentrations below the LLOQ were set to LLOQ/2. Adjusted bound aflibercept = 0.717*bound aflibercept. Post-dose samples and

samples collected during the dense PK sub-study (from post dose on Day 0 through Day 21) were excluded.

[000105]**Figure 31:** Structural Representation of a Population Pharmacokinetic Model Following IV, SC, and IVT Administration of Aflibercept. CMT = compartment, IV = intravenous, IVT = intravitreal, K20 = elimination rate constant for free aflibercept, K40 = elimination rate constant for adjusted bound aflibercept, K62 = rate of absorption from subcutaneous injection depot compartment, K70 = elimination rate constant from tissue (platelet) compartment; QE = inter-compartmental clearance between ocular compartment and central compartment of free aflibercept, QF1 and QF2 = inter-compartmental clearances of free aflibercept, VMK24, KM = saturable Michaelis-Menten type binding of free aflibercept with VEGF; VMK27, KMK27 = saturable elimination from plasma compartment to tissue compartment (platelets) CMT 2 and CMT 4 are both representative of the plasma compartment and volumes are assumed to be equal.

[000106]**Figure 32:** Mean (±SD) Concentrations (mg/l) of Free and Adjusted Bound Aflibercept Over 28 Days for Single 2 mg and 8 mg IVT Doses of Aflibercept in nAMD or DME in the Dense PK Sub-studies (DPKS, Log-Scaled). LQ = below limit of quantification, DME = Diabetic Macular Edema, DPKS = dense pharmacokinetic sub-studies, HDq12 = aflibercept 8 mg administered every 12 weeks following 3 initial monthly injections, HDq16 = aflibercept 8 mg administered every 16 weeks following 3 initial monthly injections, IVT = intravitreally, LLOQ = lower limit of quantification, N = number of participants, nAMD = neovascular age-related macular degeneration, SD = standard deviation Adjusted Bound Aflibercept = 0.717*Bound Aflibercept Note: Concentrations below the LLOQ (0.0156 mg/L for Free and 0.0224 mg/L for Adjusted Bound Aflibercept) were set to LLOQ/2. Note: 8 mg HD aflibercept data for the first 28 days (obtained from PULSAR or PHOTON) is a combination of data from participants who received HDq12 or HDq16. One participant in PULSAR with an outlier free aflibercept concentration at day 28 that is greater than 10-fold of the mean concentration is excluded. Records after fellow-eye treatment are excluded. Data Source: drug concentration data from the week 48 database lock for PULSAR and PHOTON and final lock for CANDELA.

[000107]**Figure 33**: Observed and Model-Predicted Concentrations (mg/l) of Free and Adjusted Bound Aflibercept in Plasma Over 28 days After a Single IVT Injection for Participants with nAMD or DME in the Dense PK Sub-studies (DPKS), Stratified by Dose and Population. DME = diabetic macular edema, IVT = intravitreally, LLOQ = lower limit of quantitation, nAMD = neovascular age-related macular degeneration, PK = pharmacokinetic Observed concentrations below the lower limit of quantitation (LLOQ; 0.0156 mg/L for free and 0.0224 mg/L for adjusted

bound aflibercept) were set to LLOQ/2. Data source: Drug concentration data from dense PK sub-study in PHOTON, PULSAR, and CANDELA.

[000108]**Figure 34**: Overlay of Observed and Model-Predicted Concentrations (mg/l) of Free and Adjusted Bound Aflibercept in Plasma for Combined nAMD and DME Populations. 2q8 = aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals, 2q12 = aflibercept 2 mg administered every 12 weeks, after 3 initial injections at 4-week intervals, DME = diabetic macular edema, HDq12 = aflibercept 8 mg administered every 12 weeks following 3 initial monthly injections, HDq16 = aflibercept 8 mg administered every 16 weeks following 3 initial monthly injections, IVT = intravitreally, LLOQ = lower limit of quantification, nAMD = neovascular age-related macular degeneration Observed concentrations below the lower limit of quantitation (LLOQ; 0.0156 mg/L for free and 0.0224 mg/L for adjusted bound aflibercept) were set to LLOQ/2. Data source: Drug concentration data from CANDELA, PHOTON, and PULSAR.

[000109]**Figure 35**: Model-Predicted Amounts (mg) of Aflibercept Exposures After a Single IVT Injection, Stratified by Dosing Regimen in Combined Participants with nAMD and DME. DME = diabetic macular edema, HD = aflibercept 8 mg, IVT = intravitreal, nAMD = neurovascular age-related macular degeneration, PI = prediction interval, PK = pharmacokinetics, QE = inter-compartmental clearance between ocular compartment and central compartment of free aflibercept Adjusted LLOQ (0.0624 µg), set as the LLOQ of free aflibercept in plasma (that is, 0.0156 mg/L) times the assumed volume of the study eye compartment in the PK model (that is, 4 mL). Since the concentrations of (free or bound) aflibercept were not measured in the study eye in the clinical studies included in the Population PK analysis dataset, this target was selected arbitrarily on the basis of the LLOQ in plasma and was used as reference for comparison across dosing regimens and to assess the effect of the effect of HD aflibercept on QE.

[000110]**Figure 36**: Mean (±SD) Concentrations (mg/l) of Free and Adjusted Bound Aflibercept Over 28 Days for Single 2 mg and 8 mg IVT Doses of Aflibercept in Participants with nAMD in the Dense PK Sub-studies (DPKS, Log-Scaled) - No Outlier. DME = diabetic macular edema, DPKS = dense pharmacokinetic sub-studies, HDq12 = aflibercept 8 mg administered every 12 weeks following 3 initial monthly injections, HDq16 = aflibercept 8 mg administered every 16 weeks following 3 initial monthly injections, IVT = intravitreally, LLOQ = lower limit of quantification, N = number of participants, nAMD = neovascular age-related macular degeneration, PK = pharmacokinetic, SD = standard deviation Adjusted Bound Aflibercept = 0.717*Bound Aflibercept. Note: Concentrations below the LLOQ (0.0156 mg/L for Free and 0.0224 mg/L for Adjusted Bound Aflibercept) were set to LLOQ/2. Note: 8 mg data for the first

28 days (obtained from PULSAR or PHOTON) is a combination of data from participants who received HDq12 or HDq16 Data source: drug concentration from the week 48 lock for PULSAR and PHOTON and final lock for CANDELA. Records after fellow-eye treatment are excluded.

[000111]**Figure 37**: Mean (±SD) Concentrations (mg/l) of Free and Adjusted Bound Aflibercept Over 28 Days for Single 2 mg and 8 mg IVT Doses of Aflibercept in Participants with nAMD in the Dense PK Sub-study (DPKS, Log-Scaled) -Outlier Included. DME = diabetic macular edema, DPKS = dense pharmacokinetic sub-studies, HDq12 = aflibercept 8 mg administered every 12 weeks following 3 initial monthly injections, HDq16 = aflibercept 8 mg administered every 16 weeks following 3 initial monthly injections, IVT = intravitreally, LLOQ = lower limit of quantification, N = number of participants, nAMD = neovascular age-related macular degeneration, PK = pharmacokinetic, SD = standard deviation Adjusted Bound Aflibercept = 0.717*Bound Aflibercept. Note: Concentrations below the lower limit of quantification (LLOQ, 0.0156 mg/L for Free and 0.0224 mg/L for Adjusted Bound Aflibercept) were set to LLOQ/2. Data source: drug concentration from the week 48 lock for PULSAR and final lock for CANDELA. Data from VGFTOD-0702 are included as a reference (the concentration in PK sub-study is subtracted by pre-dose concentration when it is >LLOQ). Records after fellow-eye treatment are excluded.

[000112]**Figure 38**: Mean (±SD) Concentrations (mg/l) of Free and Adjusted Bound Aflibercept Over 28 Days for Single 2 mg and 8 mg IVT Doses of Aflibercept in Participants with DME in the Dense PK Sub-studies (DPKS, Log-Scaled). BLQ = below limit of quantification, DME = diabetic macular edema, DPKS = dense pharmacokinetic analysis set, HDq12 = aflibercept 8 mg administered every 12 weeks following 3 initial monthly injections, HDq16 = aflibercept 8 mg administered every 16 weeks following 3 initial monthly injections, IVT = intravitreally, LLOQ = lower limit of quantification, N = number of participants, nAMD = neovascular age-related macular degeneration, SD = standard deviation Note: Concentrations below the LLOQ (0.0156 mg/L for Free and 0.0224 mg/L for Adjusted Bound Aflibercept) were set to LLOQ/2. Adjusted Bound Aflibercept = 0.717*Bound Aflibercept. Note: 8 mg data for the first 28 days (obtained from PULSAR or PHOTON) is a combination of data from participants who received HDq12 or HDq16. Note: The Concentration is subtracted by baseline concentration if participants took the Aflibercept prior to study drug started within 12 weeks and the baseline concentration is > BLQ. Data source: drug concentration data from the week 48 lock for PHOTON. Drug concentration data from VGFT-OD-0706 (historical data) are included as a reference. Records after fellow-eye treatment are excluded.

[000113]**Figure 39**: Overlay of Observed and Model-Predicted Concentrations (mg/l) of Free and Adjusted Bound Aflibercept in Plasma for Participants with nAMD. 2q8 = aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals, 2q12 = aflibercept 2 mg administered every 12 weeks, after 3 initial injections at 4-week intervals, DME = diabetic macular edema, HDq12 = aflibercept 8 mg administered every 12 weeks following 3 initial monthly injections, HDq16 = aflibercept 8 mg administered every 16 weeks following 3 initial monthly injections, IVT = intravitreally, LLOQ = lower limit of quantitation, nAMD = neovascular age-related macular degeneration, PK = pharmacokinetics Observed concentrations below the lower limit of quantitation (LLOQ; 0.0156 mg/L for free and 0.0224 mg/L for adjusted bound aflibercept) were set to LLOQ/2. Data from PULSAR and CANDELA.

[000114]**Figure 40**: Overlay of Observed and Model-Predicted Concentrations (mg/l) of Free and Adjusted Bound Aflibercept in Plasma for Participants with Diabetic Macular Edema in study PHOTON. 2q8 = aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals, HDq12 = aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals, HDq16 = aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals, IVT = intravitreally, LLOQ = lower limit of quantitation Data from PHOTON.

[000115]**Figure 41**: Dosing schedule and dose regimen modification (DRM) criteria of PULSAR clinical trial (to week 48).

[000116]**Figure 42**: Key eligibility criteria (inclusion criteria and exclusion criteria) of PULSAR clinical trial.

[000117]**Figure 43**: Dosing schedule and dose regimen modification (DRM) criteria for PULSAR clinical trial.

[000118]**Figure 44**: Criteria for dose regimen modifications (DRMs) of PULSAR clinical trial.

[000119]**Figure 45**: Patient disposition at week 48 in PULSAR clinical trial.

[000120]**Figure 46**: Baseline demographics of subjects in PULSAR clinical trial.

[000121]**Figure 47**: Baseline characteristics of the study eye of subjects in PULSAR clinical trial.

[000122]**Figure 48**: Mean number of injections through week 48 in PULSAR clinical trial.

[000123]**Figure 49**: Mean change in Best Corrected Visual Acuity (BCVA) through week 48 in PULSAR clinical trial. Least squares mean change from baseline at week 48 shown in table.

[000124]**Figure 50**: Percentage of subjects maintaining Q12 and Q16 week intervals through week 48 in PULSAR clinical trial.

[000125]**Figure 51**: Key secondary endpoint of percentage of subjects without retinal fluid in center subfield at week 16 in PULSAR clinical trial.

[000126]**Figure 52**: Percentage of subjects without retinal fluid in center subfield at week 48 in PULSAR clinical trial.

[000127]**Figure 53A and 53B**: Mean change from baseline in central retinal thickness through week 48 (A); and central retinal thickness through week 48 (B).

[000128]**Figure 54A and 54B**: Ocular serious Treatment Emergent Adverse Events (TEAEs) through week 48 (A); and Most Frequent Ocular Adverse Events (AEs) through week 48 in PULSAR clinical trial (B).

[000129]**Figure 55**: Treatment emergent intraocular inflammation through week 48 in PULSAR clinical trial.

[000130]**Figure 56**: Mean change from baseline in intraocular pressure through week 48 in PULSAR clinical trial.

[000131]**Figure 57**: Percentage of subjects meeting intraocular pressure criteria in PULSAR clinical trial.

[000132]**Figure 58**: Non-Ocular Serious TEAEs ≥0.5% through week 48 in PULSAR clinical trial.

[000133]**Figures 59A and 59B**: Treatment emergent Anti-Platelet Trialists' Collaboration (APTC) events through week 48 (A); Non-Ocular Safety through week 48 (B) in PULSAR clinical trial.

[000134]**Figure 60**: Treatment emergent hypertension events though week 48 in PULSAR clinical trial.

[000135]**Figure 61**: Potentially Clinically Significant Values (PCSVs) for blood pressure through week 48 in PULSAR clinical trial.

[000136]**Figure 62**: Mean change from baseline in systolic blood pressure through week 48 in PULSAR clinical trial. Mean change from baseline to week 9 and mean baseline pressure shown in insets.

[000137]**Figure 63**: Mean change from baseline in diastolic blood pressure through week 48 in PULSAR clinical trial. Mean change from baseline to week 9 and mean baseline pressure shown in insets.

[000138]**Figure 64**: Deaths through week 48 in PULSAR clinical trial.

[000139]**Figure 65**: PULSAR dosing schedule out to week 60. Dose regimen modification criteria are set forth in the inset.

[000140]**Figure 66**: Absolute BCVA and change in BCVA from baseline (ETDRS letters) out to week 60 [PULSAR]. Least squares mean change from baseline at week 60 shown.

[000141]**Figure 67**: Proportion of PULSAR Patients Maintaining HDq12 (8q12)- and HDq16 (8q16) Intervals Through Week 60.

[000142]**Figure 68**: Mean Number of Injections through Week 60 in each group [PULSAR].

[000143]**Figure 69A, 69B and 69C**: Central Retinal Thickness (CRT) and Change from Baseline to through Week 60 [PULSAR]. (A) central retinal thickness (micrometers) over time (observed values-censoring data post ICE); (B) Mean change from baseline in CST (central subfield retinal thickness (interchangeable with CRT); micrometers) by visit through week 60, OC prior to ICE in the full analysis set; (C) LS_{mean} (95% CIs) changes from baseline in CST (micrometers) by visit, MMRM (mixed model for repeated measurements) in the full analysis set (to week 48).

[000144]**Figure 70A, 70B, 70C, 70D, 70E, 70F and 70G**: PULSAR Safety data Summary, (Fig. 70A) Ocular TEAEs ≥2% through Week 60, (Fig. 70B) Ocular Serious TEAEs through Week 60, (Fig. 70C) Non-Ocular TEAEs ≥2% through Week 60, (Fig. 70D) Non-Ocular Serious TEAEs ≥0.5% through Week 60, (Fig. 70E) Deaths through Week 60, (Fig. 70F) Mean Change in Systolic Blood Pressure at week 60, and (Fig. 70G) Mean Change in Diastolic Blood Pressure at week 60, for PULSAR.

[000145]**Figure 71**: Changes of 5, 10 and 15 letters at Week 60. Observed (OC) (censoring data post ICE) [PULSAR].

[000146]**Figure 72**: % PULSAR Subjects Without Retinal Fluid in Center Subfield by Visit (weeks and schedules doses shown) to week 60. LOCF (censoring data post ICE).

[000147]**Figure 73**: Proportion of PHOTON Patients Who Maintained or Extended Intervals Through Week 96. Patients completing Week 96. Values may not add up to 100% due to rounding. Q8, every 8 weeks; Q12, every 12 weeks; Q16, every 16 weeks; Q20, every 20 weeks; Q24, every 24 weeks.

[000148]**Figure 74A and 74B**: BCVA and CRT in PULSAR Case Report 1 Patient Over Time. (A) Displayed are the patient's characteristics along with images of the patient's retina at baseline, at week 12 and at week 96. A timeline of the absolute BCVA and absolute CRV achieved by the patient is set forth at the bottom. The particular maintenance dosing interval (q16, q20 or q24) to which the patient was assigned at various times is indicated. Dosage regimen modification assessments were performed at the weeks indicated with a box. (B) Patient's assigned interval among that of the overall population of PULSAR participants.

[000149]**Figure 75A and 75B**: BCVA and CRT in PULSAR Case Report 2 Patient Over Time. (A) Displayed are the patient's characteristics along with images of the patient's retina at baseline, at week 12 and at week 96. A timeline of the absolute BCVA and absolute CRV achieved by the patient is set forth at the bottom. The particular maintenance dosing interval (q12 and q16) to which the patient was assigned at various times is indicated. Dosage regimen modification assessments were performed at the weeks indicated with a box. (B) Patient's assigned interval among that of the overall population of PULSAR participants.

[000150]**Figure 76**: BCVA and CRT in PHOTON Case Report Patient Over Time. (A) Displayed are the patient's characteristics along with images of the patient's retina at baseline, at week 12 and at week 96. A timeline of the absolute BCVA and absolute CRV achieved by the patient is set forth at the bottom. The particular maintenance dosing interval (q16, q20 and q24) to which the patient was assigned at various times is indicated. Dosage regimen modification assessments were performed at the weeks indicated with a box.

[000151]**Figure 77**: Forest Plots of Geometric Mean Ratios (90% Confidence Interval) of Post Hoc Model-Based Predictions of Exposure Metrics of Free and Adjusted Bound Aflibercept in Participants From the CANDELA, PULSAR, and PHOTON Studies for HDq12. * = includes 6 participants with renal failure ; ** = includes 5 participants with moderate hepatic failure; [or] indicates that the respective limit is included in the interval; (or) indicates that the respective limit is not included in the interval. Dashed lines indicate standard reference limits of 0.8 and 1.25;

AUCweek56-68 = Area under the concentration versus time curve between week 56 and week 68; Cmax,week8-12 = Maximum concentration between week 8 and week 12; DME = Diabetic macular edema; HDq12 = 8 mg aflibercept every 12 weeks following 3 initial monthly injections; nAMD = Neovascular age-related macular degeneration.

[000152]**Figure 78:** Stochastic Simulations of Aflibercept Concentrations in the Eye in 5,000 Virtual Participants With Neovascular Age-Related Macular Degeneration and 5,000 Virtual Participants With Diabetic Macular Edema After Repeated Intravitreal Injections of 2 mg or 8 mg Aflibercept.

IVT = Intravitreal ; K_D = Dissociation constant; LLOQ = Lower limit of quantitation; VEGF-A = Vascular endothelial growth factor-A;

[a]Concentration of free aflibercept, fo llowing intravitreal injection, at the end of an 8-week dosing interval with aflibercept 2 mg;

[b] 1 x, 9x, and 99x K_D represent the free aflibercept concentrations required to inhibit VEGF-A by 50%, 90%, or 99% in an *in vitro* setting.

[000153]**Figure 79:** Forest Plots of Geometric Mean Ratios (90% Confidence Interval) of Post Hoc Model-Based Predictions of Exposure Metrics of Free and Adjusted Bound Aflibercept in Participants From the CANDELA, PULSAR, and PHOTON Studies for HDq12, Stratified by Manufacturing Process of HD Aflibercept.
AUCweek56-68 = Area under the concentration curve from weeks 56 to 68; CV= Coefficient of variation, Cmax,week8-12 =Maximum concentration from weeks 8 to 12; Cmax,week56-60 = Maximum concentration from weeks 56 to 60; n = Number of participants in each group; HDq12 = 8 mg aflibercept every 12 weeks following 3 initial monthly injections
[or] indicates that the respective limit is included in the interval ; (or) indicates that the respective limit is not included in the interval. Dashed lines indicate standard reference limits 0.8 and 1.25.
[000154]**Figure 80**: Distribution of Ocular Distribution Clearance in Patients With Neovascular Age-Related Macular Degeneration in the PULSAR Study, Stratified by Assigned Dosing Interval at the Last Study Eye Dose of High Dose Aflibercept Through Week 96
[000155]**Figure 81**: Distribution of Ocular Distribution Clearance in Patients With Diabetic Macular Edema in the PHOTON Study, Stratified by Assigned Dosing Interval at the Last Study Eye Dose of High Dose Aflibercept Through Week 96.
[000156]**Figure 82**: Distribution of Baseline Central Retinal Thickness in Patients With Neovascular Age-Related Macular Degeneration in the PULSAR Study, Stratified by Assigned Dosing Interval at the Last Study Eye Dose of High Dose Aflibercept Through Week 96.
[000157]**Figure 83**: Distribution of Baseline Central Retinal Thickness in Patients With Diabetic Macular Edema in the PHOTON Study, Stratified by Assigned Dosing Interval at the Last Study Eye Dose of High Dose Aflibercept Through Week 96.
[000158]**Figure 84**: Visual Predictive Check for Probability of Assignment to a 24-Week Dosing Interval at the Last Dose of High Dose Aflibercept Through Week 96, Stratified by Disease Population and Tertiles of Ocular Distribution Clearance and Baseline Central Retinal Thickness.
[000159]**Figure 85**: Kaplan-Meier Plot of Time to First Dose Regimen Modification of High Dose Aflibercept, Stratified by Neovascular Age-Related Macular Degeneration Versus Diabetic Macular Edema Population.
[000160]**Figure 86**: Kaplan-Meier Plot of Time to First Dose Regimen Modification of High Dose Aflibercept, Stratified by Neovascular Age-Related Macular Degeneration Versus Diabetic Macular Edema Population and Tertile of Exposure in the Study Eye.

[000161]**Figure 87**: Model-Predicted Hazard Ratio for Dose Regimen Modification of High Dose Aflibercept by Neovascular Age-Related Macular Degeneration Versus Diabetic Macular Edema Population and Ocular Distribution Clearance.

[000162]**Figure 88**: Kaplan-Meier Plot of Time to First Dose Regimen Extension of High Dose Aflibercept, Stratified by Dose Regimen at Randomization.

[000163]**Figure 89**: Kaplan-Meier Plot of Time to First Dose Regimen Extension of High Dose Aflibercept, Stratified by Neovascular Age-Related Macular Degeneration Versus Diabetic Macular Edema Population and Tertile of Exposure in the Study Eye.

[000164]**Figure 90**: Model-Predicted Hazard Ratio for Dose Regimen Extension of High Dose Aflibercept by Randomized Dosing Regimen and Ocular Distribution Clearance.

[000165]**Figure 91**: Distribution of Individual Ocular Distribution Clearance Estimates Versus Time of Last Study Eye Dose of H.igh Dose Aflibercept Stratified by Study and Overall.

[000166]**Figure 92**: Visual Predictive Check for Probability of Last Dosing Interval Assignment in Participants With Neovascular Age-Related Macular Degeneration Receiving High Dose Aflibercept, Stratified by Tertile of Ocular Distribution Clearance and Baseline Central Retinal Thickness.

[000167]**Figure 93**: Visual Predictive Check for Probability of Last Dosing Interval Assignment in Participants With Diabetic Macular Edema Receiving High Dose Aflibercept, Stratified by Tertile of Ocular Distribution Clearance and Baseline Central Retinal Thickness.

DETAILED DESCRIPTION OF THE INVENTION

[000168]The present invention provides, in part, a safe and effective high-dose aflibercept IVT injection which extends the maintenance dosing interval past 8 weeks, with at least similar functional and potentially improved anatomic outcomes. The regimen exhibited an unexpectedly high level of durability in subjects which exceeded that which would have been expected simply based on administration of more aflibercept.

[000169]EYLEA has become the standard-of-care for neovascular age related macular degeneration (nAMD), diabetic macular edema (DME) and diabetic retinopathy (DR). Eylea is prescribed for DME and DR at a dose of 2 mg once a month for 5 doses followed by maintenance dosing every 8 weeks. The dosing regimen of the present invention has demonstrated that a remarkably high percentage of subjects can be maintained on 12- and 16-week dosing intervals. In trials testing these dosing regimens, nearly 90% of subjects with diabetic macular edema were able to maintain a 16-week dosing regimen. The HDq12 and HDq16 PHOTON trial groups achieved similar BCVA gains compared to 2q8 at Week 96, with

up to 6 fewer injections. Through Week 96, 88% of HDq12 patients and 84% of HDq16 patients maintained ≥12- and ≥16-week dosing intervals, respectively. At Week 96, 43% of HDq12 patients and 47% of HDq16 patients had a last assigned dosing interval of ≥20 weeks. Of the participants assigned to a 24-week interval as their last assigned dosing interval prior to week 96 in the PULSAR and PHOTON clinical trial studies, a subset entered into the extension phase and successfully completed a 24-week dosing interval between weeks 96 and 108 without the need for shortening based on dose regimen modification (DRM) criteria. These durability data coupled with a safety profile consistent with that of EYLEA support high-dose aflibercept as a potential new standard-of-care in angiogenic eye disorders such as DR or DME.

[000170]Standard methods in molecular biology are described Sambrook, Fritsch and Maniatis (1982 & 1989 2nd Edition, 2001 3rd Edition) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Sambrook and Russell (2001) Molecular Cloning, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Wu (1993) Recombinant DNA, Vol. 217, Academic Press, San Diego, Calif.). Standard methods also appear in Ausbel, *et al.* (2001) Current Protocols in Molecular Biology, Vols. 1-4, John Wiley and Sons, Inc. New York, N.Y., which describes cloning in bacterial cells and DNA mutagenesis (Vol. 1), cloning in mammalian cells and yeast (Vol. 2), glycoconjugates and protein expression (Vol. 3), and bioinformatics (Vol. 4).

[000171]General methods for protein purification including immunoprecipitation, chromatography, electrophoresis, centrifugation, and crystallization are described (Coligan *et al.* (2000) Current Protocols in Protein Science, Vol. 1, John Wiley and Sons, Inc., New York). Chemical analysis, chemical modification, post-translational modification, production of fusion proteins, glycosylation of proteins are described (see *e.g.*, Coligan *et al.* (2000) Current Protocols in Protein Science, Vol. 2, John Wiley and Sons, Inc., New York; Ausubel, *et al.* (2001) Current Protocols in Molecular Biology, Vol. 3, John Wiley and Sons, Inc., NY, N.Y., pp. 16.0.5-16.22.17; Sigma-Aldrich, Co. (2001) Products for Life Science Research, St. Louis, Mo.; pp. 45-89; Amersham Pharmacia Biotech (2001) BioDirectory, Piscataway, N.J., pp. 384-391). Production, purification, and fragmentation of polyclonal and monoclonal antibodies are described (Coligan *et al.* (2001) Current Protcols in Immunology, Vol. 1, John Wiley and Sons, Inc., New York; Harlow and Lane (1999) Using Antibodies, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Harlow and Lane, *supra*). Standard techniques for characterizing ligand/receptor interactions are available (see, *e.g.*, Coligan *et al.* (2001) Current Protocols in Immunology, Vol. 4, John Wiley, Inc., New York).

[000172]Methods for flow cytometry, including fluorescence activated cell sorting (FACS), are available (see, *e.g.*, Owens *et al.* (1994) Flow Cytometry Principles for Clinical Laboratory Practice, John Wiley and Sons, Hoboken, N.J.; Givan (2001) Flow Cytometry, 2nd ed.; Wiley-Liss, Hoboken, N.J.; Shapiro (2003) Practical Flow Cytometry, John Wiley and Sons, Hoboken, N.J.). Fluorescent reagents suitable for modifying nucleic acids, including nucleic acid primers and probes, polypeptides, and antibodies, for use, *e.g.*, as diagnostic reagents, are available (Molecular Probes (2003) Catalogue, Molecular Probes, Inc., Eugene, Oreg.; Sigma-Aldrich (2003) Catalogue, St. Louis, Mo.).

[000173]Standard methods of histology of the immune system are described (see *e.g.*, Muller-Harmelink (ed.) (1986) Human Thymus: Histopathology and Pathology, Springer Verlag, New York, N.Y.; Hiatt *et al.* (2000) Color Atlas of Histology, Lippincott, Williams, and Wilkins, Phila, Pa.; Louis *et al.* (2002) Basic Histology: Text and Atlas, McGraw-Hill, New York, N.Y.).

[000174]"Isolated" VEGF antagonists and VEGF receptor fusion proteins (*e.g.*, aflibercept), polypeptides, polynucleotides and vectors, are at least partially free of other biological molecules from the cells or cell culture from which they are produced. Such biological molecules include nucleic acids, proteins, other VEGF antagonists and VEGF receptor fusion proteins, lipids, carbohydrates, or other material such as cellular debris and growth medium. An isolated VEGF antagonist or VEGF receptor fusion protein may further be at least partially free of expression system components such as biological molecules from a host cell or of the growth medium thereof. Generally, the term "isolated" is not intended to refer to a complete absence of such biological molecules (*e.g.*, minor or insignificant amounts of impurity may remain) or to an absence of water, buffers, or salts or to components of a pharmaceutical formulation that includes the VEGF antagonists or VEGF receptor fusion proteins.

[000175]Subject and patient are used interchangeably herein. A subject or patient is a mammal, for example a human, mouse, rabbit, monkey or non-human primate, preferably a human. A subject or patient may be said to be “suffering from” an angiogenic eye disorder such as nAMD. Such a subject or patient has the disorder in one or both eyes. In an embodiment of the invention, a subject or patient (preferably a human) has one or more of the following characteristics (presently or in the past):

1. ≥50 years of age, *e.g.*, 61, 62, 63, 74 or 75;
2. Has active subfoveal CNV secondary to nAMD, *e.g.*, including juxtafoveal lesions that affect the fovea in an eye;
3. Has Best Corrected Visual Acuity (BCVA) Early Treatment Diabetic Retinopathy Study

(ETDRS) letter score of about 78 to 24, 73-78, <73, 58, 59, 60, 61, 62 or 63 (Snellen equivalent of 20/40, 20/63, 20/50, 20/32 or 20/320), *e.g.*, due to DME or wet AMD;

4. Central retinal thickness of ≥300 micrometers or ≥320 micrometers, or about 367, 368, 369, 370, 450, 451, 452, 453, 454 or 455 micrometers; or and/or DME with central involvement in an eye with CRT ≥300 micrometers (or ≥320 micrometers on Spectralis);

5. Total lesion area of about 6 or 7 mm^2, *e.g.*, wherein the lesion type is occult, predominantly classic or minimally classic;

6. DRSS score of better or equal to Level 43, Level 47 or worse;

7. Type 1 or type 2 diabetes mellitus (insulin dependent or non-insulin dependent) (*e.g.*, for about 15 or more years);

8. Hemoglobin A1C (%) of about 7 or 8 or more;

9. Body mass index of about 30 or 31 or more; and/or

10. A history of diabetic retinal oedema, diabetic retinopathy, dry eye, vitreous detachment, retihopathy hypersensitive, retinal hemorrhage, cataract operation, retinal laser coagulation, and intraocular lens implant, hypertension,

and/or, has or lacks any one or more of the following characteristics:

1. Evidence of macular edema due to any cause other than diabetes mellitus in an eye;

2. IOP ≥ 25 mmHg in an eye;

3. History of glaucoma filtration surgery in the past, or likely to need filtration surgery in the future in an eye;

4. Evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye within 4 weeks (28 days) of treatment;

5. Any intraocular inflammation and/or ocular infection in an eye within 12 weeks (84 days) of treatment;

6. History of idiopathic or autoimmune uveitis in an eye;

7. Vitreomacular traction or epiretinal membrane in an eye, *e.g.*, as evident on biomicroscopy or OCT that is thought to affect central vision;

8. Preretinal fibrosis involving the macula in an eye;

9. Any history of macular hole of stage 2 and above in an eye;

10. Current iris neovascularization, vitreous hemorrhage, or tractional retinal detachment visible at the screening assessments in an eye;

11. History of corneal transplant or corneal dystrophy in an eye;

12. Any concurrent ocular condition in an eye which, in the opinion of the treating physician, could either increase the risk to the subject beyond what is to be expected

from standard procedures of IVT injections, or which otherwise may interfere with the VEGF antagonist injection procedure;
13. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of the VEGF antagonist;
14. Any prior systemic (IV) anti-VEGF administration;
15. Uncontrolled diabetes mellitus as defined by hemoglobin A1c (HbA1c) >12%;
16. Uncontrolled blood pressure (defined as systolic >160 mmHg or diastolic >95 mmHg);
17. History of cerebrovascular accident or myocardial infarction within 24 weeks (168 days) of treatment;
18. Renal failure, dialysis, or history of renal transplant;
19. Known sensitivity to any of the compounds to be administered in treatment; and/or
20. Pregnant or breastfeeding woman

[000176]Thus, the present invention includes a method for treating or preventing DR and/or DME, in a subject in need thereof
1. who is ≥50 years of age;
2. who has active subfoveal CNV;
3. who has Best Corrected Visual Acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of about 78 to 24;
4. who has a central retinal thickness of ≥300 micrometers or ≥320 micrometers;
5. who has a lesion area of about 6 or 7 mm^2;
6. who has a DRSS score of better or equal to Level 43, Level 47 or worse; and/or
7. has Type 1 or type 2 diabetes mellitus;
and/or,
1. who lacks evidence of macular edema due to any cause other than diabetes mellitus in an eye;
2. does not have an IOP ≥ 25 mmHg in an eye;
3. who does not have a history of glaucoma filtration surgery in the past, or is not likely to need filtration surgery in the future in an eye;
4. who does not have evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye within 4 weeks (28 days) of treatment;
5. who does not have any intraocular inflammation and/or ocular infection in an eye within 12 weeks (84 days) of treatment;

6. who does not have a history of idiopathic or autoimmune uveitis in an eye;
7. who does not have vitreomacular traction or epiretinal membrane in an eye;
8. who does not have preretinal fibrosis involving the macula in an eye;
9. who does not have any history of macular hole of stage 2 and above in an eye;
10. who does not have current iris neovascularization, vitreous hemorrhage, and/or tractional retinal detachment;
11. who does not have a history of corneal transplant or corneal dystrophy in an eye;
12. who does not have any concurrent ocular condition in an eye which, in the opinion of the treating physician, could either increase the risk to the subject beyond what is to be expected from standard procedures of IVT injections, or which otherwise may interfere with the VEGF antagonist injection procedure;
13. who does not have a history of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of the VEGF antagonist;
14. who has not had any prior systemic (IV) anti-VEGF administration;
15. who does not have uncontrolled diabetes mellitus as defined by hemoglobin A1c (HbA1c) >12%;
16. who does not have uncontrolled blood pressure (defined as systolic >160 mmHg or diastolic >95 mmHg);
17. who does not have a history of cerebrovascular accident or myocardial infarction within 24 weeks (168 days) of treatment;
18. who does not have renal failure, dialysis, or history of renal transplant;
19. who does not have a known sensitivity to any of the compounds to be administered in treatment; and/or
20. who is not pregnant or a breastfeeding woman;
comprising administering to an eye of the subject (preferably by intravitreal injection), a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, preferably aflibercept, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose.

VEGF Antagonists

[000177]The present invention includes methods for using a VEGF antagonist for treating or preventing angiogenic eye disorders. VEGF antagonists include molecules which interfere with the interaction between VEGF and a natural VEGF receptor, *e.g.*, molecules which bind to VEGF or a VEGF receptor and prevent or otherwise hinder the interaction between VEGF and a VEGF receptor. Specific, exemplary VEGF antagonists include anti-VEGF antibodies, anti-VEGF receptor antibodies, and VEGF receptor fusion proteins. Though VEGF receptor fusion proteins, such as aflibercept, are preferred for use in connection with the methods set forth herein, the scope of the present invention includes such methods wherein any of the VEGF antagonists described herein (*e.g.*, scFvs, DARPins, anti-VEGF antibodies) are used in place of such fusion proteins.

[000178]For purposes herein, a "VEGF receptor fusion protein" refers to a molecule that comprises one or more VEGF receptors or domains thereof, fused to another polypeptide, which interferes with the interaction between VEGF and a natural VEGF receptor, *e.g.*, wherein two of such fusion polypeptides are associated thereby forming a homodimer or other multimer. Such VEGF receptor fusion proteins may be referred to as a "VEGF-Trap" or "VEGF Trap". VEGF receptor fusion proteins within the context of the present disclosure that fall within this definition include chimeric polypeptides which comprise two or more immunoglobulin (Ig)-like domains of a VEGF receptor such as VEGFR1 (also known as Flt1) and/or VEGFR2 (also known as Flk1 or KDR), and may also contain a multimerizing domain (for example, an Fc domain). Preferably, the VEGF receptor fusion protein is aflibercept.

[000179]An exemplary VEGF receptor fusion protein is a molecule referred to as VEGF1R2-FcΔC1(a) which is encoded by the nucleic acid sequence of SEQ ID NO:1 or nucleotides 79-1374 or 79-1371 thereof.

[000180]VEGF1R2-FcΔC1(a) comprises three components:

(1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2;

(2) a VEGFR2 component comprising amino acids 130 to 231 of SEQ ID NO:2; and

(3) a multimerization component ("FcΔC1(a)") comprising amino acids 232 to 457 of SEQ ID NO:2 (the C-terminal amino acids of SEQ ID NO:2, *i.e.*, K458, may or may not be included in the VEGF receptor fusion proteins, see U.S. Patent No. 7,396,664 or 7,354,579, incorporated herein for all purposes). Note that amino acids 1 to 26 of SEQ ID NO:2 are the signal sequence.

[000181]If the multimerizing component (MC) of a VEGF receptor fusion protein is derived from an IgG (*e.g.*, IgG1) Fc domain, then the MC has no fewer amino acids than are in amino acids

232 to 457 of SEQ ID NO:2. Thus, the IgG of the MC cannot be truncated to be shorter than 226 amino acids.

[000182]In an embodiment of the invention, the VEGF receptor fusion protein comprises amino acids 27-458 or 27-457 of SEQ ID NO: 2 (*e.g.*, in the form of a homodimer).

atggtcagctactgggacaccggggtcctgctgtgcgcgctgctcagctgtctgcttctcacaggatctagttccgg
aagtgataccggtagacctttcgtagagatgtacagtgaaatccccgaaattatacacatgactgaaggaagggagc
tcgtcattccctgccgggttacgtcacctaacatcactgttactttaaaaaagtttccacttgacactttgatccct
gatggaaaacgcataatctgggacagtagaaagggcttcatcatatcaaatgcaacgtacaaagaaatagggcttct
gacctgtgaagcaacagtcaatgggcatttgtataagacaaactatctcacacatcgacaaaccaatacaatcatag
atgtggttctgagtccgtctcatggaattgaactatctgttggagaaaagcttgtcttaaattgtacagcaagaact
gaactaaatgtggggattgacttcaactgggaataccttcttcgaagcatcagcataagaaacttgtaaaccgaga
cctaaaaacccagtctgggagtgagatgaagaaatttttgagcaccttaactatagatggtgtaacccggagtgacc
aaggattgtacacctgtgcagcatccagtgggctgatgaccaagaagaacagcacatttgtcagggtccatgaaaag
gacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggaccgtcagtcttcctcttcccccaaa
acccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctg
aggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaac
agcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggt
ctccaacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgt
acaccctgcccccatcccgggatgagctgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatccc
agcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggactc
cgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgct
ccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaatga
(SEQ ID NO: 1)

MVSYWDTGVLLCALLSCLLTGSSSGSDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTS
PNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLT
HRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRD
LKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPC
PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY
TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
(SEQ ID NO: 2)

[000183]In an embodiment of the invention, the VEGF receptor fusion protein comprises

(1) an immunoglobin-like (Ig) domain 2 of a first VEGF receptor (*e.g.*, VEGFR1), and

(2) an Ig domain 3 of a second VEGF receptor (*e.g.*, VEGFR2),

(3) and, optionally, further including an Ig domain 4 of the second VEGF receptor (*e.g.*, VEGFR2) and

(4) a multimerizing component (*e.g.*, Fc domain of IgG including the hinge, CH2 and CH3 domains).

[000184]For example, in an embodiment of the invention, the VEGF receptor fusion protein has the following arrangement of said domains:

- [VEGFR1 Ig domain 2]-[VEGFR2 Ig domain 3]-[MC] (*e.g.*, a homodimer thereof) or

- [VEGFR1 Ig domain 2]-[VEGFR2 Ig domain 3]-[VEGFR2 Ig domain 4]-[MC] (*e.g.*, a homodimer thereof).

[000185]Note that the present disclosure also includes, within its scope, high concentration formulations including, instead of a VEGF receptor fusion protein, a VEGF binding molecule or anti-VEGF antibody or antigen-binding fragments thereof or biopolymer conjugate thereof (*e.g.*, KSI-301), *e.g.*,

- bevacizumab (*e.g.*, at a concentration of about 80-90 or 88 mg/ml),
- ranibizumab (*e.g.*, at a concentration of about 20-40 mg/ml, *e.g.*, 21-35, 21 or 35 mg/ml),
- an anti-VEGF aptamer such as pegaptanib (*e.g.*, pegaptanib sodium),
- a single chain (*e.g.*, V_L-V_H) anti-VEGF antibody such as brolucizumab (*e.g.*, at a concentration of about 200-400 or 200, 210, 400 or 420 mg/ml),
- an anti-VEGF DARPin such as the Abicipar Pegol DARPin (*e.g.*, at a concentration of about 70-140, 70 or 140 mg/ml), or
- a bispecific anti-VEGF antibody, *e.g.*, which also binds to ANG2, such as RG7716 (faricimab) (*e.g.*, at a concentration of about 100-400, 100, 105, 400 or 420 mg/ml).

[000186]In order to minimize the repetitiveness of the embodiments discussed herein, it is contemplated that the scope of the present invention includes embodiments wherein any of the formulations discussed herein include, in place of a VEGF receptor fusion protein, an anti-VEGF antibody or antibody fragment or other VEGF binding molecule as discussed herein (*e.g.*, substituted with an anti-VEGF DARPin) at any of the concentrations discussed herein. For example, the present invention includes a formulation having 35 or 80 mg/ml ranibizumab, a buffer, a thermal stabilizer, a viscosity reducing agent and a surfactant.

[000187]DARPins are Designed Ankyrin Repeat Proteins. DARPins generally contain three to four tightly packed repeats of approximately 33 amino acid residues, with each repeat containing a β-turn and two anti-parallel α-helices. This rigid framework provides protein stability whilst enabling the presentation of variable regions, normally comprising six amino acid residues per repeat, for target recognition.

[000188]An "anti-VEGF" antibody or antigen-binding fragment of an antibody refers to an antibody or fragment that specifically binds to VEGF.

[000189]Illustrative VEGF receptor fusion proteins include aflibercept (EYLEA®, Regeneron Pharmaceuticals, Inc.) or conbercept (sold commercially by Chengdu Kanghong Biotechnology Co., Ltd.). See International patent application publication no. WO2005/121176 or WO2007/112675. The terms "aflibercept" and "conbercept" include biosimilar versions thereof. A biosimilar version of a reference product (*e.g.*, aflibercept) generally refers to a product

comprising the identical amino acid sequence, but includes products which are biosimilar under the U.S. Biologics Price Competition and Innovation Act.

[000190]The present invention also includes embodiments including administering one or more further therapeutic agents in addition to VEGF antagonist, for example, administering (one or more doses of) a second VEGF antagonist, an antibiotic, anesthetic (*e.g.*, local anesthetic) to the eye receiving an injection, a non-steroidal anti-inflammatory drug (NSAID), a steroid (*e.g.*, a corticosteroid, dexamethasone), triamcinolone acetonide (TA), methotrexate, rapamycin, an anti-tumor necrosis factor alpha drug (*e.g.*, infliximab), daclizumab, and/or a complement component (*e.g.*, C3 or C5) inhibitor.

Pharmaceutical Formulations

[000191]The present invention includes methods in which the VEGF antagonist that is administered to the subject's eye is contained within a pharmaceutical formulation. The pharmaceutical formulation includes a VEGF antagonist along with a pharmaceutically acceptable carrier. Other agents may be incorporated into the pharmaceutical formulation to provide improved transfer, delivery, tolerance, and the like. The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the VEGF antagonist is administered. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences (15th ed, Mack Publishing Company, Easton, Pa., 1975), *e.g.*, Chapter 87 by Blaug, Seymour, therein.

[000192]Pharmaceutical formulations for use in a method of the present invention can be "high concentration". High concentration pharmaceutical formulations of the present invention include VEGF antagonist, *e.g.*, VEGF receptor fusion protein, at a concentration of at least 41 mg/ml, of at least 80 mg/ml, of at least 100 mg/ml, of at least 125 mg/ml, of at least 140 mg/ml, of at least 150 mg/ml, of at least 175 mg/ml, of at least 200 mg/ml, of at least 225 mg/ml, of at least 250 mg/ml, or of at least 275 mg/ml. "High concentration" can refer to formulations that include a concentration of VEGF antagonist of from about 140 mg/ml to about 160 mg/ml, at least about 140 mg/ml but less than 160 mg/ml, from about 41 mg/ml to about 275 mg/ml, from about 70 mg/ml to about 75 mg/ml or from about 80 mg/ml to about 250 mg/ml. In some aspects, the VEGF antagonist concentration in the formulation is about any of the following concentrations: 41 mg/ml; 42 mg/ml; 43 mg/ml; 44 mg/ml; 45 mg/ml; 46 mg/ml; 47 mg/ml; 48 mg/ml; 49

mg/ml; 50mg/ml; 51 mg/ml; 52 mg/ml; 53 mg/ml; 54 mg/ml; 55 mg/ml; 56 mg/ml; 57 mg/ml; 58 mg/ml; 59 mg/ml; 60 mg/ml; 61 mg/ml; 62 mg/ml; 63 mg/ml; 64 mg/ml; 65 mg/ml; 66 mg/ml; 67 mg/ml; 68 mg/ml; 69 mg/ml; 70 mg/ml; 71 mg/ml; 72 mg/ml; 73 mg/ml; 74 mg/ml; 75 mg/ml; 76 mg/ml; 77 mg/ml; 78 mg/ml; 79 mg/ml; 80 mg/ml; 81 mg/ml; 82mg/ml; 83 mg/ml; 84 mg/ml; 85 mg/ml; 86 mg/ml; 87mg/ml; 88 mg/ml; 89 mg/ml; 90 mg/ml; 91 mg/ml; 92 mg/ml; 93 mg/ml; 94 mg/ml; 95mg/ml; 96 mg/ml; 97 mg/ml; 98 mg/ml; 99 mg/ml; 100 mg/ml; 101 mg/ml; 102 mg/ml; 103 mg/ml; 104 mg/ml; 105 mg/ml; 106mg/ml; 107 mg/ml; 108 mg/ml; 109 mg/ml; 110 mg/ml; 111 mg/ml; 112 mg/ml; 113 mg/ml; 113.3 mg/ml; 114 mg/ml; 114.1 mg/ml; 114.2 mg/ml; 114.3 mg/ml; 114.4 mg/ml; 114.5 mg/ml; 114.6 mg/ml, 114.7 mg/ml, 114.8 mg/ml; 114.9 mg/ml; 115 mg/ml; 116 mg/ml; 117 mg/ml; 118 mg/ml; 119 mg/ml; 120 mg/ml; 121 mg/ml; 122 mg/ml; 123 mg/ml; 124 mg/ml; 125 mg/ml; 126 mg/ml; 127mg/ml; 128 mg/ml; 129 mg/ml; 130 mg/ml; 131 mg/ml; 132 mg/ml; 133 mg/ml; 133.3 mg/ml; 133.4 mg/ml, 134 mg/ml; 135 mg/ml; 136 mg/ml; 137 mg/ml; 138 mg/ml; 139 mg/ml; 140 mg/ml; 141 mg/ml; 142 mg/ml; 143 mg/ml; 144 mg/ml; 145 mg/ml; 146 mg/ml; 147 mg/ml; 148 mg/ml; 149 mg/ml; 150 mg/ml; 151 mg/ml; 152 mg/ml; 153 mg/ml; 154mg/ml; 155 mg/ml; 156 mg/ml; 157mg/ml; 158 mg/ml; 159 mg/ml; 160 mg/ml; 161 mg/ml; 162 mg/ml; 163 mg/ml; 164 mg/ml; 165 mg/ml; 166 mg/ml; 167 mg/ml; 168 mg/ml; 169 mg/ml; 170 mg/ml; 171 mg/ml; 172 mg/ml; 173 mg/ml; 174 mg/ml; 175 mg/ml; 176 mg/ml; 177 mg/ml; 178 mg/ml; 179 mg/ml; 180 mg/ml; 181 mg/ml; 182 mg/ml; 183 mg/ml; 184 mg/ml; 185 mg/ml; 186 mg/ml; 187 mg/ml; 188 mg/ml; 189 mg/ml; 190 mg/ml; 191 mg/ml; 192 mg/ml; 193 mg/ml; 194 mg/ml; 195 mg/ml; 196 mg/ml; 197 mg/ml; 198 mg/ml; 199 mg/ml; 200 mg/ml; 201 mg/ml; 202 mg/ml; 203 mg/ml; 204 mg/ml; 205 mg/ml; 206 mg/ml; 207 mg/ml; 208 mg/ml; 209 mg/ml; 210 mg/ml; 211 mg/ml; 212 mg/ml; 213 mg/ml; 214 mg/ml; 215 mg/ml; 216 mg/ml; 217 mg/ml; 218 mg/ml; 219 mg/ml; 220 mg/ml; 221 mg/ml; 222 mg/ml; 223 mg/ml; 224 mg/ml; 225 mg/ml; 226 mg/ml; 227 mg/ml; 228 mg/ml; 229 mg/ml; 230 mg/ml; 231 mg/ml; 232 mg/ml; 233 mg/ml; 234 mg/ml; 235 mg/ml; 236 mg/ml; 237mg/ml; 238 mg/ml; 239 mg/ml; 240 mg/ml; 241 mg/ml; 242 mg/ml; 243 mg/ml; 244 mg/ml; 245 mg/ml; 246 mg/ml; 247 mg/ml; 248 mg/ml; 249 mg/ml; 250 mg/ml; 251 mg/ml; 252 mg/ml; 253 mg/ml; 254 mg/ml; 255 mg/ml; 256 mg/ml; 257 mg/ml; 258 mg/ml; 259 mg/ml; 260 mg/ml; 261 mg/ml; 262 mg/ml; 263 mg/ml; 264 mg/ml; 265 mg/ml; 266 mg/ml; 267 mg/ml; 268 mg/ml; 269 mg/ml; 270 mg/ml; 271 mg/ml; 272 mg/ml; 273 mg/ml; 274 mg/ml; or 275 mg/ml. Other VEGF antagonist concentrations are contemplated herein, as long as the concentration functions in accordance with embodiments herein.

[000193]In an embodiment of the invention, a pharmaceutical formulation for use in a method of the present invention is of such a concentration as to contain about 4, 6, 8, 10, 12, 14, 16, 18 or 20 mg VEGF receptor fusion protein (*e.g.*, aflibercept), or the amount of such protein in any of the acceptable doses thereof which are discussed herein, in about 100 µl or less, about 75 µl or less or about 70 µl or less, *e.g.*, about 50 µl; 51 µl; 52 µl; 53 µl; 54 µl; 55 µl; 56 µl; 57 µl; 58 µl; 59 µl; 60 µl; 61 µl; 62 µl; 63 µl; 64 µl; 65 µl; 66 µl; 67 µl; 68 µl; 69 µl; 70 µl; 71 µl; 72 µl; 73 µl; 74 µl; 75 µl; 76 µl; 77 µl; 78 µl; 79 µl; 80 µl; 81 µl; 82 µl; 83 µl; 84 µl; 85 µl; 86 µl; 87 µl; 88 µl; 89 µl; 90 µl; 91 µl; 92 µl; 93 µl; 94 µl; 95 µl; 96 µl; 97 µl; 98 µl; 99 µl; or 100 µl.

[000194]The present invention includes methods of using (as discussed herein) any of the formulations set forth under "*Illustrative Formulations*" herein, but wherein the concentration of the VEGF receptor fusion protein (*e.g.*, aflibercept) is substituted with a concentration which is set forth in this section ("VEGF Receptor Fusion Proteins and Other VEGF inhibitors").

[000195]Buffers for use in pharmaceutical formulations herein that may be used in a method of the present invention refer to solutions that resist pH change by use of acid-base conjugates. Buffers are capable of maintaining pH in the range of from about 5.0 to about 6.8, and more typically, from about 5.8 to about 6.5, and most typically, from about 6.0 to about 6.5. In some cases, the pH of the formulation of the present invention is about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, about 6.5, about 6.6, about 6.7, or about 6.8. Example buffers for inclusion in formulations herein include histidine-based buffers, for example, histidine and histidine hydrochloride or histidine acetate. Buffers for inclusion in formulations herein can alternatively be phosphate-based buffers, for example, sodium phosphate, acetate-based buffers, for example, sodium acetate or acetic acid, or can be citrate-based, for example, sodium citrate or citric acid. It is also recognized that buffers can be a mix of the above, as long as the buffer functions to buffer the formulations in the above described pH ranges. In some cases, the buffer is from about 5 mM to about 25 mM, or more typically, about 5 mM to about 15 mM. Buffers can be about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, about 20 mM, about 21 mM, about 22 mM, about 23 mM, about 24 mM, or about 25 mM.

[000196]In an embodiment of the invention, a histidine-based buffer is prepared using histidine and histidine monohydrochloride.

[000197]Surfactant for use herein refers to ingredients that protect the higher concentration of VEGF antagonist, *e.g.*, VEGF receptor fusion protein, from various surface and interfacial

induced stresses. As such, surfactants can be used to limit or minimize VEGF receptor fusion protein aggregation, and promote protein solubility. Suitable surfactants herein have been shown to be non-ionic, and can include surfactants that have a polyoxyethylene moiety. Illustrative surfactants in this category include: polysorbate 20, polysorbate 80, poloxamer 188, polyethylene glycol 3350, and mixtures thereof. Surfactants in the formulations can be present at from about 0.02% to about 0.1% weight per volume (w/v), and more typically, about 0.02% to about 0.04% (w/v). In some cases, the surfactant is about 0.02% (w/v), about 0.03% (w/v), about 0.04% (w/v), about 0.05% (w/v), about 0.06% (w/v), about 0.07% (w/v), about 0.08% (w/v), about 0.09% (w/v), or about 0.1% (w/v).

[000198]Thermal stabilizers for use in pharmaceutical formulations that may be used in methods set forth herein refers to ingredients that provide thermal stability against thermal denaturation of the VEGF antagonist, *e.g.*, VEGF receptor fusion protein, as well as protect against loss of VEGF receptor fusion protein potency or activity. Suitable thermal stabilizers include sugars, and can be sucrose, trehalose, sorbitol or mannitol, or can be amino acids, for example L-proline, L-arginine (*e.g.*, L-arginine monohydrochloride), or taurine. Additionally, thermal stabilizers may also include substituted acrylamides or propane sulfonic acid, or may be compounds like glycerol.

[000199]In some cases, the pharmaceutical formulations for use in a method herein include both a sugar and taurine, a sugar and an amino acid, a sugar and propane sulfonic acid, a sugar and taurine, glycerol and taurine, glycerol and propane sulfonic acid, an amino acid and taurine, or an amino acid and propane sulfonic acid. In addition, formulations can include a sugar, taurine and propane sulfonic acid, glycerol, taurine and propane sulfonic acid, as well as L-proline, taurine and propane sulfonic acid.

[000200]Embodiments herein may have thermal stabilizers present alone, each independently present at a concentration of, or present in combination at a total concentration of, from about 2% (w/v) to about 10% (w/v) or 4% (w/v) to about 10% (w/v), or about 4% (w/v) to about 9% (w/v), or about 5% (w/v) to about 8% (w/v). Thermal stabilizers in the formulation can be at a concentration of about 2% (w/v), about 2.5% (w/v), about 3% (w/v), about 4% (w/v), about 5% (w/v), about 6% (w/v), about 7% (w/v), about 8% (w/v), about 9% (w/v), about 10% (w/v) or about 20% (w/v).

[000201]With respect to taurine and propane sulfonic acid, in an embodiment of the invention, these thermal stabilizers can be present in the formulations at about from 25 mM to about 100 mM, and more typically from about 50 mM to about 75 mM (as compared to the other thermal stabilizers).

[000202]Viscosity reducing agents typically are used to reduce or prevent protein aggregation. Viscosity reducing agents for inclusion herein include: sodium chloride, magnesium chloride, D- or L-arginine (*e.g.*, L-arginine monohydrochloride), lysine, or mixtures thereof. When present herein, viscosity reducing agents can be present at from about 10 mM to about 100 mM, and more typically from about 30 mM to about 75 mM, and even more typically from about 40 mM to about 70 mM. In some cases, the viscosity reducing agent is present at about 10 mM, about 15 mM, about 20 mM, about 25 mM, about 30 mM, about 35 mM, about 40 mM, about 45 mM, about 50 mM, about 55 mM, about 60 mM, about 65 mM, about 70 mM, about 75 mM, about 80 mM, about 85 mM, about 90 mM, about 95 mM or about 100 mM.

[000203]Pharmaceutical formulations for use in a method as set forth herein can also have a pharmaceutically acceptable viscosity for ocular administration, for example, intravitreal injection. Viscosity generally refers to the measure of resistance of a fluid which is being deformed by either shear stress or tensile stress (typically measured by techniques known in the art, viscometer or rheometer, for example). Typical viscosities of formulations for use in a method set forth herein are from about 5.0 cP (centipoise) to about 15 cP, from about 11 cP to about 14 cP, from about 12 cP to about 15 cP or from about 11 cP to about 12 cP. As such, formulation viscosity herein can be about 5.0 cP, about 6.0, about 7.1 cP, about 7.2 cP, about 7.3 cP, about 7.4 cP, about 7.5 cP, about 7.6 cP, about 10 cP, about 10.5 cP, about 11.0 cP, about 11.5 cP, about 12.0 cP, about 12.5 cP, about 13.0 cP, about 13.5 cP, about 14.0 cP, about 14.5 cP, or about 15.0 cP (*e.g.*, when measured at 20°C).

[000204]Various embodiments herein do not require inclusion of an inorganic salt, or other viscosity reducing agent, to maintain these highly useful viscosities. Typically, high concentration protein solutions require viscosity reducing agents to avoid protein aggregation and higher viscosity, making the formulations difficult for intravitreal injection and reducing the potency of the VEGF receptor fusion protein. As such, embodiments herein include methods of using formulations that have had substantially no, or no added, sodium chloride (NaCl), magnesium chloride ($MgCl_2$), D- or L-arginine (*e.g.*, L-arginine hydrochloride), lysine or other viscosity reducing agent.

[000205]Osmolality is a critical attribute for injectable pharmaceutical formulations for use in a method of the present invention. It is desirable to have products match physiological osmotic conditions. Furthermore, osmolality provides confirmation of soluble content in solution. In an embodiment of the invention, the osmolality of a formulation for use in a method of the present invention is less than or equal to about 506 mmol/Kg or from about 250 to about 506 mmol/Kg., *e.g.*, about 250, 260, 270, 280, 290, 299, 300, 310, 314, 315, 316, 324, 343, 346, 349, 369, 384,

403, 426, 430 or 506 mmol/Kg. In an embodiment of the invention, the osmolality is lower than about 250 mmol/Kg.

[000206]Illustrative pharmaceutical formulations for use in the methods of the present invention include the following:

Formulation A: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

Formulation B: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

Formulation C: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

Formulation D: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2.

Formulation E: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

Formulation F: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

Formulation G: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

Formulation H: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

Formulation I: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.0 3% (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

Formulation J: 80 mg/ml aflibercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

Formulation K: 80 mg/ml aflibercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

Formulation L: 80 mg/ml aflibercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.

Formulation M: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
Formulation N: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
Formulation O: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
Formulation P: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2.
Formulation Q: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
Formulation R: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
Formulation S: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation T: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2 (*e.g.*, 6.2), and, optionally, specifically excluding a viscosity reducing agent.
Formulation U: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation V: 150 mg/ml aflibercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation W: 150 mg/ml aflibercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation X: 150 mg/ml aflibercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation Y: 80 mg/ml conbercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
Formulation Z: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.

Formulation AA: 80 mg/ml conbercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
Formulation BB: 80 mg/ml conbercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2.
Formulation CC: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
Formulation DD: 80 mg/ml conbercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
Formulation EE: 80 mg/ml conbercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation FF: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation GG: 80 mg/ml conbercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation HH: 80 mg/ml conbercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation II: 80 mg/ml conbercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation JJ: 80 mg/ml conbercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation KK: 150 mg/ml conbercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
Formulation LL: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
Formulation MM: 150 mg/ml conbercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
Formulation NN: 150 mg/ml conbercept, 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 6.2.

Formulation OO: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
Formulation PP: 150 mg/ml conbercept, 10 mM citrate-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 80, and 40 mM sodium chloride, with a pH of 5.8 to 6.2.
Formulation QQ: 150 mg/ml conbercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation RR: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation SS: 150 mg/ml conbercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation TT: 150 mg/ml conbercept, 10 mM histidine-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation UU: 150 mg/ml conbercept, 10 mM phosphate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation VV: 150 mg/ml conbercept, 10 mM citrate-based buffer, 8 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 80, with a pH of 5.8 to 6.2, and, optionally, specifically excluding a viscosity reducing agent.
Formulation WW: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 50 mM taurine, with a pH of 5.8.
Formulation XX: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 mM histidine-based buffer, 4 % (w/v) proline, 0.03 % (w/v) polysorbate 20, and 50 mM arginine (*e.g.*, arginine hydrochloride), with a pH of 5.8.
Formulation YY: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 mM histidine-based buffer, 2.5 % (w/v) sucrose, 2.0 % (w/v) proline, 0.03 % (w/v) polysorbate 20, and 50 mM taurine, with a pH of 5.8.
Formulation ZZ: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 mM histidine-based buffer, 2.5 % (w/v) sucrose, 2.0 % (w/v) proline, 0.03 % (w/v) polysorbate 20, and 50 mM arginine (*e.g.*, arginine hydrochloride), with a pH of 5.8.

Formulation AAA: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03% (w/v) polysorbate 20, and 50 mM PSA, with a pH of 5.8.
Formulation BBB: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 mM histidine-based buffer, 2.5 % (w/v) sucrose, 2.0 % (w/v) proline, 0.03 % (w/v) polysorbate 20, and 50 mM PSA, with a pH of 5.8.
Formulation CCC: 80, 100, 120 or 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 50 mM arginine (*e.g.*, arginine hydrochloride), with a pH of 5.8.
Formulation DDD: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 mM histidine-based buffer, 4 % (w/v) proline, 0.03 % (w/v) polysorbate 20, and 50 mM PSA, with a pH of 5.8.
Formulation EEE: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 mM histidine-based buffer, 5 % (w/v) sucrose, and 0.03 % (w/v) polysorbate 20 and, optionally, no thermal stabilizer, with a pH of 5.8.
Formulation FFF: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10mM sodium phosphate, 5 % (w/v) sucrose and 0.03 % polysorbate 20 with a pH of 6.2.
Formulation GGG: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5% sucrose; 0.03 % polysorbate 20; 50 mM sodium sulfate
Formulation HHH: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5% sucrose; 0.03 % polysorbate 20; 50 mM sodium thiocyanate
Formulation III: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose, 0.03 % polysorbate 20; 40 mM sodium citrate
Formulation JJJ: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5% Sucrose, 0.03 % polysorbate 20; 50 mM glycine
Formulation KKK: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose, 0.03 % polysorbate 20; 50 mM sodium chloride
Formulation LLL: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03 % polysorbate 20; 50 mM lysine
Formulation MMM: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03% polysorbate 20; 50 mM sodium aspartate
Formulation NNN: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03 % polysorbate 20; 50 mM sodium glutamate
Formulation OOO: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03% polysorbate 20; 50 mM sodium citrate; 50 mM arginine (*e.g.*, arginine hydrochloride)

Formulation PPP: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03% polysorbate 20; 50 mM glycine; 50 mM arginine (*e.g.*, arginine hydrochloride)
Formulation QQQ: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03% polysorbate 20; 50 mM sodium aspartate; 50 mM arginine (*e.g.*, arginine hydrochloride)
Formulation RRR: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM histidine, pH 5.8; 5 % sucrose; 0.03% polysorbate 20; 50 mM sodium glutamate; 50 mM arginine (*e.g.*, arginine hydrochloride)
Formulation SSS: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM His, pH 5.8; 5 % sucrose; 0.03 % polysorbate 20; 10 mM L-arginine (*e.g.*, L-arginine hydrochloride)
Formulation TTT: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept); 20 mM His, pH 5.8; 5 % sucrose; 0.03 % polysorbate 20; 100 mM L-arginine (*e.g.*, L-arginine hydrochloride)
Formulation UUU: 30 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2
Formulation VVV: 30 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2
Formulation WWW: 60 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2
Formulation XXX: 60 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2
Formulation YYY: 120 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2
Formulation ZZZ: 120 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, pH 6.2
Formulation AAAA: 120 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, 50 mM NaCl, pH 6.2
Formulation BBBB: 120 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 % sucrose, 10 mM phosphate, 0.03 % polysorbate 20, 50 mM NaCl, pH 6.2
Formulation CCCC: 140 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 10 mM sodium phosphate, 5 % sucrose, 40 mM sodium chloride, 0.03 % PS20, pH 6.2
Formulation DDDD: 80 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), 20 mM histidine-based buffer, 5 % (w/v) sucrose, 0.03 % (w/v) polysorbate 20, and 50 mM L-arginine (*e.g.*, L-arginine hydrochloride), with a pH of 5.8.

Formulation EEEE: 120.0 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, ± 12 mg/ml), 20 mM histidine-based buffer (*e.g.*, ± 2 mM), 5 % (w/v) sucrose (*e.g.*, ± 0.5%), 0.03 % (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine (*e.g.*, L-arginine hydrochloride) (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1).
Formulation FFFF: 113.3 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, 102-125 mg/ml), 20 mM histidine-based buffer (*e.g.*, ± 2 mM), 5 % (w/v) sucrose (*e.g.*, ± 0.5%), 0.03 % (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine (*e.g.*, L-arginine monohydrochloride) (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1).
Formulation GGGG: 114.3 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, 103-126 mg/ml), 10 mM histidine-based buffer, for example, including Histidine and Histine-HCl (*e.g.*, ± 1 mM), 5 % (w/v) sucrose (*e.g.*, ± 0.5%), 0.03 % (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine (*e.g.*, L-arginine monohydrochloride) (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1).
Formulation HHHH: 100.0 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, ± 10 mg/ml), 20 mM histidine-based buffer (*e.g.*, ± 2 mM), 5 % (w/v) sucrose (*e.g.*, ± 0.5%), 0.03 % (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine (*e.g.*, L-arginine monohydrochloride) (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1).
Formulation IIII: 133.3 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, ± 13 mg/ml), 20 mM histidine-based buffer (*e.g.*, ± 2 mM), 5 % (w/v) sucrose (*e.g.*, ± 0.5%), 0.03 % (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine (*e.g.*, L-arginine monohydrochloride) (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1).
Formulation JJJJ: 150 mg/ml aflibercept (*e.g.*, aflibercept) (*e.g.*, ± 15 mg/ml), 10 mM sodium phosphate, 8% (w/v) sucrose (*e.g.*, ± 0.8%), 0.03% (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%) and 50 mM L-arginine (*e.g.*, arginine hydrochloride), pH 6.2 (*e.g.*, 6.0-6.4 or 5.9-6.5).
Formulation KKKK: 114.3 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept) (*e.g.*, ± 14 mg/ml), 20 mM histidine-based buffer (*e.g.*, ± 2 mM), 5% (w/v) sucrose (*e.g.*, ± 0.5%), 0.03% (w/v) polysorbate 20 (*e.g.*, 0.02-0.04%), and 50 mM L-arginine (*e.g.*, arginine monohydrochloride) (*e.g.*, ± 5 mM), with a pH of 5.8 (*e.g.*, 5.6-6.0 or 5.5-6.1);
[000207]See International Patent Application Publication No. WO2019/217927.
[000208]In an embodiment of the invention, the ≥8 mg VEGF receptor fusion protein, preferably aflibercept, when administered, is in an aqueous pharmaceutical formulation comprising: a VEGF receptor fusion protein comprising two polypeptides that each comprises an immunoglobin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2, and a multimerizing component (*e.g.*, which comprises amino acids 27-457 of SEQ ID NO: 2) at a concentration of

at least about 100 mg/ml; about 5% sucrose; L-arginine (*e.g.*, L-arginine monohydrochloride); a histidine-based buffer (*e.g.*, containing histidine HCl); and about 0.03% surfactant; wherein the formulation has a pH of about 5.0 to about 6.8 (*e.g.*, 5.8 to 6.5, for example 5.8). Preferably the formulation is suitable for intravitreal administration. Other components that may be included are sodium sulfate, sodium thiocyanate, glycine, NaCl, sodium aspartate and/or sodium glutamate. In an embodiment of the invention, the VEGF receptor fusion protein is at a concentration of: about 100 mg/ml; about 111.5 mg/ml; about 112.0 mg/ml; about 113.3 mg/ml; about 114.3 mg/ml; about 115.6 mg/ml; about 116.3 mg/ml; about 120 mg/ml; about 133 mg/ml; about 140 mg/ml; about 150 mg/ml; about 200 mg/ml; or about 250 mg/ml. The formulation may be characterized by (i) an osmolality of about 299 to about 506 mmol/Kg; and/or (ii) a viscosity of from about 6-15 cP at 20°C. The surfactant may be a non-ionic surfactant such as polysorbate 20, polysorbate 80, poloxamer 188, polyethylene glycol 3350 or mixtures thereof. The histidine-based buffer may be at a concentration of about 10 mM to 20 mM. In an embodiment of the invention, the VEGF receptor fusion protein has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8°C.

[000209]In an embodiment of the invention, the ≥8 mg VEGF receptor fusion protein is, when administered in an aqueous pharmaceutical formulation, comprising: at least about 100 mg/ml of a VEGF receptor fusion protein comprising two polypeptides that each comprises an immunoglobin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2, and a multimerizing component (*e.g.*, aflibercept); about 10-100 mM L-arginine; sucrose; a histidine-based buffer; and a surfactant; wherein the formulation has a pH of about 5.0 to about 6.8; wherein the VEGF receptor fusion protein has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8°C.

[000210]In an embodiment of the invention, the aqueous pharmaceutical formulation includes:

- ≥ about 100 mg/ml VEGF receptor fusion protein (*e.g.*, aflibercept), histidine-based buffer and L-arginine;
- about 140 mg/ml aflibercept; 20 mM histidine-based buffer; 5% sucrose; 0.03 % polysorbate 20; 10 mM L-arginine; pH 5.8;
- about 150 ± 15 mg/ml aflibercept, 10 mM phosphate-based buffer, 8 ± 0.8% (w/v) sucrose, 0.02-0.04% (w/v) polysorbate 20 and 50 mM L-arginine, pH 5.9-6.5;

- about 103-126 mg/ml aflibercept, 10 ± 1 mM histidine-based buffer, 5 ± 0.5% (w/v) sucrose, 0.02-0.04% (w/v) polysorbate 20, and 50 ± 5 mM L-arginine, pH 5.5-6.1;
- about 140 mg/ml aflibercept, 10 mM histidine-based buffer, 2.5 % (w/v) sucrose, 2.0 % (w/v) proline, 0.03 % (w/v) polysorbate 20 and 50 mM L-arginine, pH 5.8;
- about 114.3 mg/ml aflibercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20 and 50 mM L-arginine, pH 5.8;
- ≥ about 100 mg/ml aflibercept, histidine-based buffer and L-arginine;
- ≥ about 100 mg/ml aflibercept at about pH 5.8, wherein the formulation forms <3% HMW aggregates after incubation at 5°C for 2 months;
- about 114.3 mg/mL aflibercept; 10 mM – 50 mM histidine-based buffer, sugar, non-ionic surfactant, L-Arginine, pH 5.8;

or

- about 114.3 mg/mL aflibercept; 10 mM His/His-HCl-based buffer, 5% sucrose, 0.03% polysorbate-20, 50 mM L-Arginine, pH 5.8.

[000211]In an embodiment of the invention, the ≥8 mg VEGF receptor fusion protein is, when administered in an aqueous pharmaceutical formulation comprising
aflibercept at a concentration of at least about 100 mg/ml (*e.g.*, about 111.5 mg/ml; 112.0 mg/ml; 113.3 mg/ml; about 114.3 mg/ml; about 115.6 mg/ml; or about 116.3 mg/ml);
a thermal stabilizer which is a sugar, an amino acid, sucrose, mannitol, sorbitol, trehalose, L-proline, glycine, glycerol, taurine or propane sulfonic acid (*e.g.*, at about 2% (w/v) to about 10% (w/v), for example, 5% (w/v));
a buffer which is a histidine-based buffer, a phosphate-based buffer, an acetate-based buffer (*e.g.*, at a concentration of about 5-25 mM, *e.g.*, 10 mM or 20 mM); or a citrate-based buffer;
a non-ionic surfactant, such as for example, polyoxyethylene-based, polysorbate 20, polysorbate 80, poloxamer 188 or polyethylene glycol 3350 (*e.g.*, at a concentration of about 0.02% to about 0.1 % (w/v), *e.g.*, 0.03% (w/v)); and
a viscosity reducing agent which is NaCl, $MgCl_2$, D-arginine, L-arginine or L-lysine (*e.g.*, at a concentration of about 10-100 mM, *e.g.*, 50 mM),
wherein the formulation has a pH of about 5.0 to about 6.8 (*e.g.*, 5.0-6.0 or 5.8).
[000212]In an embodiment of the invention, the aflibercept is at a concentration in the aqueous pharmaceutical formulation of about 100 mg/ml; 101 mg/ml; 102 mg/ml; 103 mg/ml; 104 mg/ml; 105 mg/ml; 106 mg/ml; 107 mg/ml; 108 mg/ml; 109 mg/ml; 110 mg/ml; 111 mg/ml; 112 mg/ml; 113 mg/ml; 113.3 mg/ml; 114 mg/ml; 114.1 mg/ml; 114.2 mg/ml; 114.3 mg/ml; 114.4 mg/ml;

114.5 mg/ml; 114.6 mg/ml, 114.7 mg/ml, 114.8 mg/ml; 114.9 mg/ml; 115 mg/ml; 116 mg/ml; 117 mg/ml; 118 mg/ml; 119 mg/ml; 120 mg/ml; 121 mg/ml; 122 mg/ml; 123 mg/ml; 124 mg/ml; 125 mg/ml; 126 mg/ml; 127 mg/ml; 128 mg/ml; 129 mg/ml; 130 mg/ml; 131 mg/ml; 132 mg/ml; 133 mg/ml; 133.3 mg/ml; 133.4 mg/ml, 134 mg/ml; 135 mg/ml; 136 mg/ml; 137 mg/ml; 138 mg/ml; 139 mg/ml; 140 mg/ml; 141 mg/ml; 142 mg/ml; 143 mg/ml; 144 mg/ml; 145 mg/ml; 146 mg/ml; 147 mg/ml; 148 mg/ml; 149 mg/ml; 150 mg/ml; 151 mg/ml; 152 mg/ml; 153 mg/ml; 154mg/ml; 155 mg/ml; 156 mg/ml; 157mg/ml; 158 mg/ml; 159 mg/ml; 160 mg/ml; 161 mg/ml; 162 mg/ml; 163 mg/ml; 164 mg/ml; 165 mg/ml; 166 mg/ml; 167 mg/ml; 168 mg/ml; 169 mg/ml; 170 mg/ml; 171 mg/ml; 172 mg/ml; 173 mg/ml; 174 mg/ml; 175 mg/ml; 176 mg/ml; 177 mg/ml; 178 mg/ml; 179 mg/ml; 180 mg/ml; 181 mg/ml; 182 mg/ml; 183 mg/ml; 184 mg/ml; 185 mg/ml; 186 mg/ml; 187 mg/ml; 188 mg/ml; 189 mg/ml; 190 mg/ml; 191 mg/ml; 192 mg/ml; 193 mg/ml; 194 mg/ml; 195 mg/ml; 196 mg/ml; 197 mg/ml; 198 mg/ml; 199 mg/ml; 200 mg/ml; 201 mg/ml; 202 mg/ml; 203 mg/ml; 204 mg/ml; 205 mg/ml; 206 mg/ml; 207 mg/ml; 208 mg/ml; 209 mg/ml; 210 mg/ml; 211 mg/ml; 212 mg/ml; 213 mg/ml; 214 mg/ml; 215 mg/ml; 216 mg/ml; 217 mg/ml; 218 mg/ml; 219 mg/ml; 220 mg/ml; 221 mg/ml; 222 mg/ml; 223 mg/ml; 224 mg/ml; 225 mg/ml; 226 mg/ml; 227 mg/ml; 228 mg/ml; 229 mg/ml; 230 mg/ml; 231 mg/ml; 232 mg/ml; 233 mg/ml; 234 mg/ml; 235 mg/ml; 236 mg/ml; 237mg/ml; 238 mg/ml; 239 mg/ml; 240 mg/ml; 241 mg/ml; 242 mg/ml; 243 mg/ml; 244 mg/ml; 245 mg/ml; 246 mg/ml; 247 mg/ml; 248 mg/ml; 249 mg/ml; 250 mg/ml; 251 mg/ml; 252 mg/ml; 253 mg/ml; 254 mg/ml; 255 mg/ml; 256 mg/ml; 257 mg/ml; 258 mg/ml; 259 mg/ml; 260 mg/ml; 261 mg/ml; 262 mg/ml; 263 mg/ml; 264 mg/ml; 265 mg/ml; 266 mg/ml; 267 mg/ml; 268 mg/ml; 269 mg/ml; 270 mg/ml; 271 mg/ml; 272 mg/ml; 273 mg/ml; 274 mg/ml; or 275 mg/ml.

[000213]In an embodiment of the invention, the aqueous pharmaceutical formulation includes aflibercept at a concentration of at least about 100 mg/ml; sucrose, mannitol, sorbitol, trehalose; a histidine-based buffer; polysorbate 20 or polysorbate 80; and L-arginine, at a pH of about 5.0 to about 6.8; wherein the aflibercept has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8ºC.

[000214]In an embodiment of the invention, the sucrose, mannitol, sorbitol or trehalose is at a concentration of about 2-10% (w/v); the L-arginine is at a concentration of about 10-100 mM; the polysorbate 20 or polysorbate 80 is at a concentration of about 0.02-0.1% (w/v); and the histidine-based buffer is at a concentration of about 5-25 mM; at a pH of about 5.0 to about 6.8.

Treatment and Administration

[000215]The present invention provides methods for treating angiogenic eye disorders (*e.g.,* nAMD, DR and/or DME) in a subject in need thereof including the step of administering to an eye of the subject (preferably by intravitreal injection), about 8 mg or more of VEGF antagonist or inhibitor, for example, a VEGF receptor fusion protein, preferably aflibercept, about every 8-24, 12-24, 16-24, 20-24, 21-24, 21, 22, 23 or 24 weeks (preferably, about 24 weeks).

[000216]The present invention provides methods for treating angiogenic eye disorders (*e.g.,* nAMD, DR and/or DME) by sequentially administering to an eye of the subject (preferably by intravitreal injection) an initial loading dose (*e.g.*, 2 mg or more, 4 mg or more or, preferably, about 8 mg or more of VEGF antagonist or inhibitor, for example, a VEGF receptor fusion protein, preferably, aflibercept) (*e.g.*, about every 2-4 or 3-5 weeks, preferably 4) followed by additional doses about every 8-24, 12-24, 16-24, 20-24, 21-24, 21, 22, 23 or 24 weeks (preferably, about 24 weeks). For example, the present invention provides methods for treating or preventing angiogenic eye disorders, such as neovascular age related macular degeneration (nAMD), diabetic macular edema (DME) and/or diabetic retinopathy (DR), by administering to an eye of the subject (preferably, by intravitreal injection), sequentially, one or more (*e.g.*, 3 or 4 or 5) doses of about 8 mg or more of VEGF antagonist (*e.g.*, a VEGF receptor fusion protein, preferably, aflibercept) about every 2-4 or 3-5 weeks, *e.g.*, every month (or about every 28 days, 28 $\pm$ 5 days or about every 4 weeks), followed by one or more doses of about 8 mg or more VEGF antagonist (*e.g.*, a VEGF receptor fusion protein, preferably, aflibercept) every 8-24, 12-24, 16-24, 20-24, 21-24, 21, 22, 23 or 24 weeks (preferably, about 24 weeks) (or about every 6 months or about every other quarter year or about every 168 days). The dosing regimen including the about 24 week tertiary dosing interval may be referred to herein as a 24 week dosing regimen or 8q24 or HDq24. The teritary dosing interval may, in an embodiment of the invention, be 8-24, 12-24, 16-24, 20-24, 21-24, 21, 22, 23 or 24 weeks (preferably, about 24 weeks) weeks.

[000217] "8 mg (±0.8 mg)" includes, for example, 7.2, 8.0, and 8.8 mg.

[000218]The present invention also provides methods for treating angiogenic eye disorders (*e.g.,* nAMD, DR and/or DME) by sequentially administering to any eye of the subject (preferably, by intravitreal injection) an initial loading dose (*e.g.*, 2 mg or more, 4 mg or more or, preferably, about 8 mg or more of VEGF antagonist or inhibitor, for example, a VEGF receptor fusion protein, preferably, aflibercept) (*e.g.*, about every 2-4 or 3-5 weeks) followed by additional doses every 12, 16, 20, 12-16, 12-20, 16-20, 16-24, 8-24, 12-24, 16-24, 20-24, 21-24, 21, 22,

23 or 24 weeks (preferably, about 24 weeks) wherein the patient receives such treatment of at least 60, 64, 68, 72, 76, 80, 84, 88, 92 or 96 or more weeks.

[000219]In addition, the present invention includes methods for treating angiogenic eye disorders (*e.g.*, nAMD, DR and/or DME) by administering to an eye of the subject (preferably by intravitreal injection), one or more times, ≥8 mg VEGF receptor fusion protein, preferably aflibercept, about every 24 weeks; as well as about every 4 weeks for the first 3, 4 or 5 doses followed by dosing about every 24 weeks.

[000220]In an embodiment of the invention, a subject begins receiving the ≥8 mg maintenance doses (preferably by intravitreal injection) of about every 24 weeks after the ≥8 mg monthly loading doses with no intervening doses. The subject enters the maintenance dose phase rapidly/immediately after the loading dose phase. In an embodiment of the invention, the subject continues receiving the ≥8 mg 24-week doses without any intervening doses.

[000221] For example, the present invention also provides methods for treating angiogenic eye disorders (preferably, nAMD, DME or DR) by administering to an eye of the subject (preferably by intravitreal injection):

doses of about ≥8 mg (for example, in about 100 μl or less, about 75 μl or less or about 70 μl or less, *e.g.*, about 50 μl; 51 μl; 52 μl; 53 μl; 54 μl; 55 μl; 56 μl; 57 μl; 58 μl; 59 μl; 60 μl; 61 μl; 62 μl; 63 μl; 64 μl; 65 μl; 66 μl; 67 μl; 68 μl; 69 μl; 70 μl; 71 μl; 72 μl; 73 μl; 74 μl; 75 μl; 76 μl; 77 μl; 78 μl; 79 μl; 80 μl; 81 μl; 82 μl; 83 μl; 84 μl; 85 μl; 86 μl; 87 μl; 88 μl; 89 μl; 90 μl; 91 μl; 92 μl; 93 μl; 94 μl; 95 μl; 96 μl; 97 μl; 98 μl; 99 μl; or 100 μl) about once every 24 weeks.

[000222]In an embodiment of the invention, the subject does not receive a dosing regimen modification (DRM) and/or does not terminate treatment for at least 1, 2, 3, 4 or 5 years.

[000223]The present invention also provides methods for improving visual acuity in subjects with type 1 or type 2 diabetes mellitus (*e.g.*, subjects with neovascular age related macular degeneration (nAMD), diabetic macular edema or diabetic retinopathy), by administering to an eye of the subject (preferably by intravitreal injection), sequentially, one or more (*e.g.*, 3 or 4 or 5) doses about every month (or about every 28 days, 28 ± 5 days or about every 4 weeks), followed by one or more doses every 24 weeks.

[000224]The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept). Thus, the "initial dose" is the dose which is administered (preferably by intravitreal injection) at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered (preferably by intravitreal

injection) after the initial dose; and the "tertiary doses" are the doses which are administered (preferably by intravitreal injection) after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept), but will generally differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept) contained in the initial, secondary and/or tertiary doses will vary from one another (*e.g.*, adjusted up or down as appropriate) during the course of treatment.

[000225]Thus, a dosing regimen of the present invention may be expressed as follows:

a method for treating an angiogenic eye disorder (*e.g.*, nAMD, DME or DR) in a subject in need thereof including administering to an eye of the subject in need thereof (preferably by intravitreal injection),

a single initial dose of about ≥8 mg (for example, in about 100 μl or less, about 75 μl or less or about 70 μl or less, *e.g.*, about 50 μl; 51 μl; 52 μl; 53 μl; 54 μl; 55 μl; 56 μl; 57 μl; 58 μl; 59 μl; 60 μl; 61 μl; 62 μl; 63 μl; 64 μl; 65 μl; 66 μl; 67 μl; 68 μl; 69 μl; 70 μl; 71 μl; 72 μl; 73 μl; 74 μl; 75 μl; 76 μl; 77 μl; 78 μl; 79 μl; 80 μl; 81 μl; 82 μl; 83 μl; 84 μl; 85 μl; 86 μl; 87 μl; 88 μl; 89 μl; 90 μl; 91 μl; 92 μl; 93 μl; 94 μl; 95 μl; 96 μl; 97 μl; 98 μl; 99 μl; or 100 μl) of a VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept), followed by

one or more (*e.g.*, 2, or 3 or 4, preferably 2) secondary doses of the VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept), followed by

one or more tertiary doses of the VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept);

wherein each secondary dose is administered about 2 to 4 weeks (preferably, about 4 weeks) after the immediately preceding dose; and

wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose.

[000226]The present invention also provides methods for treating angiogenic eye disorders (*e.g.*, nAMD, DR or DME) by administering to an eye of the subject in need thereof (preferably by intravitreal injection) about ≥8 mg (for example, in about 100 μl or less, about 75 μl or less or about 70 μl or less, *e.g.*, about 50 μl; 51 μl; 52 μl; 53 μl; 54 μl; 55 μl; 56 μl; 57 μl; 58 μl; 59 μl; 60 μl; 61 μl; 62 μl; 63 μl; 64 μl; 65 μl; 66 μl; 67 μl; 68 μl; 69 μl; 70 μl; 71 μl; 72 μl; 73 μl; 74 μl; 75 μl; 76 μl; 77 μl; 78 μl; 79 μl; 80 μl; 81 μl; 82 μl; 83 μl; 84 μl; 85 μl; 86 μl; 87 μl; 88 μl; 89 μl; 90 μl; 91

μl; 92 μl; 93 μl; 94 μl; 95 μl; 96 μl; 97 μl; 98 μl; 99 μl; or 100 μl) of VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept) on a PRN basis.

[000227]A *pro re nata* (PRN) treatment protocol calls for intervals between doctor visits to remain fixed (*e.g.*, once every 2, 3, 4, 8, 12, 16, 20 or 24 weeks) and decisions to carry out an injection of VEGF receptor fusion protein to be based on the anatomic findings at each respective visit. A capped PRN dosing regimen is PRN wherein subjects must be treated at a certain minimal frequency, *e.g.*, at least once every 2 or 3 or 4 or 6 months.

[000228]Treat & Extend (T&E) regimens call for the time interval between doctor visits to be adjusted based on the patient's clinical course—*e.g.*, if a subject shows no sign of an active disease (*e.g.*, the macula remains dry, without any leakage), the next one or more intervals can be extended; if there is fluid accumulation, the next interval will be shortened. At each visit following T&E, an injection of VEGF receptor fusion protein will be performed; the current clinical status only has an impact on the duration of the next injection interval.

[000229]The present invention includes embodiments wherein, at any point during a HDq24 treatment regimen, the patient can be switched to a PRN, capped PRN or T&E regimen. The PRN, capped PRN and/or T&E may be continued indefinitely or can be stopped at any point and then the HDq24 regimen is re-initiated at any phase thereof. Any HDq24 regimen can be preceded or followed by a period of PRN, capped PRN and/or T&E.

[000230]The present invention includes methods wherein one or more additional, non-scheduled doses, in addition to any of the scheduled initial, secondary and/or tertiary doses of VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept) are administered to a subject. Such doses are typically administered at the discretion of the treating physician depending on the particular needs of the subject.

[000231]Thus, the present invention includes methods comprising administering the required doses of the HDq24 regimen, wherein each of the tertiary doses is administered about 24 weeks after the immediately preceding dose, wherein the treatment interval between two tertiary doses is extended (*e.g.*, from about 4, 8, 12, 16 or 20 weeks to about 24 weeks), for example, until signs of disease activity recur or vision deteriorates and then either continuing dosing at the last tertiary interval used or the penultimate tertiary interval used.

[000232]The present invention includes methods comprising administering the required doses of the HDq24 regimen, wherein the treatment interval between any two tertiary doses is reduced (*e.g.*, from about 24 weeks to about 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 weeks), for example, until signs of disease activity decrease or vision improves

(*e.g.*, BCVA stabilizes or improves and/or CRT stabilizes or reduces) whereupon, optionally, the interval between doses can be extended, *e.g.*, back to a greater interval length.

[000233]For example, in an embodiment of the invention, the interval between doses, *e.g.*, during the 12, 16, 20 or 24 week dosing phase, can be lengthened, for example by 4 week increments as appropriate (*e.g.*, from 20 weeks to 24 weeks), for example if:

- <5 letter loss in BCVA, *e.g.*, from week 12; and/or
- CRT <300 μm on SD-OCT (or <320 μm on Spectralis SD-OCT).

In an embodiment of the invention, the subject receives the initial dose, the secondary doses and, then, 20 week tertiary intervals and, then, after about 1 year, extending the tertiary intervals to about 24 weeks.

[000234]In an embodiment of the invention, a method of treating an angiogenic eye disorder, such as nAMD, DR or DME, as set forth herein includes the step of evaluating BCVA and/or CRT and lengthening the interval as discussed if one or both of the criteria are met.

[000235]For example, in an embodiment of the invention, the interval between doses, *e.g.*, during the 24 week dosing phase, can be shortened (*e.g.*, from 24 weeks to 20, 16, 12 or 8 weeks), for example if:

- greater than 5 or 10 letters are lost in BCVA (ETDRS or Snellen equivalent) (*e.g.*, relative to the BCVA observed at about 12 or 16 weeks after treatment initiation) occurs, for example, due to or in association with persistent or worsening nAMD, DR and/or DME; and/or
- greater than 25 or 50 micrometers increase in CRT is observed (*e.g.*, relative to the CRT observed at about 12 weeks after treatment initiation).

[000236]In an embodiment of the invention, a tertiary dosing interval is increased or decreased at increments of 4 weeks. Decisions to increase or decrease a tertiary dosing interval can be made at one or more office visits to the treating physician.

[000237]In an embodiment of the invention, if the criteria for reducing the interval between doses is met in a subject receiving the HDq24 regimen, the interval between doses is decreased to 20 weeks. In an embodiment of the invention, the interval is not decreased to anything shorter than 8 weeks. In an embodiment of the invention, a method of treating an angiogenic eye disorder such as nAMD, DR or DME as set forth herein includes the step of evaluating BCVA and/or CRT and shortening the interval as discussed if one or both of the criteria are met.

[000238]See Figure 3 or Figure 4.

[000239]Dosing every "24 weeks" refers to dosing about every 6 months, about every 168 days (± 5 days) or about every other quarter or about twice per year.

[000240]Dosing every "month" or after a "month" refers to dosing after about 28 days, about 4 weeks, or about 28 ± 5 days and may encompass up to 5 weeks ± 5 days. Dosing every "4 weeks" or after "4 weeks" refers to dosing after about 28 days (± 5 days), about a month or about 28 (± 5 days), and may encompass up to every 5 weeks (± 5 days).

[000241]Dosing every "2-4 weeks" or after "2-4 weeks" refers to dosing after about 2 weeks (± 5 days), 3 weeks (± 5 days) or 4 weeks (± 5 days). Dosing every "8 weeks" or after "8 weeks" refers to dosing after about 2 months (± 5 days) or about 56 (± 5 days).

[000242]Dosing every "12 weeks" or after "12 weeks" refers to dosing after about 3 months, about 84 days (± 5 days), about 90 days (± 5 days) or about 84 (± 5 days). Dosing every "16 weeks" or after "16 weeks" refers to dosing after about 4 months or about 112 days (± 5 days).

[000243]Dosing every "12-20 weeks" or after "12-20 weeks" refers to dosing after 12, 13, 14, 15, 16, 17, 18, 19 or 20 weeks (± 5 days), preferably about 12-16 weeks (± 5 days), about 12 weeks (± 5 days), about 16 weeks (± 5 days) or about 20 weeks (± 5 days).

[000244]Dosing every "12-20 weeks" refers to dosing after about 12, 13, 14, 15, 16, 17, 18, 19 or 20 weeks (± 5 days), preferably about 12-16 weeks (± 5 days), about 12 weeks (± 5 days), about 16 weeks (± 5 days) or about 20 weeks (± 5 days).

[000245]A dose of ≥ 8 mg encompasses a dose of about 8 mg or doses exceeding 8 mg, for example, about 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg.

[000246]Any dosing frequency specified herein may, in an embodiment of the invention, be expressed as the specific frequency "± 5 days" (*e.g.*, where "24 weeks" is stated, the present invention also includes embodiments such as 24 weeks ± 5 days). The term ± 5 days includes ±1, ±2, ±3, ±4 and/or ±5 days.

[000247]"Sequentially administering" means that each dose of VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept) is administered to the eye of a subject at a different point in time, *e.g.*, on different days separated by a predetermined interval (*e.g.*, hours, days, weeks or months). The present invention includes methods which comprise sequentially administering to the eye of a subject a single initial dose of a VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept), followed by one or more secondary doses of the VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept), followed by one or more tertiary doses of the VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept).

[000248]An effective or therapeutically effective dose of VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept), for treating or preventing an angiogenic eye disorder refers to the amount of VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept) sufficient to alleviate one or more signs and/or symptoms of the disease or condition in the treated subject, whether by inducing the regression or elimination of such signs and/or symptoms or by inhibiting the progression of such signs and/or symptoms. In an embodiment of the invention, an effective or therapeutically effective dose of VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept) is about $\geq$8 mg every month, for 3 doses, followed by once every 24 weeks. In an embodiment of the invention, the alleviation of signs and/or symptoms is achievement, *e.g.*, by 1 year, of a gain of ≥5, 10 or 15 letters BCVA (relative to baseline) (*e.g.*, $\geq$5 letters improvement in a nAMD subject and/or 8-14 letters improvement in a DME patient/subject); achieving a BCVA ≥ 69 letters; achieving no fluid at foveal center; reduction in central retinal thickness (CRT) by about 150 micrometers or more (*e.g.*, below 300 micrometers in an nAMD subject/patient; and/or reduction by at least about 200 micrometers in a DR or RVO patient/subject) or achievement of normal CRT (*e.g.*, about 300 micrometers or less); and/or achievement of no leakage on fluorescein angiography.

[000249]Baseline values refer to values prior to initiation of a treatment (pre-dose).

[000250]An "angiogenic eye disorder" means any disease of the eye which is caused by or associated with the growth or proliferation of blood vessels or by blood vessel leakage. Non-limiting examples of angiogenic eye disorders that are treatable or preventable using the methods of the present invention include:

- age-related macular degeneration (neovascular (nAMD)),
- macular edema (ME),
- macular edema following retinal vein occlusion (ME-RVO),
- retinal vein occlusion (RVO),
- central retinal vein occlusion (CRVO),
- branch retinal vein occlusion (BRVO),
- diabetic macular edema (DME),
- choroidal neovascularization (CNV),
- iris neovascularization,
- neovascular glaucoma,
- post-surgical fibrosis in glaucoma,
- optic disc neovascularization,

- corneal neovascularization,
- retinal neovascularization,
- vitreal neovascularization,
- pannus,
- pterygium,
- vascular retinopathy,
- diabetic retinopathies (DR) (*e.g.*, non-proliferative diabetic retinopathy (*e.g.*, characterized by a Diabetic Retinopathy Severity Scale (DRSS) level of about 47 or 53) or proliferative diabetic retinopathy; *e.g.*, in a subject that does not suffer from DME), and
- Diabetic retinopathy in a subject who has diabetic macular edema (DME).

[000251]The scope of the present invention includes any method set forth herein relating to, for example, nAMD, DR and/or DME, as well as methods relating to an angiogenic eye disorder set forth herein (*e.g.*, ME-RVO).

[000252]The present invention provides methods for treating angiogenic eye disorders (*e.g.*, nAMD, DR and/or DME) in an eye of a subject in need thereof (preferably by intravitreal injection), by sequentially administering initial loading doses (*e.g.*, 2 mg or more, 4 mg or more or, preferably, about 8 mg or more of VEGF antagonist or inhibitor, for example, a VEGF receptor fusion protein such as aflibercept) (*e.g.*, about every 2-4 or 3-5 weeks, preferably every 4 weeks; preferably, three initial loading doses) followed by additional doses about every 24 weeks, wherein the subject achieves and/or maintains, *e.g.*, by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 or 96 weeks after treatment initiation,:

- an improvement in Diabetic Retinopathy Severity Scale (DRSS), *e.g.*, by at least 2 or 3 steps;
- an improvement in best corrected visual acuity;
- a dry retina;
- a gain in best corrected visual acuity;
- a gain in best corrected visual acuity of 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 letters or $\geq$5, $\geq$10 or $\geq$15 letters;
- a BCVA of at least 69 letters;
- a decrease in central retinal thickness (CRT), *e.g.*, by about 100, 125, 150, 175 or 200 micrometers;
- no vascular leakage as measured by fluorescein angiography (FA);

- an improvement from pre-treatment baseline in National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) total score;
- a retina without fluid (total fluid, intraretinal fluid [IRF] and/or subretinal fluid [SRF]) at the foveal center and in center subfield;
- maintenance of a fluid-free retina (total fluid, IRF and/or SRF at foveal center and in the center subfield);
- a lack of macular edema;
- a retina free of fluid on spectral domain optical coherence tomography (SD-OCT); and/or
- Does not deviate from the HDq24 treatment regimen once started.

[000253]In an embodiment of the invention, a subject receiving a HDq24 treatment for an angiogenic eye disorder (*e.g.*, nAMD, DR and/or DME) as set forth herein achieves one or more of the following:

- Does not receive a dose regimen modification, *e.g.*, wherein the interval between doses (*e.g.*, tertiary doses) is reduced from the HDq24, HDq12-20 or HDq12 or HDq16 or HDq20 treatment regimen once started, *e.g.*, for at least 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 or 96 weeks;
- Receives 100% of all scheduled doses, *e.g.*, for at least 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 or 96 weeks;
- Non-inferior BVCA compared to that of aflibercept which is intravitreally dosed at 2 mg approximately every 4 weeks for the first 3, 4 or 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months;
- Increase in BCVA (according to ETDRS letter score) of about 7, 8 or 9 letters by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 or 96, *e.g.*, wherein the baseline BCVA is about 61, 62 and 63;
- Improvement in BCVA, by 4 weeks after initiation of treatment, of about 4 or 5 letters (ETDRS or Snellen equivalent) when on HDq12 or HDq24 regimen; or of about 4 or 5 letters (ETDRS or Snellen equivalent) when on HDq16 or HDq24 regimen;
- Improvement in BCVA, by 8 weeks after initiation of treatment, of about 6 letters (ETDRS or Snellen equivalent) when on HDq12 or HDq24 regimen; or of about 5 or 6 letters (ETDRS or Snellen equivalent) when on HDq16 or HDq24 regimen;

- Improvement in BCVA, by 12 weeks after initiation of treatment, of about 6 or 7 letters (ETDRS or Snellen equivalent) when on HDq12 or HDq24 regimen; or of about 6 letters (ETDRS or Snellen equivalent) when on HDq16 or HDq24 regimen;
- Improvement in BCVA, by 16 weeks after initiation of treatment, of about 6 or 7 letters (ETDRS or Snellen equivalent) when on HDq12 or HDq24 regimen; or of 7 letters (ETDRS or Snellen equivalent) when on HDq16 or HDq24 regimen;
- Improvement in BCVA, by 20 weeks after initiation of treatment, of about 6 letters (ETDRS or Snellen equivalent) when on HDq12 or HDq24 regimen; or of about 6 letters (ETDRS or Snellen equivalent) when on HDq16 or HDq24 regimen;
- Improvement in BCVA, by 24 weeks after initiation of treatment, of about 7 letters (ETDRS or Snellen equivalent) when on HDq12 or HDq24 regimen; or of about 5 or 6 letters (ETDRS or Snellen equivalent) when on HDq16 or HDq24 regimen;
- Improvement in BCVA, by 28 weeks after initiation of treatment, of about 7 or 8 letters (ETDRS or Snellen equivalent) when on HDq12 or HDq24 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on HDq16 or HDq24 regimen;
- Improvement in BCVA, by 32 weeks after initiation of treatment, of about 7 letters (ETDRS or Snellen equivalent) when on HDq12 or HDq24 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on HDq16 or HDq24 regimen;
- Improvement in BCVA, by 36 weeks after initiation of treatment, of 8 letters (ETDRS or Snellen equivalent) when on HDq12 or HDq24 regimen; or of about 6 or 7 letters (ETDRS or Snellen equivalent) when on HDq16 or HDq24 regimen;
- Improvement in BCVA, by 40 weeks after initiation of treatment, of about 8 letters (ETDRS or Snellen equivalent) when on HDq12 or HDq24 regimen; or of about 6 or 7 letters (ETDRS or Snellen equivalent) when on HDq16 or HDq24 regimen;
- Improvement in BCVA, by 44 weeks after initiation of treatment, of about 8 letters (ETDRS or Snellen equivalent) when on HDq12 or HDq24 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on HDq16 or HDq24 regimen;
- Improvement in BCVA, by 48 weeks after initiation of treatment, of about 8 or 9 letters (ETDRS or Snellen equivalent) when on HDq12 or HDq24 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on HDq16 or HDq24 regimen *e.g.*, wherein the baseline BCVA is about 61, 62 or 63 letters (ETDRS or Snellen equivalent);
- Improvement in BCVA, by 60 weeks after initiation of treatment, of about 8 or 9 letters (ETDRS or Snellen equivalent) when on HDq12 or HDq24 regimen; or of about 7 or 8 letters

(ETDRS or Snellen equivalent) when on HDq16 or HDq24 regimen, *e.g.*, wherein the baseline BCVA is about 61, 62 or 63 letters (ETDRS or Snellen equivalent);

- Improvement in BCVA, by 96 weeks after initiation of treatment, of about 5 or 6 letters (ETDRS or Snellen equivalent) when on HDq12 or HDq24 regimen; or of about 5, 6 or 7 letters (ETDRS or Snellen equivalent) when on HDq16 or HDq24 regimen, *e.g.*, wherein the baseline BCVA is about 60, 61, 62 or 63 letters (ETDRS or Snellen equivalent);
- An improvement in BCVA between weeks 48 and 60 of about 8 or 9 letters, or up to 40 letters (ETDRS or Snellen equivalent) when on the HDq12 or HDq24 regimen, *e.g.*, when the basline BCVA is about 63 or 64; or an improvement in BCVA between weeks 48 and 60 of about 7 or 8 letters or up to 40 letters (ETDRS or Snellen equivalent) when on the HDq16 or HDq24 regimen *e.g.*, when the basline BCVA is about 61 or 62;
- An improvement in BCVA by about week 8 after initiation of treatment which is maintained (*e.g.*, within about $\pm$1 or $\pm$2 ETDRS letters or Snellen equivalent) thereafter during the treatment regimen, *e.g.*, to at least week 48;
- Improvement in best corrected visual acuity (according to ETDRS letter score) (*e.g.*, by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment);
- Improvement in best corrected visual acuity (BVCA) by week 4, week 8, week 12, week 16, week 20, week 24, week 28, week 32, week 36, week 40, week 44, or week 48 from start of treatment;
- Increase in BCVA, *e.g.*, as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart or Snellen equivalent (*e.g.*, by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 or 48 weeks from start of treatment) by ≥4 letters, ≥5 letters, ≥6 letters, ≥7 letters, ≥8 letters, ≥ 9 letters or ≥ 10 letters;
- Between weeks 36 and 48, a change in BCVA score (according to ETDRS letter score) from initiation of treatment of about 7, 8 or 9, *e.g.*, wherein the BCVA at any point between week 36 to 48 is about 60 or 70;
- Between weeks 36 and 48, a change in BCVA score (according to ETDRS letter score) from initiation of treatment of up to 38 letters when on the HDq12 or HDq16 regimen, *e.g.*, wherein BCVA at baseline is between about 27 and 79;
- Between weeks 48 and 60, a change in BCVA score (according to ETDRS letter score) from initiation of treatment of about 7, 8 or 9; *e.g.*, wherein the BCVA at any point between week 48 to 60 is about 69, 70, 71, 72 or 73;

- A BCVA improvement, *e.g.*, by week 48 following treatment initiation, of about 9 or 10 letters (ETDRS or Snellen equivalent) when baseline BCVA is about ≤73 ETDRS letters when on HDq12 or HDq24regimen;
- A BCVA improvement, *e.g.*, by week 48 following treatment initiation, of about 5 or 6 letters (ETDRS or Snellen equivalent) when baseline BCVA is about >73 ETDRS letters when on HDq12 or HDq24 regimen;
- A BCVA improvement, *e.g.*, by week 48 following treatment initiation, of about 8 or 9 letters (ETDRS or Snellen equivalent) when baseline BCVA is about ≤73 ETDRS letters when on HDq16 or HDq24 regimen;
- A BCVA improvement, *e.g.*, by week 48 following treatment initiation, of about 4 or 5 letters (ETDRS or Snellen equivalent) when baseline BCVA is about >73 ETDRS letters when on HDq16 or HDq24 regimen;
- A BCVA improvement, *e.g.*, by week 48 following treatment initiation, of about 7 or 8 letters (ETDRS or Snellen equivalent) when baseline CRT is < about 400 micrometers when on HDq12 or HDq24 regimen;
- A BCVA improvement, *e.g.*, by week 48 following treatment initiation, of about 9 or 10 letters (ETDRS or Snellen equivalent) when baseline CRT is ≥400 micrometers when on HDq12 or HDq24 regimen;
- A BCVA improvement, *e.g.*, by week 48 following treatment initiation, of about 5 or 6 letters (ETDRS or Snellen equivalent) when baseline CRT is < about 400 micrometers when on HDq16 or HDq24 regimen;
- A BCVA improvement, *e.g.*, by week 48 following treatment initiation, of about 9 or 10 letters (ETDRS or Snellen equivalent) when baseline CRT is ≥ about 400 micrometers when on HDq16 or HDq24 regimen;
- Did not lose 5, 10 or 15 letters by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 or 96 (according to ETDRS letter score);
- Gains at least 5, 10 or 15 letter by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 or 96 (according to ETDRS letter score);
- Does not lose 5, 10, 15 or 69 letters or more BCVA (*e.g.*, after week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 or 96 from start of treatment);
- Between weeks 48 and 60, a BCVA score (according to ETDRS letter score) of about 69, 70, 71, 72 or 73;

- BCVA (according to ETDRS letter score) of at least about 69 letters, *e.g.*, by week 48 or 60;
- A BCVA by 4 weeks after initiation of treatment of about 68 letters (ETDRS or Snellen equivalent) when on the HDq12 or HDq24 regimen; or a BCVA of about 66 letters (ETDRS or Snellen equivalent) when on the or HDq24 HDq16 regimen;
- A BCVA by 8 weeks after initiation of treatment of about 70 letters (ETDRS or Snellen equivalent) when on the HDq12 or HDq24 regimen; or a BCVA of about 67 letters (ETDRS or Snellen equivalent) when on the HDq16 or HDq24 regimen;
- A BCVA by 12 weeks after initiation of treatment of about 70 letters (ETDRS or Snellen equivalent) when on the HDq12 or HDq24 regimen; or a BCVA of about 68 letters (ETDRS or Snellen equivalent) when on the HDq16 or HDq24 regimen;
- A BCVA by 16 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 or HDq24 regimen; or a BCVA of about 69 letters (ETDRS or Snellen equivalent) when on the HDq16 or HDq24 regimen;
- A BCVA by 20 weeks after initiation of treatment of about 70 letters (ETDRS or Snellen equivalent) when on the HDq12 or HDq24 regimen; or a BCVA of about 68 letters (ETDRS or Snellen equivalent) when on the HDq16 or HDq24 regimen;
- A BCVA by 24 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 or HDq24 regimen; or a BCVA of about 67 letters (ETDRS or Snellen equivalent) when on the HDq16 or HDq24 regimen;
- A BCVA by 28 weeks after initiation of treatment of about 72 letters (ETDRS or Snellen equivalent) when on the HDq12 or HDq24 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 or HDq24 regimen;
- A BCVA by 32 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 or HDq24 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 or HDq24 regimen;
- A BCVA by 36 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 or HDq24 regimen; or a BCVA of about 68 letters (ETDRS or Snellen equivalent) when on the HDq16 or HDq24 regimen;
- A BCVA by 40 weeks after initiation of treatment of about 72 letters (ETDRS or Snellen equivalent) when on the HDq12 or HDq24 regimen; or a BCVA of about 69 letters (ETDRS or Snellen equivalent) when on the HDq16 or HDq24 regimen;

- A BCVA by 44 weeks after initiation of treatment of about 72 letters (ETDRS or Snellen equivalent) when on the HDq12 or HDq24regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 or HDq24 regimen;
- A BCVA by 48 weeks after initiation of treatment of about 73 letters (ETDRS or Snellen equivalent) when on the HDq12 or HDq24regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 or HDq24 regimen;
- A BCVA by 96 weeks after initiation of treatment of about 66, 67, 68, 69 or 70 letters (ETDRS or Snellen equivalent) when on the HDq12 or HDq24 regimen; or a BCVA of about 66, 67, 68, 69 or 70 letters (ETDRS or Snellen equivalent) when on the HDq16 or HDq24 regimen;
- A BCVA between weeks 36 and 48 of about 71, 72, 73 or 74 (ETDRS or Snellen equivalent) when on the HDq12 or HDq24 regimen, *e.g.*, when the basline BCVA is about 57, 58, 59, 60, 61, 62, 63 or 64; or a BCVA between weeks 36 and 48 of about 69, 70, 71, 72 or 73 (ETDRS or Snellen equivalent) when on the HDq16 or HDq24 regimen *e.g.*, when the basline BCVA is about 55, 56, 57, 58, 59, 60, 61, or 62;
- A BCVA between weeks 48 and 60 of about 69 or 70 or up to 94 (ETDRS or Snellen equivalent) when on the HDq12 or HDq24 regimen, *e.g.*, when the basline BCVA is about 63 or 64; or a BCVA between weeks 48 and 60 of about 72 or 73 or up to 89 (ETDRS or Snellen equivalent) when on the HDq16 or HDq24regimen *e.g.*, when the basline BCVA is about 61 or 62;
- Gain of ≥5, ≥10 or ≥15 letters BCVA (according to ETDRS letter score) (*e.g.*, by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 or 96 from start of treatment);
- ≥ 2 step improvement in Diabetic Retinopathy Severity Scale (DRSS) (*e.g.*, by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 72, 84, 90 or 96 from start of treatment);
- ≥ 3 step improvement in diabetic retinopathy severity scale (DRSS) (*e.g.*, by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 72, 84, 90 or 96 weeks from start of treatment);
- Retina without fluid (total fluid, intraretinal fluid [IRF] and/or subretinal fluid [SRF]) at the foveal center or center subfield (*e.g.*, by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 or 96 from start of treatment) (*e.g.*, as measured by optical coherence tomography (OCT);
- No vascular leakage in the retina as measured by fluorescein angiography (FA) (*e.g.*, by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 or 96 from start of treatment);

- Maintenance of a fluid-free retina (total fluid, IRF and/or SRF at foveal center and in the center subfield) (*e.g.*, by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 or 96 from start of treatment);
- Reduction in total area of fluorescein leakage within ETDRS grid (mm^2) at week 48 or 60 by about 12, 12.6, 13, 13.6, 13.9 or 14 mm^2 or more, or up to abou 57 or 68 mm^2 (*e.g.*, as measured by fluorescein angiography);
- Reduction in total area of fluorescein leakage within ETDRS grid (mm^2) at week 48 by about 13. 13.3, 13.9 or 14 mm^2 or more (*e.g.*, up to about 52 mm^2) (*e.g.*, as measured by fluorescein angiography) when on the HDq12 or HDq24 regimen;
- Reduction in total area of fluorescein leakage within ETDRS grid (mm^2) at week 48 by about 7, 7.7, 8, 9, 9.4 or 10 mm^2 or more (*e.g.*, up to about 55 mm^2) (*e.g.*, as measured by fluorescein angiography) when on the HDq16 or HDq24 regimen;
- Retina free of fluid on spectral domain optical coherence tomography (SD-OCT) (*e.g.*, by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment);
- Retina without fluid (total fluid, intraretinal fluid [IRF] and/or subretinal fluid [SRF]) at the foveal center (*e.g.*, by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 or 48 weeks from start of treatment);
- Dry retina (*e.g.*, by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 or 96 from start of treatment);
- Foveal center without fluid (*e.g.*, by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92 or 96 from start of treatment) (*e.g.*, as measured by optical coherence tomography (OCT);
- A change in central retinal thickness, by 4 weeks after initiation of treatment of about -118 or -118.3 micrometers ($\pm$17, 18 or 19 micrometers) when on the HDq12 or HDq24 regimen; or of about -124 or -125 or -124.9 or -125.5 micrometers ($\pm$17, 18 or 19 micrometers) when on the HDq16 or HDq24 regimen;
- A change in central retinal thickness, by 8 weeks after initiation of treatment of about -137 or -137.4 micrometers ($\pm$17, 18 or 19 micrometers) when on the HDq12 or HDq24 regimen; or of about -139 or -140 or -139.6 or -140.3 micrometers ($\pm$17, 18 or 19 micrometers) when on the HDq16 or HDq24 regimen;
- A change in central retinal thickness, by 12 weeks after initiation of treatment of about -150 or -150.1 micrometers ($\pm$17, 18 or 19 micrometers) when on the HDq12 or HDq24 regimen; or of about -152 or -153 or -152.7 or -153.4 micrometers ($\pm$17, 18 or 19 micrometers) when on the HDq16 or HDq24regimen;

- A change in central retinal thickness, by 16 weeks after initiation of treatment of about -139 or -139.4 micrometers (±17, 18 or 19 micrometers) when on the HDq12 or HDq24 regimen; or of about -145 or -146 or -145.5 or -146.4 micrometers (±17, 18 or 19 micrometers) when on the HDq16 or HDq24 regimen;
- A change in central retinal thickness, by 20 weeks after initiation of treatment of about -117 or -117.1 micrometers (±17, 18 or 19 micrometers) when on the HDq12 or HDq24 regimen; or of about -112 or -113 or -112.5 or -113.3 micrometers (±17, 18 or 19 micrometers) when on the HDq16 or HDq24 regimen;
- A change in central retinal thickness, by 24 weeks after initiation of treatment of about -158 or -158.1 micrometers (±17, 18 or 19 micrometers) when on the HDq12 or HDq24 regimen; or of about -103 or -104 or -103.8 or -104.3 micrometers (±17, 18 or 19 micrometers) when on the HDq16 or HDq24 regimen;
- A change in central retinal thickness, by 28 weeks after initiation of treatment of about -146 or -147 or -146.7 micrometers (±17, 18 or 19 micrometers) when on the HDq12 or HDq24 regimen; or of about -162 or -162.3 micrometers (±17, 18 or 19 micrometers) when on the HDq16 or HDq24 regimen;
- A change in central retinal thickness, by 32 weeks after initiation of treatment of about -132 micrometers (±17, 18 or 19 micrometers) when on the HDq12 or HDq24 regimen; or of about -145 or -146 or -145.8 micrometers (±17, 18 or 19 micrometers) when on the HDq16 or HDq24 regimen;
- A change in central retinal thickness, by 36 weeks after initiation of treatment of about -168 or -168.1 micrometers (±17, 18 or 19 micrometers) when on the HDq12 or HDq24 regimen; or of about -124 or -125 or -124.7 or -125.2 micrometers (±17, 18 or 19 micrometers) when on the HDq16 or HDq24 regimen;
- A change in central retinal thickness, by 40 weeks after initiation of treatment of about -163 micrometers (±17, 18 or 19 micrometers) when on the HDq12 or HDq24regimen; or of about -122 or -123 or -122.5 or -123.1 micrometers (±17, 18 or 19 micrometers) when on the HDq16 or HDq24 regimen;
- A change in central retinal thickness, by 44 weeks after initiation of treatment of about -147 or -148 or -147.4 micrometers (±17, 18 or 19 micrometers) when on the HDq12 or HDq24regimen; or of about -164 or -164.1 or -164.3 micrometers (±17, 18 or 19 micrometers) when on the HDq16 or HDq24 regimen;
- A change in central retinal thickness, by 48 weeks after initiation of treatment of about -171 or -172 or -171.7, -172, -173, -174, -175, -176 or -176.77 micrometers (± 5, 6, 7, 8, 9, 10,

11, 12, 13, 14, 15, 16, 17, 18 or 19 micrometers) when on the HDq12 or HDq24 regimen; or of about -148 or -149 or -148.3 or -149.4 micrometers (±9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or 19 micrometers) when on the HDq16 or HDq24 regimen, *e.g.*, wherein baseline CRT is about 449, 450, 455 or 460 micrometers;

- A change in central retinal thickness, by 96 weeks after initiation of treatment of about -115; -116; -117; -118; -119; -120; -121; -122; -123; -124; -125; -126; -127; -128; -129; -130; -131; -132; -133; -134; -135; -136; -137; -138; -139; -140; -141; -142; -143; or -144 micrometers (± 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or 19 micrometers) when on the HDq12 or HDq24 regimen; or of about -121; -122; -123; -124; -125; -126; -127; -128; -129; -130; -131; -132; -133; -134; -135; -136; -137; -138; -139; -140; -141; -142; -143; -144; -145; -146; -147; -148; -149; -150; -151; -152; -153; micrometers (±9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or 19 micrometers) when on the HDq16 or HDq24 regimen, *e.g.*, wherein baseline CRT is about 350 or 370 micrometers;
- A change in central retinal thickness, by 60 weeks after initiation of treatment of about -181, -182, -181.95, -176, -176.24 or -177 (± 6, 10, 17, 18 or 19 micrometers) micrometers when on the HDq12 or HDq24 regimen (*e.g.*, wherein the baseline CRT is about 460 micrometers); or of about -166, -166.26, -167 or -167.18 micrometers (±8, 9, 10, 17, 18 or 19 micrometers) when on the HDq16 or HDq24 regimen (*e.g.*, wherein the baseline CRT is about 457 micrometers);
- A change in central retinal thickness of about -118 or -119 or -118.3 micrometers, between initiation of treatment (week 0) and week 4 when on the HDq12 or HDq24 regimen;
- A change in central retinal thickness of about -19, -20 or -19.1 micrometers, between weeks 4 and 8 when on the HDq12 or HDq24 regimen;
- A change in central retinal thickness of about -12, -13 or -12.7 micrometers, between weeks 8 and 12 when on the HDq12 or HDq24regimen;
- A change in central retinal thickness of about -40, or -41 micrometers, between weeks 20 and 24 when on the HDq12 or HDq24 regimen;
- A change in central retinal thickness of about -36, -37 or -36.1 micrometers, between weeks 32 and 36 when on the HDq12 or HDq24 regimen;
- A change in central retinal thickness of about -24, -25 or -24.3 micrometers, between weeks 44 and 48 when on the HDq12 or HDq24 regimen;
- A change in central retinal thickness of about -124, -125 or -124.9 micrometers, between initiation of treatment (week 0) and week 4 when on the HDq16 or HDq24 regimen;

- A change in central retinal thickness of about –14, -15 or -14.7 micrometers, between weeks 4 and 8 when on the HDq16 or HDq24 regimen;
- A change in central retinal thickness of about -13, -14 or -13.1 micrometers, between weeks 8 and 12 when on the HDq16 or HDq24 regimen;
- A change in central retinal thickness of about -58, -59 or -58.5 micrometers, between weeks 24 and 28 when on the HDq16 or HDq24 regimen;
- A change in central retinal thickness of about -41, -42 or -41.6 micrometers, between weeks 40 and 44 when on the HDq16 or HDq24 regimen;
- By week 60, a change in BCVA of at least 9 letters when on the HDq12 or HDq24 dosing regimen; and/or a change in BCVA of at least 8 letters when in the HDq16 or HDq24 dosing regimen;
- By week 64, a change in BCVA of at least 9 letters when on the HDq12 or HDq24 dosing regimen; and/or a change in BCVA of at least 8 letters when in the HDq16 or HDq24 dosing regimen;
- By week 68, a change in BCVA of at least 8 letters when on the HDq12 or HDq24 dosing regimen; and/or a change in BCVA of at least 8 letters when in the HDq16 or HDq24 dosing regimen;
- By week 72 , a change in BCVA of at least 8 letters when on the HDq12 or HDq24 dosing regimen; and/or a change in BCVA of at least 6 letters when in the HDq16 or HDq24 dosing regimen;
- By week 76, a change in BCVA of at least 8 letters when on the HDq12 or HDq24 dosing regimen; and/or a change in BCVA of at least 7 letters when in the HDq16 or HDq24 dosing regimen;
- By week 80, a change in BCVA of at least 8 letters when on the HDq12 or HDq24 dosing regimen; and/or a change in BCVA of at least 8 letters when in the HDq16 or HDq24 dosing regimen;
- By week 84, a change in BCVA of at least 8 letters when on the HDq12 or HDq24 dosing regimen; and/or a change in BCVA of at least 8 letters when in the HDq16 or HDq24 dosing regimen;
- By week 88, a change in BCVA of at least 9 letters when on the HDq12 or HDq24 dosing regimen; and/or a change in BCVA of at least 7 letters when in the HDq16 or HDq24 dosing regimen;

- By week 92, a change in BCVA of at least 9 letters when on the HDq12 or HDq24 dosing regimen; and/or a change in BCVA of at least 7 letters when in the HDq16 or HDq24 dosing regimen;
- By week 96, 9 letters when on the HDq12 or HDq24 dosing regimen; and/or a change in BCVA of at least 8letters when in the HDq16 or HDq24 dosing regimen
- By week 60 a BCVA of at least 73 letters and/or when on the HDq12 or HDq24 regimen; and/or a BCVA or at least 70 letters when on the HDq16 or HDq24 regimen;
- By week 64 a BCVA of at least 73 letters and/or when on the HDq12 or HDq24 regimen; and/or a BCVA or at least 70 letters when on the HDq16 or HDq24 regimen;
- By week 68 a BCVA of at least 72 letters and/or when on the HDq12 or HDq24 regimen; and/or a BCVA or at least 69 letters when on the HDq16 or HDq24 regimen;
- By week 72, a BCVA of at least 73 letters and/or when on the HDq12 or HDq24 regimen; and/or a BCVA or at least 68 letters when on the HDq16 or HDq24 regimen;
- By week 76, a BCVA of at least 73 letters and/or when on the HDq12 or HDq24 regimen; and/or a BCVA or at least 68 letters when on the HDq16 or HDq24 regimen;
- By week 80, a BCVA of at least 72 letters and/or when on the HDq12 or HDq24 regimen; and/or a BCVA or at least 69 letters when on the HDq16 or HDq24 regimen;
- By week 84, a BCVA of at least 72 letters and/or when on the HDq12 or HDq24 regimen; and/or a BCVA or at least 70 letters when on the HDq16 or HDq24 regimen;
- By week 88, a BCVA of at least 73 letters and/or when on the HDq12 or HDq24 regimen; and/or a BCVA or at least 69 letters when on the HDq16 or HDq24 regimen;
- By week 92, a BCVA of at least 73 letters and/or when on the HDq12 or HDq24 regimen; and/or a BCVA or at least 69 letters when on the HDq16 or HDq24 regimen;
- By week 96, a BCVA of at least 73 letters and/or when on the HDq12 or HDq24 regimen; and/or a BCVA or at least 69 letters when on the HDq16 or HDq24 regimen;
- By week 60, a change in CRT of at least -176.2 micrometers when on the HDq12 or HDq24 regimen; and/or a change in CRT of at least -167.2 micrometers when on the HDq16 or HDq24 regimen;
- By week 64, a change in CRT of at least -173.4 micrometers when on the HDq12 or HDq24 regimen; and/or a change in CRT of at least -164.3 micrometers when on the HDq16 or HDq24 regimen;

- By week 68, a change in CRT of at least -159.4 micrometers when on the HDq12 or HDq24 regimen; and/or a change in CRT of at least -153.9 micrometers when on the HDq16 or HDq24 regimen;
- By week 72, a change in CRT of at least -166.6 micrometers when on the HDq12 or HDq24 regimen; and/or a change in CRT of at least -134.2 micrometers when on the HDq16 or HDq24 regimen;
- By week 76, a change in CRT of at least -181.1 micrometers when on the HDq12 or HDq24 regimen; and/or a change in CRT of at least -160.8 micrometers when on the HDq16 or HDq24 regimen;
- By week 80 a change in CRT of at least -168.9 micrometers when on the HDq12 or HDq24 regimen; and/or a change in CRT of at least -164 micrometers when on the HDq16 or HDq24 regimen;
- By week 84, a change in CRT of at least -177.5 micrometers when on the HDq12 or HDq24 regimen; and/or a change in CRT of at least -150.2 micrometers when on the HDq16 or HDq24 regimen;
- By week 88, a change in CRT of at least -171.2micrometers when on the HDq12 or HDq24 regimen; and/or a change in CRT of at least -144.3 micrometers when on the HDq16 or HDq24 regimen;
- By week 92, a change in CRT of at least -166.7 micrometers when on the HDq12 or HDq24 regimen; and/or a change in CRT of at least -155.5 micrometers when on the HDq16 or HDq24 regimen;
- By week 96, a change in CRT of at least -185.3 micrometers when on the HDq12 or HDq24 regimen; and/or a change in CRT of at least -155 micrometers when on the HDq16 or HDq24 regimen;
- By week 60, a CRT of 275.5 micrometers when on the HDq12 or HDq24 regimen; and/or 289.5 micrometers when on the HDq16 or HDq24 regimen;
- By week 64 a CRT of 279.4 micrometers when on the HDq12 or HDq24 regimen; and/or 289.6 micrometers when on the HDq16 or HDq24 regimen;
- By week 68, a CRT of 294.5 micrometers when on the HDq12 or HDq24 regimen; and/or 305.3 micrometers when on the HDq16 or HDq24 regimen;
- By week 72, a CRT of 284.2 micrometers when on the HDq12 or HDq24 regimen; and/or 327.2 micrometers when on the HDq16 or HDq24 regimen;

- By week 76, a CRT of 270.6 micrometers when on the HDq12 or HDq24 regimen; and/or 302 micrometers when on the HDq16 or HDq24 regimen;
- By week 80, a CRT of 284.6 micrometers when on the HDq12 or HDq24 regimen; and/or 293.5 micrometers when on the HDq16 or HDq24 regimen;
- By week 84, a CRT of 274.7 micrometers when on the HDq12 or HDq24 regimen; and/or 310.8 micrometers when on the HDq16 or HDq24 regimen;
- By week 88, a CRT of 283.7 micrometers when on the HDq12 or HDq24 regimen; and/or 312.3 micrometers when on the HDq16 or HDq24 regimen;
- By week 92, a CRT of 285.7 micrometers when on the HDq12 or HDq24 regimen; and/or 301.8 micrometers when on the HDq16 or HDq24 regimen;
- By week 60, a change in BCVA of at least 7 letters when on the HDq12 or HDq24 regimen; and/or a change in BCVA of at least 7 letters when on the HDq16 or HDq24;
- By week 64, a change in BCVA of at least 7 letters when on the HDq12 or HDq24 regimen; and/or a change in BCVA of at least 6 letters when on the HDq16 or HDq24;
- By week 68, a change in BCVA of at least 6 letters when on the HDq12 or HDq24 regimen; and/or a change in BCVA of at least 6 letters when on the HDq16 or HDq24;
- By week 72 a change in BCVA of at least 6 letters when on the HDq12 or HDq24 regimen; and/or a change in BCVA of at least 6 letters when on the HDq16 or HDq24;
- By week 76 a change in BCVA of at least 6 letters when on the HDq12 or HDq24 regimen; and/or a change in BCVA of at least 6 letters when on the HDq16 or HDq24;
- By week 80 a change in BCVA of at least 6 letters when on the HDq12 or HDq24 regimen; and/or a change in BCVA of at least 6 letters when on the HDq16 or HDq24;
- By week 84 a change in BCVA of at least 6 when on the HDq12 or HDq24 regimen; and/or a change in BCVA of at least 6 when on the HDq16 or HDq24;
- By week 88 a change in BCVA of at least 6 letters when on the HDq12 or HDq24 regimen; and/or a change in BCVA of at least 6 letters when on the HDq16 or HDq24;
- By week 92 a change in BCVA of at least 6 letters when on the HDq12 or HDq24 regimen; and/or a change in BCVA of at least 6 letters when on the HDq16 or HDq24;
- By week 96 a change in BCVA of at least 6 letters when on the HDq12 or HDq24 regimen; and/or a change in BCVA of at least 6 letters when on the HDq16 or HDq24;
- By week 60 a BCVA of 67 letters when on the HDq12 or HDq24 regimen;
- By week 64 a BCVA of 67 letters when on the HDq12 or HDq24 regimen;
- By week 68 a BCVA of 67 letters when on the HDq12 or HDq24 regimen;

- By week 72 a BCVA of 66 letters when on the HDq12 or HDq24 regimen;
- By week 76 a BCVA of 67 letters when on the HDq12 or HDq24 regimen;
- By week 80 a BCVA of 67 letters when on the HDq12 or HDq24 regimen;
- By week 84 a BCVA of 66 letters when on the HDq12 or HDq24 regimen;
- By week 88 a BCVA of 67 letters when on the HDq12 or HDq24 regimen;
- By week 92 a BCVA of 67 letters when on the HDq12 or HDq24 regimen;
- By week 96 a BCVA of 67 letters when on the HDq12 or HDq24 regimen;
- By week 60 a BCVA of 67 letters when on the HDq16 or HDq24 regimen;
- By week 64 a BCVA of 66 letters when on the HDq16 or HDq24 regimen;
- By week 68 a BCVA of 67 letters when on the HDq16 or HDq24 regimen;
- By week 72 a BCVA of 66 letters when on the HDq16 or HDq24 regimen;
- By week 76 a BCVA of 66 letters when on the HDq16 or HDq24 regimen;
- By week 80 a BCVA of 66 letters when on the HDq16 or HDq24 regimen;
- By week 84 a BCVA of 66 letters when on the HDq16 or HDq24 regimen;
- By week 88 a BCVA of 66 letters when on the HDq16 or HDq24 regimen;
- By week 92 a BCVA of 66 letters when on the HDq16 or HDq24 regimen;
- By week 96 a BCVA of 66 letters when on the HDq16 or HDq24 regimen;
- By week 60 a central subfield retinal thickness of 219 micrometers when on the HDq12 or HDq24 regimen;
- By week 64 a central subfield retinal thickness of 226 micrometers when on the HDq12 or HDq24 regimen;
- By week 68 a central subfield retinal thickness of 230 micrometers when on the HDq12 or HDq24 regimen;
- By week 72 a central subfield retinal thickness of 227 micrometers when on the HDq12 or HDq24 regimen;
- By week 76 a central subfield retinal thickness of 226 micrometers when on the HDq12 or HDq24 regimen;
- By week 80 a central subfield retinal thickness of 228 micrometers when on the HDq12 or HDq24 regimen;
- By week 84 a central subfield retinal thickness of 223 micrometers when on the HDq12 or HDq24 regimen;
- By week 88 a central subfield retinal thickness of 226 micrometers when on the HDq12 or HDq24 regimen;

- By week 92 a central subfield retinal thickness of 230 micrometers when on the HDq12 or HDq24 regimen;
- By week 96 a central subfield retinal thickness of 222 micrometers when on the HDq12 or HDq24 regimen;
- By week 60 a central subfield retinal thickness of 222 micrometers when on the HDq16 or HDq24 regimen;
- By week 64 a central subfield retinal thickness of 222 micrometers when on the HDq16 or HDq24 regimen;
- By week 68 a central subfield retinal thickness of 228 micrometers when on the HDq16 or HDq24 regimen;
- By week 72 a central subfield retinal thickness of 234 micrometers when on the HDq16 or HDq24 regimen;
- By week 76 a central subfield retinal thickness of 218 micrometers when on the HDq16 or HDq24 regimen;
- By week 80 a central subfield retinal thickness of 221 micrometers when on the HDq16 or HDq24 regimen;
- By week 84 a central subfield retinal thickness of 223 micrometers when on the HDq16 or HDq24 regimen;
- By week 88 a central subfield retinal thickness of 224 micrometers when on the HDq16 or HDq24 regimen;
- By week 92 a central subfield retinal thickness of 218 micrometers when on the HDq16 or HDq24 regimen;
- By week 96 a central subfield retinal thickness of 221 micrometers when on the HDq16 or HDq24 regimen;
- By week 60 a choroidal neovascularization size (mm^2) of 2.15when on the HDq12 or HDq24 regimen;
- By week 60 a choroidal neovascularization size (mm^2) of 2.65 when on the HDq16 or HDq24 regimen;
- By week 96a choroidal neovascularization size (mm^2) of 2.22 when on the HDq12 or HDq24 regimen;
- By week 96a choroidal neovascularization size (mm^2) of 1.78 when on the HDq16 or HDq24 regimen;
- By week 60 a total lesion area (mm^2) of 5.9 when on the HDq12 or HDq24 regimen;

- By week 60 a total lesion area (mm^2) of 6.3 when on the HDq16 or HDq24 regimen;
- By week 96 a total lesion area (mm^2) of 6.2 when on the HDq12 or HDq24 regimen;
- By week 96 a total lesion area (mm^2) of 6.5 when on the HDq16 or HDq24 regimen;
- Any of the improvements in anatomical (*e.g.*, reduction in central retinal thickness, absolute central retinal thickness or lack of retinal fluid) or visual parameters (*e.g.*, improvement in BCVA or absolute BCVA) specified in Example 1 or Example 2 herein at the particular timepoint indicated (*e.g.*, at week 48, 60, 64, 68, 72, 76, 80, 84, 88, 92 or 96), in the tables and/or figures therein, for that parameter;
- A reduction in CRT by week 4, 5, 6, 7 or 8 after initiation of treatment which is maintained (*e.g.*, within about $\pm$17, $\pm$18 or $\pm$19 micrometers) thereafter during the treatment regimen, *e.g.*, to at least week 48;
- Decrease in central retinal thickness (CRT), for example, by about 100, 125, 150, 175 or 200 micrometers (*e.g.*, by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment);
- Reduction in CRT of about 148-182 micrometers (*e.g.*, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183) by week 48 or 60 (*e.g.*, as measured by optical coherence tomography (OCT)), for example, wherein the baseline CRT is about 449, 450, 455 or 460 micrometers;
- Decrease in central retinal thickness (CRT), for example, by at least about 100, 125, 130, 135, 140, 145, 149, 150, 155, 160, 165, 170, 171, 172, 173, 174 or 175 micrometers (*e.g.*, by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 or 48 from start of treatment);
- Ocular (*e.g.*, intraocular pressure) and non-ocular safety (*e.g.*, hypertensive events or APTC events) or death rate, in a subject suffering from an angiogenic eye disorder, *e.g.*, DR or DME, similar to that of aflibercept which is intravitreally dosed at 2 mg approximately every 4 weeks for the first 3, 4 or 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months;
- At about 0.1667 days after the first dose, free aflibercept concentration in plasma of about 0.149 ($\pm$0.249) mg/l; *e.g.*, wherein at baseline free aflibercept concentration in plasma not detectable, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- At about 0.3333 days after the first dose, free aflibercept concentration in plasma of about 0.205 ($\pm$0.250) mg/l; *e.g.*, wherein at baseline free aflibercept concentration in plasma not detectable, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;

- At about 1 day after the first dose, free aflibercept concentration in plasma of about 0.266 (±0.211) mg/l; *e.g.*, wherein at baseline free aflibercept concentration in plasma not detectable, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- At about 2 days after the first dose, free aflibercept concentration in plasma of about 0.218 (±0.145) mg/l; *e.g.*, wherein at baseline free aflibercept concentration in plasma not detectable, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- At about 4 days after the first dose, free aflibercept concentration in plasma of about 0.140 (±0.0741) mg/l; *e.g.*, wherein at baseline free aflibercept concentration in plasma not detectable, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- At about 7 days after the first dose, free aflibercept concentration in plasma of about 0.0767 (±0.0436) mg/l; *e.g.*, wherein at baseline free aflibercept concentration in plasma not detectable, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- At about 14 days after the first dose, free aflibercept concentration in plasma of about 0.0309 (±0.0241) mg/l; *e.g.*, wherein at baseline free aflibercept concentration in plasma not detectable, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- At about 21 days after the first dose, free aflibercept concentration in plasma of about 0.0171 (±0.0171) mg/l; *e.g.*, wherein at baseline free aflibercept concentration in plasma not detectable, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- At about 28 days after the first dose, free aflibercept concentration in plasma of about 0.00730 (±0.0113) mg/l; *e.g.*, wherein at baseline free aflibercept concentration in plasma not detectable, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- At about 0.1667 days after the first dose, adjusted bound aflibercept concentration in plasma of about 0.00698 (±0.0276) mg/l; *e.g.*, wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept concentration, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- At about 0.3333 days after the first dose, adjusted bound aflibercept concentration in plasma of about 0.00731 (±0.0279) mg/l; *e.g.*, wherein at baseline there is about 0.00583 mg/l

(±0.0280) adjusted bound aflibercept concentration, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;

- At about 1 days after the first dose, adjusted bound aflibercept concentration in plasma of about 0.0678 (±0.0486) mg/l; *e.g.*, wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept concentration, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- At about 2 days after the first dose, adjusted bound aflibercept concentration in plasma of about 0.138 (±0.0618) mg/l; *e.g.*, wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept concentration, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- At about 4 days after the first dose, adjusted bound aflibercept concentration in plasma of about 0.259 (±0.126) mg/l; *e.g.*, wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept concentration, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- At about 7 days after the first dose, adjusted bound aflibercept concentration in plasma of about 0.346 (±0.151) mg/l; *e.g.*, wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept concentration, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- At about 14 days after the first dose, adjusted bound aflibercept concentration in plasma of about 0.374 (±0.110) mg/l; *e.g.*, wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept concentration, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- At about 21 days after the first dose, adjusted bound aflibercept concentration in plasma of about 0.343 (±0.128) mg/l; *e.g.*, wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept concentration, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- At about 28 days after the first dose, adjusted bound aflibercept concentration in plasma of about 0.269 (±0.149) mg/l; *e.g.*, wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept concentration, for example, wherein the subject has not received intravitreal VEGF inhibitor (*e.g.*, aflibercept) treatment for at least 12 weeks;
- The maximum concentration of free aflibercept in the plasma is reached about 0.965 (*e.g.*, about 1) day after the first dose;
- Reaches a maximum concentration of about 0.310 mg/l (±0.263) free aflibercept in the plasma;

- Individual free aflibercept concentration (C_{max}) in the plasma of from about 0 to about 1.08 mg/L (0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0 or 1.1 mg/l);
- Free aflibercept in the plasma maximum (mg/l) per dose (mg) of aflibercept of about 0.0388 (±0.00328) mg/l/mg;
- The maximum concentration of adjusted bound aflibercept in the plasma is reached about 14 days after the first dose;
- Reaches a maximum concentration of about 0.387 mg/l (±0.135) adjusted bound aflibercept in the plasma;
- Adjusted bound aflibercept concentration in the plasma of from about 0.137 to about 0.774 mg/L (0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 mg/l);
- Adjusted bound aflibercept concentration in the plasma maximum (mg/l) per dose (mg) of aflibercept of about 0.0483 (±0.0168) mg/l/mg;
- Does not have anti-drug antibodies against aflibercept after 48 or 60 weeks of treatment;
- Improvement from pre-treatment baseline in National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) total score (*e.g.*, by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment), *e.g.*, by about 4, 5 or 6 when on the HDq12 or HDq24 regimen or by about 2, 3 or 4 when on the HDq16 or HDq24 regimen; *e.g.*, wherein the baseline score is about 76 or 77;
- Lack of macular edema (*e.g.*, by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment); and/or
- Efficacy and/or safety, in a subject suffering from DR or DME, similar to that of aflibercept which is intravitreally dosed at 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months, *e.g.*, wherein efficacy is measured as increase in BCVA and/or reduction in central retinal thickness, *e.g.*, wherein safety is as measured as the incidence of adverse events (treatment-emergent adverse events occurring anytime within 30 days of any injection) such as blood pressure increase, intraocular pressure increase, visual impairment, vitreous floaters, vitreous detachment, iris neovascularization and/or vitreous hemorrhage.

[000254]Thus, the present invention provides the following:

- A method for achieving a non-inferior BVCA compared to that of aflibercept which is intravitreally dosed at 2 mg approximately every 4 weeks for the first 3, 4 or 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME)

comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HD24 regimen) after the immediately preceding dose.

- A method for achieving an increase in BCVA (according to ETDRS letter score) of about 7, 8 or 9 letters by week 60 wherein the baseline BCVA is about 61, 62 and 63; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a BCVA (according to ETDRS letter score) of at least about 69 letters by week 48 or 60; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a BCVA wherein there is not a loss of 5, 10, 15 or 69 letters or more after week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding

dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving an improvement in best corrected visual acuity (according to ETDRS letter score) by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving an improvement in best corrected visual acuity (BVCA) by week 4, week 8, week 12, week 16, week 20, week 24, week 28, week 32, week 36, week 40, week 44, week 48 or week 60 from start of treatment; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving between weeks 48 and 60 from treatment initiation, a BCVA score (according to ETDRS letter score) of about 69, 70, 71, 72 or 73; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving between weeks 36 and 48, a change in BCVA score (according to ETDRS letter score) from initiation of treatment of about 7, 8 or 9, wherein the BCVA

at any point between week 36 to 48 is about 60 or 70; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving between weeks 48 and 60, a change in BCVA score (according to ETDRS letter score) from initiation of treatment of about 7, 8 or 9 wherein the BCVA at any point between week 48 to 60 is about 69, 70, 71, 72 or 73; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving an increase in BCVA as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart or Snellen equivalent by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 or 60 weeks from start of treatment by ≥4 letters, ≥5 letters, ≥6 letters, ≥7 letters, ≥8 letters, ≥ 9 letters or ≥ 10 letters; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a BCVA wherein there is not a loss of 5, 10 or 15 letters by week 48 or 60 (according to ETDRS letter score); in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye

of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving an gain at least 5, 10 or 15 letter by week 48 or 60 (according to ETDRS letter score); in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving an improvement in BCVA, by 4 weeks after initiation of treatment, of about 4 or 5 letters (ETDRS or Snellen equivalent) when on a HDq12 regimen; or of about 4 or 5 letters (ETDRS or Snellen equivalent) when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving an improvement in BCVA, by 8 weeks after initiation of treatment, of about 6 letters (ETDRS or Snellen equivalent) when on a HDq12 regimen; or of about 5 or 6 letters (ETDRS or Snellen equivalent) when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each

secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving an improvement in BCVA, by 12 weeks after initiation of treatment, of about 6 or 7 letters (ETDRS or Snellen equivalent) when on aHDq12 regimen; or of about 6 letters (ETDRS or Snellen equivalent) when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving an improvement in BCVA, by 16 weeks after initiation of treatment, of about 6 or 7 letters (ETDRS or Snellen equivalent) when on a HDq12 regimen; or of 7 letters (ETDRS or Snellen equivalent) when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving an improvement in BCVA, by 20 weeks after initiation of treatment, of about 6 letters (ETDRS or Snellen equivalent) when on a HDq12 regimen; or of about 6 letters (ETDRS or Snellen equivalent) when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding

dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving an improvement in BCVA, by 24 weeks after initiation of treatment, of about 7 letters (ETDRS or Snellen equivalent) when on a HDq12 regimen; or of about 5 or 6 letters (ETDRS or Snellen equivalent) when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving an improvement in BCVA, by 28 weeks after initiation of treatment, of about 7 or 8 letters (ETDRS or Snellen equivalent) when on a HDq12 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving an improvement in BCVA, by 32 weeks after initiation of treatment, of about 7 letters (ETDRS or Snellen equivalent) when on a HDq12 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding

dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving an improvement in BCVA, by 36 weeks after initiation of treatment, of 8 letters (ETDRS or Snellen equivalent) when on a HDq12 regimen; or of about 6 or 7 letters (ETDRS or Snellen equivalent) when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving an improvement in BCVA, by 40 weeks after initiation of treatment, of about 8 letters (ETDRS or Snellen equivalent) when on a HDq12 regimen; or of about 6 or 7 letters (ETDRS or Snellen equivalent) when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving an improvement in BCVA, by 44 weeks after initiation of treatment, of about 8 letters (ETDRS or Snellen equivalent) when on a HDq12 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding

dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving an improvement in BCVA, by 48 weeks after initiation of treatment, of about 8 or 9 letters (ETDRS or Snellen equivalent) when on a HDq12 regimen; or of about 7 or 8 letters (ETDRS or Snellen equivalent) when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving an improvement in BCVA by about week 8 after initiation of treatment which is maintained (within about ±1 or ±2 ETDRS letters or Snellen equivalent) thereafter during the treatment regimen to at least week 48 or 60; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a BCVA by 4 weeks after initiation of treatment of about 68 letters (ETDRS or Snellen equivalent) when on the a HDq12 regimen; or a BCVA of about 66 letters (ETDRS or Snellen equivalent) when on the a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding

dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving a BCVA by 8 weeks after initiation of treatment of about 70 letters (ETDRS or Snellen equivalent) when on the a HDq12 regimen; or a BCVA of about 67 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a BCVA by 12 weeks after initiation of treatment of about 70 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 68 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a BCVA by 16 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 69 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein

each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving a BCVA by 20 weeks after initiation of treatment of about 70 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 68 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a BCVA by 24 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 67 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a BCVA by 28 weeks after initiation of treatment of about 72 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein

each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving a BCVA by 32 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a BCVA by 36 weeks after initiation of treatment of about 71 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 68 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a BCVA by 40 weeks after initiation of treatment of about 72 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 69 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein

each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving a BCVA by 44 weeks after initiation of treatment of about 72 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a BCVA by 48 weeks after initiation of treatment of about 73 letters (ETDRS or Snellen equivalent) when on the HDq12 regimen; or a BCVA of about 70 letters (ETDRS or Snellen equivalent) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a BCVA improvement, by week 48 following treatment initiation, of about 9 or 10 letters (ETDRS or Snellen equivalent) when baseline BCVA is about ≤73 ETDRS letters when on HDq12 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 12 weeks (HDq12 regimen after the immediately preceding dose.

- A method for achieving a BCVA improvement by week 48 following treatment initiation, of about 5 or 6 letters (ETDRS or Snellen equivalent) when baseline BCVA is about >73 ETDRS letters when on HDq12 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 12 weeks (HDq12 regimen) after the immediately preceding dose.
- A method for achieving a BCVA improvement, by week 48 following treatment initiation, of about 8 or 9 letters (ETDRS or Snellen equivalent) when baseline BCVA is about ≤73 ETDRS letters when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 16 weeks (HDq16 regimen) after the immediately preceding dose.
- A method for achieving a BCVA improvement, by week 48 following treatment initiation, of about 4 or 5 letters (ETDRS or Snellen equivalent) when baseline BCVA is about >73 ETDRS letters when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 16 weeks (HDq16 regimen) after the immediately preceding dose.
- A method for achieving a BCVA improvement, by week 48 following treatment initiation, of about 7 or 8 letters (ETDRS or Snellen equivalent) when baseline CRT is < about 400 micrometers when on a HDq12 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye

of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 12 weeks (HDq12 regimen) after the immediately preceding dose.

- A method for achieving a BCVA improvement, by week 48 following treatment initiation, of about 9 or 10 letters (ETDRS or Snellen equivalent) when baseline CRT is ≥400 micrometers when on a HDq12 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 12 weeks (HDq12 regimen) after the immediately preceding dose.
- A method for achieving a BCVA improvement, by week 48 following treatment initiation, of about 5 or 6 letters (ETDRS or Snellen equivalent) when baseline CRT is < about 400 micrometers when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 16 weeks (HDq16 regimen) after the immediately preceding dose.
- A method for achieving a BCVA improvement, by week 48 following treatment initiation, of about 9 or 10 letters (ETDRS or Snellen equivalent) when baseline CRT is ≥ about 400 micrometers when on a HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2

to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 16 weeks (HDq16 regimen) after the immediately preceding dose.

- A method for achieving a gain of ≥5, ≥10 or ≥15 letters BCVA (according to ETDRS letter score) by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment); in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 12 weeks (HDq12 regimen) or 16 weeks (HDq16 regimen) or 20 weeks (HDq20 regimen) after the immediately preceding dose.
- A method for achieving a ≥ 2 or ≥3 step improvement in Diabetic Retinopathy Severity Scale (DRSS) by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a ≥ 2 step improvement in diabetic retinopathy severity scale (DRSS) by 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 or 60 weeks from start of treatment); in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving a retina without fluid (total fluid, intraretinal fluid [IRF] and/or subretinal fluid [SRF]) at the foveal center and in center subfield by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment as measured by optical coherence tomography (OCT); in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a no vascular leakage from the retina as measured by fluorescein angiography (FA) by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a maintenance of a fluid-free retina (total fluid, IRF and/or SRF at foveal center and in the center subfield) by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a reduction in total area of fluorescein leakage within ETDRS grid (mm^2) at week 48 or 60 by about 12, 13 or 14 mm^2 or more as measured by fluorescein angiography; in a subject in need thereof having an angiogenic eye disorder

(preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving a retina free of fluid on spectral domain optical coherence tomography (SD-OCT) by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a retina without fluid (total fluid, intraretinal fluid [IRF] and/or subretinal fluid [SRF]) at the foveal center by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 or 48 weeks from start of treatment); in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a dry retina by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after

the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving a foveal center without fluid by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment as measured by optical coherence tomography (OCT); in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a change in central retinal thickness, by 4 weeks after initiation of treatment of about -118 or -118.3 micrometers (±17, 18 or 19 micrometers) when on the HDq12 regimen; or of about -124 or -125 or -124.9 or -125.5 micrometers (±17, 18 or 19 micrometers) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a change in central retinal thickness, by 8 weeks after initiation of treatment of about -137 or -137.4 micrometers (±17, 18 or 19 micrometers) when on the HDq12 regimen; or of about -139 or -140 or -139.6 or -140.3 micrometers (±17, 18 or 19 micrometers) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving a change in central retinal thickness, by 12 weeks after initiation of treatment of about -150 or -150.1 micrometers (±17, 18 or 19 micrometers) when on the HDq12 regimen; or of about -152 or -153 or -152.7 or -153.4 micrometers (±17, 18 or 19 micrometers) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a change in central retinal thickness, by 16 weeks after initiation of treatment of about -139 or -139.4 micrometers (±17, 18 or 19 micrometers) when on the HDq12 regimen; or of about -145 or -146 or -145.5 or -146.4 micrometers (±17, 18 or 19 micrometers) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a change in central retinal thickness, by 20 weeks after initiation of treatment of about -117 or -117.1 micrometers (±17, 18 or 19 micrometers) when on the HDq12 regimen; or of about -112 or -113 or -112.5 or -113.3 micrometers (±17, 18 or 19 micrometers) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving a change in central retinal thickness, by 24 weeks after initiation of treatment of about -158 or -158.1 micrometers (±17, 18 or 19 micrometers) when on the HDq12 regimen; or of about -103 or -104 or -103.8 or -104.3 micrometers (±17, 18 or 19 micrometers) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a change in central retinal thickness, by 28 weeks after initiation of treatment of about -146 or -147 or -146.7 micrometers (±17, 18 or 19 micrometers) when on the HDq12 regimen; or of about -162 or -162.3 micrometers (±17, 18 or 19 micrometers) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a change in central retinal thickness, by 32 weeks after initiation of treatment of about -132 micrometers (±17, 18 or 19 micrometers) when on the HDq12 regimen; or of about -145 or -146 or -145.8 micrometers (±17, 18 or 19 micrometers) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving a change in central retinal thickness, by 36 weeks after initiation of treatment of about -168 or -168.1 micrometers (±17, 18 or 19 micrometers) when on the HDq12 regimen; or of about -124 or -125 or -124.7 or -125.2 micrometers (±17, 18 or 19 micrometers) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a change in central retinal thickness, by 40 weeks after initiation of treatment of about -163 micrometers (±17, 18 or 19 micrometers) when on the HDq12 regimen; or of about -122 or -123 or -122.5 or -123.1 micrometers (±17, 18 or 19 micrometers) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a change in central retinal thickness, by 44 weeks after initiation of treatment of about -147 or -148 or -147.4 micrometers (±17, 18 or 19 micrometers) when on the HDq12 regimen; or of about -164 or -164.1 or -164.3 micrometers (±17, 18 or 19 micrometers) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving a change in central retinal thickness, by 48 weeks after initiation of treatment of about -171 or -172 or -171.7 micrometers (±17, 18 or 19 micrometers) when on the HDq12 regimen; or of about -148 or -149 or -148.3 or -149.4 micrometers (±17, 18 or 19 micrometers) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a change in central retinal thickness, by 60 weeks after initiation of treatment of about -181.95 or -176.24 (±17, 18 or 19 micrometers) micrometers when on the HDq12 regimen; or of about -166.26 or -167.18 micrometers (±17, 18 or 19 micrometers) when on the HDq16 regimen; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a reduction in CRT by week 4, 5, 6, 7 or 8 after initiation of treatment which is maintained (within about ±17, ±18 or ±19 micrometers) thereafter during the treatment regimen to at least week 48 or 60; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving a decrease in central retinal thickness (CRT) by about 100, 125, 150, 175 or 200 micrometers by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a reduction in CRT of about 148-182 micrometers by week 48 or 60 as measured by optical coherence tomography (OCT) wherein the baseline CRT is about 449, 450, 455 or 460 micrometers; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a decrease in central retinal thickness (CRT) by at least about 100, 125, 130, 135, 140, 145, 149, 150, 155, 160, 165, 170, 171, 172, 173, 174 or 175 micrometers by week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 or 60 from start of treatment; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving at about 0.1667 days after the first dose, free aflibercept in plasma of about 0.149 (±0.249) mg/l; wherein at baseline free aflibercept in plasma not detectable, wherein the subject has not received intravitreal aflibercept treatment for at

least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving at about 0.3333 days after the first dose, free aflibercept in plasma of about 0.205 (±0.250) mg/l; wherein at baseline free aflibercept in plasma not detectable, for example, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving at about 1 day after the first dose, free aflibercept in plasma of about 0.266 (±0.211) mg/l; wherein at baseline free aflibercept in plasma not detectable, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving at about 2 days after the first dose, free aflibercept in plasma of about 0.218 (±0.145) mg/l; wherein at baseline free aflibercept in plasma not detectable, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of

about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving at about 4 days after the first dose, free aflibercept in plasma of about 0.140 (±0.0741) mg/l; wherein at baseline free aflibercept in plasma not detectable, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving at about 7 days after the first dose, free aflibercept in plasma of about 0.0767 (±0.0436) mg/l; wherein at baseline free aflibercept in plasma not detectable, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving at about 14 days after the first dose, free aflibercept in plasma of about 0.0309 (±0.0241) mg/l; wherein at baseline free aflibercept in plasma not detectable, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered

about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving at about 21 days after the first dose, free aflibercept in plasma of about 0.0171 (±0.0171) mg/l; wherein at baseline free aflibercept in plasma not detectable, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving at about 28 days after the first dose, free aflibercept in plasma of about 0.00730 (±0.0113) mg/l; wherein at baseline free aflibercept in plasma not detectable, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving at about 0.1667 days after the first dose, adjusted bound aflibercept in plasma of about 0.00698 (±0.0276) mg/l; wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving at about 0.3333 days after the first dose, adjusted bound aflibercept in plasma of about 0.00731 (±0.0279) mg/l; wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept, for example, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving at about 1 days after the first dose, adjusted bound aflibercept in plasma of about 0.0678 (±0.0486) mg/l; wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept, for example, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving at about 2 days after the first dose, adjusted bound aflibercept in plasma of about 0.138 (±0.0618) mg/l; wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept, wherein the subject has not received intravitreal aflibercept protein treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving at about 4 days after the first dose, adjusted bound aflibercept in plasma of about 0.259 (±0.126) mg/l; wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving at about 7 days after the first dose, adjusted bound aflibercept in plasma of about 0.346 (±0.151) mg/l; wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving at about 14 days after the first dose, adjusted bound aflibercept in plasma of about 0.374 (±0.110) mg/l; wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving at about 21 days after the first dose, adjusted bound aflibercept in plasma of about 0.343 (±0.128) mg/l; wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving at about 28 days after the first dose, adjusted bound aflibercept in plasma of about 0.269 (±0.149) mg/l; wherein at baseline there is about 0.00583 mg/l (±0.0280) adjusted bound aflibercept, wherein the subject has not received intravitreal aflibercept treatment for at least 12 weeks; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a maximum level of free aflibercept in the plasma that is reached about 0.965 day after the first dose; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a maximum level of about 0.310 mg/l (±0.263) free aflibercept in the plasma; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose

of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving free aflibercept in the plasma of from about 0 to about 1.08 mg/L (0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0 or 1.1 mg/l); in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving free aflibercept in the plasma maximum (mg/l) per dose (mg) of aflibercept of about 0.388 (±0.0328) mg/l/mg; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a maximum level of adjusted bound aflibercept in the plasma that is reached about 14 days after the first dose; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a maximum level of about 0.387 mg/l (±0.135) adjusted bound aflibercept in the plasma; in a subject in need thereof having an angiogenic eye disorder

(preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving adjusted bound aflibercept in the plasma of from about 0.137 to about 0.774 mg/L; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving adjusted bound aflibercept in the plasma maximum (mg/l) per dose (mg) of aflibercept of about 0.483 (±0.0168) mg/l/mg; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving undetectable plasma concentrations of anti-drug antibodies against aflibercept after 48 or 60 weeks of treatment; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of aflibercept, followed by one or more secondary doses of about 8 mg or more of the aflibercept, followed by one or more tertiary doses of about 8 mg or more of the aflibercept; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.

- A method for achieving an improvement from pre-treatment baseline in National Eye Institute Visual Function Questionnaire (NEI-VFQ) total score by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment; in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving a lack of macular edema by week 12, 24, 36, 48, 60, 72, 84, 90 or 96 from start of treatment in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks (HDq24 regimen) after the immediately preceding dose.
- A method for achieving:
  a change in central retinal thickness of about -118 or -119 or -118.3 micrometers, between initiation of treatment (week 0) and week 4 when on the HDq12 regimen;
  a change in central retinal thickness of about -19, -20 or -19.1 micrometers, between weeks 4 and 8 when on the HDq12 regimen;
  a change in central retinal thickness of about -12, -13 or -12.7 micrometers, between weeks 8 and 12 when on the HDq12 regimen;
  a change in central retinal thickness of about -40, or -41 micrometers, between weeks 20 and 24 when on the HDq12 regimen;
  a change in central retinal thickness of about -36, -37 or -36.1 micrometers, between weeks 32 and 36 when on the HDq12 regimen;
  a change in central retinal thickness of about -24, -25 or -24.3 micrometers, between weeks 44 and 48 when on the HDq12 regimen;
  a change in central retinal thickness of -4, -5 or -4.5 micrometers, between weeks 48 and 60 when on the HDq12 regimen;

a change in central retinal thickness of about -124, -125 or -124.9 micrometers, between initiation of treatment (week 0) and week 4 when on the HDq16 regimen;
a change in central retinal thickness of about –14, -15 or -14.7 micrometers, between weeks 4 and 8 when on the HDq16 regimen;
a change in central retinal thickness of about -13, -14 or -13.1 micrometers, between weeks 8 and 12 when on the HDq16 regimen;
a change in central retinal thickness of about -58, -59 or -58.5 micrometers, between weeks 24 and 28 when on the HDq16 regimen;
a change in central retinal thickness of about -41, -42 or -41.6 micrometers, between weeks 40 and 44 when on the HDq16 regimen; and/or
a change in central retinal thickness of -18, -19 or -18.9 micrometers, between weeks 48 and 60 when on the HDq16 regimen,
in a subject in need thereof having an angiogenic eye disorder (preferably DR and/or DME) comprising administering to an eye of the subject, a single initial dose of about 8 mg or more of a VEGF receptor fusion protein, followed by one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein; wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and wherein each tertiary dose is administered about 12 weeks (HDq12 regimen) or 16 weeks (HDq16 regimen) after the immediately preceding dose.

[000255]The molecular weight adjusted concentration of bound aflibercept (adjusted bound aflibercept) is calculated by multiplying the observed concentrations by 0.717 to account for the target VEGF weight in the complex in plasma in the concentration-time profiles discussed herein.

[000256]In an embodiment of the invention, CRT and/or retinal fluid is as measured on spectral domain optical coherence tomography (SD-OCT). In an embodiment of the invention, any of such achievements are maintained as long as the subject is receiving the treatment regimen. In an embodiment of the invention, a subject receiving a treatment for an angiogenic eye disorder, *e.g.*, neovascular age related macular degeneration, diabetic macular edema (DME) and/or diabetic retinopathy (DR), does not experience or is no more likely to experience than a subject receiving Eylea according to the prescribed dosage regimen:

- Ocular serious TEAE (*e.g.*, through week 96 after treatment initiation), for example, cataract subcapsular, retinal detachment, ulcerative keratitis, vitreous

haemorrhage or increased intraocular pressure, angle closure glaucoma, cataract, choroidal detachment, retinal detachment, retinal haemorrhage, skin laceration and/or vitreous haemorrhage;

- TEAE intraocular inflammation (*e.g.*, through week 96 after treatment initiation), for example, chorioretinitis, iridocyclitis, iritis, uveitis, vitreal cells and/or vitritis;
- Non-ocular serious TEAEs (*e.g.*, through week 96 after treatment initiation), for example, acute left ventricular failure, acute myocardial infarction, cardiac arrest, coronary artery disease, myocardial infarction, covid-19 pneumonia, gangrene, pneumonia, hyponatraemia, cerebrovascular accident, acute kidney injury, acute respiratory failure, angina pectoris, chest pain, cellulitis, pneumonia, pyelonephritis acute, urinary tract infection, upper limb fracture, hyponatraemia, osteoarthritis, bladder neoplasm and/or cerebrovascular accident;
- Treatment emergent APTC event (*e.g.*, through week 96 after treatment initiation), for example, non-fatal myocardial infarction, non-fatal stroke and/or vascular death;
- Treatment emergent hypertension events (*e.g.*, through week 96 after treatment initiation), for example, blood pressure increased (diastolic and/or systolic), hypertension, diastolic hypertension, systolic hypertension, hypertensive crisis, hypertensive emergency, hypertensive urgency, labile hypertension and/or white coat hypertension;
- Potentially clinically significant values (*e.g.*, through week 96 after treatment initiation), for example, systolic blood pressure≥160 mmHg and an increase from baseline of ≥20 mmHg; and/or diastolic blood pressure ≥110 mmHg and an increase from baseline of ≥10 mmHg; and/or
- Death (*e.g.*, through week 96 after treatment initiation), for example, due to cardiac arrest, cardio-respiratory arrest, left ventricular failure, myocardial infarction, death, sudden death, covid-19, pneumonia, diabetic metabolic decompensation, endometrial cancer, acute kidney injury, abdominal strangulated hernia, pneumonia aspiration, skull fracture, metastatic neoplasm and/or non-small cell lung cancer

[000257]The present invention further includes methods for achieving a pharmacokinetic effect in a subject suffering from DR and/or DME comprising administering to an eye of the subject, at least one dose (*e.g.*, a first dose) of about ≥8 mg VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept). The pharmacokinetic effect can be one or more set forth below:

- Decreasing ocular clearance of free VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept), *e.g.*, by about 34% relative to that of a dose of 2 mg of the VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept);
- 0.2-0.3 (*e.g.*, 0.310 or 0.245) mg/l free VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept) in the plasma, *e.g.*, within about 1, 2 or 3 days of the first dose;
- About 0.38 or 0.5 mg/l adjusted bound VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept) in the plasma, *e.g.*, within about 14, 15 or 16 days of the first dose;
- Reaches LLOQ of free VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept) (about 15.6 ng/ml) in the plasma by about 3 or 4 weeks of the first dose;
- Reaches LLOQ of free VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept) (about 15.6 ng/ml) in the ocular compartment by about 15 weeks of the first dose;
- Reaches LLOQ of free VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept) (about 15.6 ng/ml) that is about 6 weeks longer than achieved for a 2 mg dose of the antagonist;
- A clearance of the VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept) from the ocular compartment of about 0.41 ml/day;

for example, wherein the subject is administered:

a single initial dose of about ≥8 mg or more of a VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept), followed by one or more secondary doses of about ≥8 mg or more of the VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept), followed by one or more tertiary doses of about ≥8 mg or more of the VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept); wherein each secondary dose is administered about 2 to 4 weeks (preferably, 4 weeks) after the immediately preceding dose; and wherein each tertiary dose is administered about 24 weeks after the immediately preceding dose.

[000258]In an embodiment of the invention, the method for treating or preventing diabetic macular edema (DME), in a subject in need thereof comprises administering to an eye of the subject (preferably by intravitreal injection) ≥8 mg aflibercept (*e.g.*, in a volume of 0.07 mL or 70 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days, monthly) for the first three doses, followed by ≥8 mg aflibercept (*e.g.*, in a volume of 0.07 mL) via intravitreal injection once every 24 weeks (+/- 7 days).

[000259]In an embodiment of the invention, the method for treating or preventing diabetic retinopathy (DR), in a subject in need thereof comprises administering to an eye of the subject (preferably by intravitreal injection) ≥8 mg aflibercept (*e.g.*, in a volume of 0.07 mL or 70 microliters) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days, monthly) for the first three doses, followed by ≥8 mg aflibercept (*e.g.*, in a volume of 0.07 mL) via intravitreal injection once every 24 weeks (2 – 4 months, +/- 7 days).

[000260]Some subject may be excluded from administration based, for example, on the existence of certain exclusion criteria. For example, in an embodiment of the invention, the criteria are one or more of ocular infection, periocular infection; active intraocular inflammation; and/or hypersensitivity, *e.g.*, to aflibercept or any component of a formulation thereof. The method presented herein may include the step of evaluating the subject for such exclusion criteria and excluding the subject from said administration if any one or more if found in the subject; and proceeding with administration if exclusion criteria are not found.

[000261]In an embodiment of the invention, a subject receiving VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept) is monitored for adverse events (AEs) such as conjunctival hemorrhage, cataract, vitreous detachment, vitreous floaters, corneal epithelium defect and/or increased intraocular pressure. If an AE is found, the AE can be treated in the subject and treatment can either be discontinued or continued.

[000262]The methods of present invention can include preparatory steps that include use of

- one single-dose glass vial having a protective plastic cap and a stopper containing an aqueous formulation comprising ≥8 mg aflibercept in about 70 microliters;
- one 18-gauge x 1½-inch, 5-micron, filter needle that includes a tip and a bevel;
- one 30-gauge x ½-inch injection needle; and
- one 1-mL Luer lock syringe having a graduation line marking for 70 microliters of volume;

packaged together (kits including such items form part of the present invention). The steps can include, for example: (1) visually inspecting the aqueous formulation in the vial and, if particulates, cloudiness, or discoloration are visible, then using another vial of aqueous formulation containing the aflibercept; (2) removing the protective plastic cap from the vial; and (3) cleaning the top of the vial with an alcohol wipe; then, using aseptic technique the following steps: (4) removing the 18-gauge x 1½-inch, 5-micron, filter needle and the 1 mL syringe from their packaging; (5) attaching the filter needle to the syringe by twisting it onto the Luer lock syringe tip; (6) pushing the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or a bottom edge of the vial; (7)

withdrawing all of the aflibercept vial contents into the syringe, keeping the vial in an upright position, slightly inclined, while ensuring the bevel of the filter needle is submerged into the liquid; (8) continuing to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the formulation; (9) drawing the plunger rod sufficiently back when emptying the vial in order to completely empty the filter needle; (10) removing the filter needle from the syringe and disposing of the filter needle; (11) removing the 30-gauge x ½-inch injection needle from its packaging and attaching the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip; (12) holding the syringe with the needle pointing up, and checking the syringe for bubbles, wherein if there are bubbles, gently tapping the syringe with a finger until the bubbles rise to the top; and (13) slowly depressing the plunger so that the plunger tip aligns with the graduation line that marks 70 microliters on the syringe. Preferably injection of VEGF antagonist (*e.g.*, a VEGF receptor fusion protein such as aflibercept) as performed in methods of the present invention is performed under controlled aseptic conditions, which comprise surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) and anesthesia and a topical broad–spectrum microbicide are administered prior to the injection.

Switching

[000263]The present invention includes embodiments wherein a subject has a history of receiving one or more doses of aflibercept or any other VEGF antagonist (*e.g.*, 2 mg aflibercept such as Eylea (*e.g.*, 2q8 regimen) or one or more doses of about ≥8 mg (± 0.8 mg) aflibercept) and is then switched to a dosing regimen of the present invention, *e.g.,* HDq24, starting at any step in the regimen.

[000264]For example, a subject may have been initially administered aflibercept manufactured by a first process (a first aflibercept) and then is switched to aflibercept manufactured by a different process (*e.g.*, a second aflibercept; *e.g.*, a biosimilar aflibercept); for example, wherein each process is carried out by a different manufacturer.

[000265]Subjects may initially be receiving aflibercept according to a 2q8 dosing regimen comprising administering 3, 4 or 5 initial monthly doses followed by one or more maintenance doses every 8 weeks (*e.g.*, Eylea) and then switch to a HDq24 dosing regimen. The aflibercept administered in the HDq24 dosing regimen may have been manufactured by a different process, *e.g.*, by a different manufacturer.

[000266]In addition, a subject may be receiving a HDq24 dosing regimen with aflibercept and then switch to aflibercept manufactured by a different process, *e.g.*, by a different manufacturer, while remaining on the HDq24 dosing regimen.

[000267]The present invention encompasses, but is not limited to, methods for treating an angiogenic eye disorder, preferably nAMD, DR and/or DME, wherein a subject is switched, from a first aflibercept (manufactured by one process) for use in a HDq24 regimen to a second aflibercept (manufactured by another process) for use in a HDq24 regimen. The present invention includes embodiments wherein the subject initiates treatment of the second aflibercept HDq24 regimen at any dosing phase-initial, secondary or tertiary/maintenance—after having received the initial dose, one or more secondary doses or one or more tertiary/maintenance doses of the first aflibercept HDq24 regimen. Thus, the present invention includes embodiments wherein, the subject is switched from any phase of the first HDq24 regimen into any phase of the second HDq24 regimen. Preferably, the subject will pick up receiving the second aflibercept HDq24 regimen at the dosing phase that corresponds to where dosing was stopped with the first HDq24 regimen, *e.g.*, if a particular secondary dose was due with the first aflibercept therapy, the subject would timely receive the same secondary dose with the second aflibercept and, for example, continue receiving the second aflibercept according to the HDq24 regimen as needed thereafter.

[000268]The present invention also encompasses, but is not limited to, methods for treating an angiogenic eye disorder wherein a subject is switched, from a first aflibercept for use in a 2q8 regimen to a second aflibercept for use in a HDq24 regimen. The present invention includes embodiments wherein the subject initiates treatment of the second aflibercept HDq24 regimen at any dosing phase-initial, secondary or tertiary/maintenance—after having received the initial dose, one or more secondary doses or one or more tertiary/maintenance doses of the first aflibercept 2q8 regimen. Thus, the present invention includes embodiments wherein, for example, the subject is switched directly to the maintenance phase of the HDq24 regimen with second aflibercept after having received the initial and a single secondary dose in the 2q8 regimen with the first aflibercept.

[000269]In an embodiment of the invention, a subject who has received an initial, one or more secondary doses and/or one or more tertiary doses of 2 mg aflibercept (*e.g.*, Eylea) therapy (*e.g.*, 2q8) according to the prescribed dosing regimen may receive an $\geq$8 mg ($\pm$ 0.8 mg) dose of aflibercept, undergo an evaluation by a treating physician in about 8 or 10 or 12 weeks and, if, in the judgment of a treating physician, dosing every 24 weeks is appropriate (*e.g.*, there is no

undue loss in BCVA and/or increase in CRT), then continuing to dose the subject every 24 weeks with ≥8 mg (± 0.8 mg) aflibercept.

[000270]The present invention includes methods for treating or preventing an angiogenic eye disorder, preferably nAMD, DR or DME, in a subject in need thereof, by administering to said subject ≥8 mg (± 0.8 mg) aflibercept, wherein:

- the subject has received an initial ≥8 mg dose of aflibercept then the method comprises, after 1 month, administering to the subject the first ≥8 mg secondary dose of aflibercept and 1 month thereafter, administering the 2nd ≥8 mg secondary dose of aflibercept; and then, every 24 weeks thereafter, administering one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;

or

- the subject has received an initial ≥8 mg dose of aflibercept & 1st ≥8 mg secondary dose of aflibercept after 1 month, then the method comprises, after another 1 month, administering to the subject the 2nd ≥8 mg secondary dose of aflibercept; and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;

or

- the subject has received an initial ≥8 mg dose of aflibercept & 1st ≥8 mg secondary dose of aflibercept after 1 month & the 2nd ≥8 mg secondary dose of aflibercept after another month, then the method comprises, after 24 weeks administering to the subject the 1st ≥8 mg maintenance dose of aflibercept and all further ≥8 mg maintenance doses of aflibercept every 24 weeks according to HDq24 dosing regimen;

or

- the subject has received an initial ≥8 mg dose of aflibercept & a 1st ≥8 mg secondary dose of aflibercept after 1 month & the 2nd ≥8 mg secondary dose of aflibercept after another month, then every 24 weeks thereafter, the subject has received one or more ≥8 mg maintenance doses of aflibercept; and, then the method comprises, after 24 weeks from the last maintenance dose of aflibercept, administering to the subject one or more ≥8 mg maintenance doses of aflibercept and all further ≥8 mg maintenance doses of aflibercept every 24 weeks according to the HDq24 dosing regimen.

[000271]Patients may switch from a reference 2 mg aflibercept dosing regimen to a particular step in the HDq24 dosing regimen. For example, a subject may receive only the initial 2 mg dose of reference, and then, skipping the initial and secondary doses of the HDq24 dosing regimen, begin receiving the HDq24 maintenance doses. The present invention includes

methods for treating or preventing nAMD, DR and/or DME, in a subject in need thereof, by administering to said subject ≥8 mg (± 0.8 mg) aflibercept, wherein:

(1) the subject has received an initial 2 mg dose of aflibercept, then the method comprises, after 1 month, administering to the subject the initial ≥8 mg dose of aflibercept and, 1 month thereafter, the 1st ≥8 mg secondary dose of aflibercept; and, 1 month thereafter, the 2nd ≥8 mg secondary dose of aflibercept; and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;

(2) the subject has received an initial 2 mg dose of aflibercept, then the method comprises, after 1 month, administering to the subject the first ≥8 mg secondary dose of aflibercept and, 1 month thereafter, the 2nd ≥8 mg secondary dose of aflibercept; and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;

(3) the subject has received an initial 2 mg dose of aflibercept, then the method comprises, after 1 month, administering to the subject the 2nd ≥8 mg secondary dose of aflibercept and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;

(4) the subject has received an initial 2 mg dose of aflibercept, then the method comprises, after 1 month, administering to the subject the 1st ≥8 mg maintenance dose of aflibercept and all further ≥8 mg maintenance doses of aflibercept every 24 weeks according to the HDq24 dosing regimen;

(5) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month, then the method comprises, after another 1 month, administering to the subject the initial ≥8 mg dose of aflibercept and, 1 month thereafter, the 1st ≥8 mg secondary dose of aflibercept; and 1 month thereafter, the 2nd ≥8 mg secondary dose of aflibercept; and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;

(6) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month, then the method comprises, after another 1 month, administering to the subject a first ≥8 mg secondary dose of aflibercept and, 1 month thereafter, the 2nd ≥8 mg secondary dose of aflibercept; and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;

(7) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month, then the method comprises, after another 1 month, administering to the subject the 2nd ≥8 mg secondary dose of aflibercept and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;

(8) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month, then the method comprises, after another 1 month, administering to the subject the 1st ≥8 mg maintenance dose of aflibercept and all further ≥8 mg maintenance doses of aflibercept every 24 weeks according to the HDq24 dosing regimen;
(9) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month, then the method comprises, after another 1 month, administering to the subject the initial ≥8 mg dose of aflibercept and, 1 month thereafter, the 1st ≥8 mg secondary dose of aflibercept; and 1 month thereafter, the 2nd ≥8 mg secondary dose of aflibercept; and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;
(10) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month, then the method comprises, after another 1 month, administering to the subject the first ≥8 mg secondary dose of aflibercept and, 1 month thereafter, the 2nd ≥8 mg secondary dose of aflibercept; and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;
(11) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month, then the method comprises, after another 1 month, administering to the subject the 2nd ≥8 mg secondary dose of aflibercept and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;
(12) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month, then the method comprises, after 2 months, administering to the subject the 1st ≥8 mg maintenance dose of aflibercept and, all further ≥8 mg maintenance doses of aflibercept every 24 weeks according to the HDq24 dosing regimen;
(13) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month and a 3rd 2 mg secondary dose of aflibercept after 1 month, then the method comprises, after 1 month, administering to the subject the initial ≥8 mg dose of aflibercept and 1 month thereafter, the 1st ≥8 mg secondary dose of aflibercept; and 1 month thereafter, the 2nd ≥8 mg secondary dose of aflibercept; and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;

(14) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month and a 3rd 2 mg secondary dose of aflibercept after 1 month, then the method comprises, after 1 month, administering to the subject the first ≥8 mg secondary dose of aflibercept and 1 month thereafter, the 2nd ≥8 mg secondary dose of aflibercept; and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;
(15) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month and a 3rd 2 mg secondary dose of aflibercept after 1 month, then the method comprises, after 1 month, administering to the subject the 2nd ≥8 mg secondary dose of aflibercept and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;
(16) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month and a 3rd 2 mg secondary dose of aflibercept after 1 month, then the method comprises, after 2 months, administering to the subject the 1st ≥8 mg maintenance dose of aflibercept and all further ≥8 mg maintenance doses of aflibercept every 24 weeks according to the HDq24 dosing regimen;
(17) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month and a 3rd 2 mg secondary dose of aflibercept after 1 month; and a 4th 2 mg secondary dose of aflibercept after 1 month; thereafter, then the method comprises, after 2 months, administering to the subject the initial ≥8 mg dose of aflibercept and, 1 month thereafter, the 1st ≥8 mg secondary dose of aflibercept; and 1 month thereafter, the 2nd ≥8 mg secondary dose of aflibercept; and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;
(18) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month and a 3rd 2 mg secondary dose of aflibercept after 1 month; and a 4th 2 mg secondary dose of aflibercept after 1 month; thereafter, then the method comprises, after 2 months, administering to the subject the first ≥8 mg secondary dose of aflibercept and, 1 month thereafter, the 2nd ≥8 mg secondary dose of aflibercept; and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;

(19) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month and a 3rd 2 mg secondary dose of aflibercept after 1 month, and a 4th 2 mg secondary dose of aflibercept after 1 month; thereafter, then the method comprises, after 2 months, administering to the subject the 2nd ≥8 mg secondary dose of aflibercept and, 12-20 or 12 or 16 or 20 weeks thereafter, one or more 24 weekly ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;

(20) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month and a 3rd 2 mg secondary dose of aflibercept after 1 month, and a 4th 2 mg secondary dose of aflibercept after 1 month, thereafter, then the method comprises, after 2 months, administering to the subject the 1st ≥8 mg maintenance dose of aflibercept and, all further ≥8 mg maintenance doses of aflibercept every 24 weeks according to the HDq24 dosing regimen;

(21) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month and a 3rd 2 mg secondary dose of aflibercept after 1 month, and a 4th 2 mg secondary dose of aflibercept after 1 month; and one or more 2 mg maintenance doses every 8 weeks thereafter, then the method comprises, 2 months after the last aflibercept maintenance dose, administering to the subject the initial ≥8 mg dose of aflibercept and, 1 month thereafter, the 1st ≥8 mg secondary dose of aflibercept; and 1 month thereafter, the 2nd ≥8 mg secondary dose of aflibercept; and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;

(22) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month and a 3rd 2 mg secondary dose of aflibercept after 1 month; and a 4th 2 mg secondary dose of aflibercept after 1 month; and one or more 2 mg maintenance doses every 8 weeks thereafter, then the method comprises, 2 months after the last aflibercept maintenance dose administering to the subject the first ≥8 mg secondary dose of aflibercept and, 1 month thereafter, the 2nd ≥8 mg secondary dose of aflibercept; and then, every 24 weeks thereafter, one or more ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;

(23) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month and a 3rd 2 mg secondary dose of aflibercept after 1 month; and a 4th 2 mg secondary dose of aflibercept after 1 month; and one or more 2 mg maintenance doses every 8 weeks thereafter,

then the method comprises, 2 months after the last aflibercept maintenance dose, administering to the subject the 2nd ≥8 mg secondary dose of aflibercept and, 24 weeks thereafter, one or more 24 weekly ≥8 mg maintenance doses of aflibercept according to the HDq24 dosing regimen;

or

(24) the subject has received an initial 2 mg dose of aflibercept and a 1st 2 mg secondary dose of aflibercept after 1 month and a 2nd 2 mg secondary dose of aflibercept after another 1 month and a 3rd 2 mg secondary dose of aflibercept after 1 month; and a 4th 2 mg secondary dose of aflibercept after 1 month; and one or more 2 mg maintenance doses every 8 weeks thereafter, then the method comprises, 2 months after the last aflibercept maintenance dose, administering to the subject the 1st ≥8 mg maintenance dose of aflibercept and, all further ≥8 mg maintenance doses of aflibercept every 24 weeks according to the HDq24 dosing regimen.

Precision Dose Drug Delivery

[000272]The present invention provides methods as set forth herein wherein a VEGF antagonist (*e.g.*, aflibercept) is delivered with a high amount of precision, *e.g.*, with a drug delivery device (DDD) (*e.g.*, with a 0.5 mL volume), whether pre-filled or capable of being filled from a vial, and delivering a volume of between 70 and 100 microliter with an average volume of about 81 or 82 or 81-82 microliters, *e.g.*, with a standard deviation of about 4 or 5 or 4-5 microliters (*e.g.*, about 4.5 or 4.46 microliters) or less. In an embodiment of the invention, the DDD is a syringe, *e.g.*, with a 30 gauge, ½ inch needle.

[000273]One means for ensuring precision of a dose to be delivered with a device, such as a syringe, is by employing a syringe wherein the dose volume is device-determined. If the dose volume is device-determined, the device is designed only to deliver a single volume (*e.g.*, 87 microliters) or a single volume with a limited amount of acceptable error (± 4-5 microliters). Thus, if used properly, the user cannot deliver the wrong dose (*e.g.*, cannot deliver more than the intended volume from the device).

[000274]The present invention includes embodiments wherein, a precise dosage of about 8 mg or more is a dose of about 9, 9.3, 9.33, 9.7, 9.8, 9.9, 9.7-9.9 mg or more ± about 0.5, or ± about 0.51 mg is delivered to a subject's eye. The volume in which a dose is delivered can be, for example, about 70, 81, 82, 81.7, 85, 86, 87, 85-87 microliters ± about 4, 4.45, 4.5, or 5 microliters. Doses may be delivered with a dose delivery device (DDD) which is a syringe.

[000275]Highly precise doses of VEGF antagonist (*e.g.*, aflibercept) may be delivered, for example, in a volume that is device-determined (wherein the device is a syringe), by a method

that includes the steps: (a) priming the syringe (*e.g.*, a pre-filled syringe), thereby removing air from the syringe and, thus avoiding injection of air into the eye, by advancing the plunger rod by a predetermined distance into the syringe body until advancement of the plunger rod is resisted by a stop; (b) rotating the plunger rod about a longitudinal axis; and (c) actuating the plunger rod to dispense a predetermined (device-determined) volume (*e.g.*, about 70, 81, 82, 81.7, 85, 86, 87, 85-87 microliters, ± about 4, 4.45, 4.5, or 5 microliters) of the formulation.

[000276]In an embodiment of the invention, the drug delivery device (DDD), comprises:

- a barrel including a longitudinal axis, a proximal end region, and a distal end region, the proximal end region including an opening, wherein the barrel is configured to receive a drug therein;
- a plunger rod disposed at least partially inside the barrel and protruding from the opening, wherein the plunger rod includes a rack having a plurality of teeth; and
- a pinion having a plurality of teeth configured to engage with the plurality of teeth of the rack,

wherein rotation of the pinion against the rack moves at least a part of the plunger rod along the longitudinal axis of the barrel; for example, which further comprises a shaft affixed to the pinion, wherein rotation of the shaft rotates the pinion against the rack which may include a knob affixed to the shaft. In an embodiment of the invention, the DDD further includes a magnifier disposed on the distal end region of the barrel. In an embodiment of the invention, the DDD further includes a stopper inside the barrel, wherein the stopper is affixed to a distal end of the plunger rod. In an embodiment of the invention, the DDD further includes a circular ratchet disposed coaxially with the pinion, wherein the circular ratchet has a diameter smaller than a diameter of the pinion; a spring-loaded pawl disposed on an internal circumference of the pinion, wherein the pawl is configured to engage the ratchet; and a shaft affixed to the ratchet, wherein rotation of the shaft in one direction causes rotation of the pinion, and rotation of the shaft in a second direction does not cause rotation of the pinion for example wherein the ratchet is disposed inside the pinion. In an embodiment of the invention, the pinion includes a plurality of teeth having a first height, and a stopper tooth having a second height greater than the first height, for example, wherein the second height of the stopper tooth prevents the pinion from engaging the plurality of teeth of the rack, and/or wherein the second height of the stopper tooth is configured to contact one of the plunger rod and the rack to stop rotation of the pinion. In an embodiment of the invention, the plunger rod includes an inner column and an outer lumen, and wherein the rack is disposed on the inner column, *e.g.*, wherein rotation of the pinion against the rack moves the inner column of the plunger rod independently of the outer lumen, and/or further

including a shaft removably affixed to the pinion, wherein the shaft prevents movement of the outer lumen of the plunger rod relative to the barrel, and wherein removal of the shaft allows for movement of the outer lumen of the plunger rod relative to the barrel. In an embodiment of the invention, the plunger rod further includes a body and a flange, the flange extending partially along a longitudinal length of the body and having a width greater than a width of the body; wherein the barrel further comprises a plunger lock, the plunger lock including a through hole configured to allow the flange to pass through the second plunger lock in a specific orientation.

[000277]In an embodiment of the invention, the drug delivery device (DDD), comprises:

- a barrel including a longitudinal axis, a proximal end region, a distal end region, and an interior, the proximal end region including an opening and the interior including a threaded region; and
- a plunger rod disposed at least partially inside the barrel and protruding from the opening, the plunger rod including a threaded region configured to engage the threaded region of the barrel interior,

wherein rotation of the plunger rod about the longitudinal axis of the drug delivery device moves the plunger rod along the longitudinal axis. In an embodiment of the invention, the plunger rod further includes a tab protruding from the plunger rod in a first direction and located proximally from the threaded region of the plunger rod, and wherein the threaded region in the interior of the barrel further includes a slot sized and configured to allow for the tab to pass through the threaded region in the interior of the barrel, *e.g.*, wherein the slot includes a first segment parallel to the longitudinal axis of the drug delivery device and a second segment perpendicular to the longitudinal axis of the drug delivery device—the

slot may include a third segment parallel to the longitudinal axis of the drug delivery device, wherein the second segment is in between the first segment and the third segment. In an embodiment of the invention, the tab is a first tab, and wherein the plunger rod further includes a second tab protruding from the plunger rod in a second direction opposite to the first direction, and wherein the threaded region in the interior of the barrel further includes a second slot sized and configured to allow for the second tab to pass through the threaded region in the interior of the barrel.

[000278]In an embodiment of the invention, the drug delivery device, includes:

- a barrel having a proximal end region, a distal end region, an opening in the proximal end region, an interior, and a threaded region in the interior;

- a sleeve disposed partly inside the barrel and protruding from the opening in the proximal end region of the barrel, the sleeve including a threaded region engaged with the threaded region of the barrel interior;
- a plunger rod disposed at least partially inside the sleeve; and
- a stopper inside the barrel and located distally from the sleeve, the stopper connected to a distal end of the plunger rod,

wherein rotation of the sleeve in a first direction around a longitudinal axis of the drug delivery device moves the sleeve towards the distal end region of the barrel. In an embodiment of the invention, rotation of the sleeve in the first direction moves the stopper towards the distal end region of the barrel. In an embodiment of the invention; the sleeve includes an inner passage, and the stopper has a diameter larger than a diameter of the inner passage; and/or the sleeve includes a tab disposed on an exterior of the sleeve, the tab located proximally from the threaded region of the barrel interior, and wherein the tab stops movement of the sleeve towards the distal end region of the barrel, *e.g.*, wherein the tab is configured to stop movement of the sleeve towards the distal end region of the barrel after the drug delivery device has been primed or wherein the tab is a first tab, and wherein the sleeve further includes a second tab disposed on an exterior of the sleeve, the second tab located distally from the threaded region of the barrel interior, wherein the second tab stops movement of the sleeve towards the proximal end region of the barrel.

[000279]In an embodiment of the invention, the drug delivery device, comprises:

- a barrel including a proximal end region and a distal end region, the proximal end region including an opening;
- a plunger rod including a body and a flange, the flange extending partially along a longitudinal length of the body and having a width greater than a width of the body, the plunger rod disposed at least partially inside the barrel and protruding from the opening;
- a first plunger lock disposed on the barrel, the first plunger lock configured to block the flange from entering the barrel; and
- a second plunger lock disposed in the barrel, the second plunger lock including a through hole configured to allow the flange to pass through the second plunger lock in a specific orientation.

[000280]For example, in an embodiment of the invention, the first plunger lock is removable and/or frangible. In an embodiment of the invention, a distance between the first plunger lock and the second plunger lock is equivalent to the distance that the stopper must travel to prime

the drug delivery device; and/or the plunger rod is rotatable around a longitudinal axis of the drug delivery device.

[000281]Substances from such a DDD (*e.g.*, a formulation including aflibercept as described herein), having a plunger rod and a barrel, may be dispensed as follows:

- advancing the plunger rod by a predetermined distance into the barrel until advancement of the plunger rod is resisted by a stop;
- deactivating the stop; and
- actuating the plunger rod (*e.g.*, which includes a flange, wherein the stop includes a lock that prevents the flange from entering the barrel; or which includes a flange, wherein the stop comprises a lock that prevents the flange from entering the barrel) to deliver the substance.

[000282]Advancing the plunger rod may include the step of rotating a pinion against a rack disposed on the plunger rod, *e.g.*, wherein the stop comprises a shaft removably affixed to the pinion, and wherein deactivating the stop comprises removing the shaft from the pinion. Deactivating the stop may include the step of rotating the plunger rod. In an embodiment of the invention, deactivating the stop includes the step of removing the lock and/or breaking the lock.

[000283]In an embodiment of the invention, the drug delivery device, includes:

- a barrel including a longitudinal axis, a proximal end region, and a distal end region, the proximal end region including an opening and a rack disposed on the interior of the barrel, the rack having a plurality of teeth, wherein the barrel is configured to receive a drug therein;
- a plunger rod disposed at least partially inside the barrel and protruding from the opening, wherein the plunger rod includes a rack having a plurality of teeth; a pinion having a plurality of teeth configured to engage with the plurality of teeth of the plunger rod rack; and
- an inner plunger coupled to the pinion by a rod, wherein rotation of the pinion against the plunger rod rack results in movement of the inner plunger along the longitudinal axis of the barrel;

for example, wherein the teeth of the pinion are further configured to engage with the plurality of teeth of the rack disposed on the barrel. In an embodiment of the invention, the pinion is a first pinion, and further includes: a second pinion disposed coaxially with the first pinion, the second pinion having a diameter smaller than a diameter of the first pinion and a plurality of teeth configured to engage with the plurality of the teeth of the rack disposed on the barrel, wherein rotation of the first pinion results in rotation of the second pinion against the rack disposed on the barrel and in movement of the inner plunger along the longitudinal axis of the barrel.

[000284]See International patent application publication no. WO2019/118588.

[000285]In an embodiment of the invention, the drug delivery device (DDD), includes:

- a body;
- a plunger rod disposed partially inside the body;
- a protrusion extending from the plunger rod; and
- a blocking component coupled to a proximal end portion of the body, wherein the blocking component is a flange piece,

wherein, when the protrusion is in a first position relative to the blocking component, the blocking component restricts distal movement of the plunger rod to a first stopping point, and when the protrusion is in a second position relative to the blocking component, the blocking component restricts distal movement of the plunger rod to a second stopping point. In an embodiment of the invention, the DDD further includes: a stopper disposed in the body, wherein distal movement of the plunger rod distally moves the stopper; and a drug substance disposed in the body in between the stopper and a distal end of the body, wherein distal movement of the plunger rod to the first stopping point primes the drug delivery device, and distal movement of the plunger rod to the second stopping point dispenses a predetermined volume of the drug substance from a distal end of the device.

[000286]In an embodiment of the invention, moving the protrusion from the first position to the second position includes twisting the plunger rod relative to the blocking component. In an embodiment of the invention, the DDD further includes: a cavity in a proximal side of the blocking component, the cavity sized and configured to receive a portion of the protrusion, wherein when the protrusion is in the second position relative to the blocking component, the protrusion is positioned proximally from the cavity, such that distal movement of the plunger rod moves the protrusion into the cavity; *e.g.*, wherein the cavity is a first cavity, and further includes: a second cavity in a proximal side of the blocking component, the second cavity sized and configured to receive a portion of the protrusion, wherein the first and second cavity are located on opposite sides of a central longitudinal axis of the drug delivery device. In an embodiment of the invention, the plunger rod passes through an opening in the blocking component. In an embodiment of the invention the DDD further includes an actuation portion at a proximal end portion of the plunger rod, wherein the protrusion extends from the actuation portion, *e.g.*, wherein the actuation portion includes a generally cylindrical shape having a diameter greater than a width of the remainder of the plunger rod, wherein the protrusion extends from a side of the generally cylindrical shape, and wherein the actuation portion further comprises: a thumb pad on a proximal end of the actuation portion; and a ring on an exterior surface on the side of the generally cylindrical shape; *e.g.*, further including a proximal collar on the blocking component, wherein the actuation portion partially fits inside the proximal collar;

e.g., wherein the plunger rod further includes a pair of extensions protruding distally from the actuation portion and the blocking component (*e.g.*, which includes one or more indents formed along a bottom wall of the blocking component; and wherein a portion of each extension is configured to be received by the one or more indents upon distal movement of the plunger rod relative to the blocking component to allow distal movement of the plunger rod to the second stopping point; or, which includes one or more indents formed along a bottom wall of the blocking component; and wherein a portion of each extension is configured to be received by the one or more indents upon distal movement of the plunger rod relative to the blocking component to allow distal movement of the plunger rod to the second stopping point; or, which includes a pair of internal grooves formed along a sidewall of the blocking component; and wherein a portion of each extension is configured to be received by at least one of the pair of internal grooves upon rotation of the plunger rod relative to the blocking component to expand the extensions radially-outward from a compressed state to a relaxed state) includes a pair of openings; and wherein a portion of each extension is configured to be received by one of the pair of openings in the first stopping point. In an embodiment of the invention, the protrusion is a first protrusion, and further includes a second protrusion extending from the plunger rod in a direction opposite to the first protrusion. In an embodiment of the invention, the blocking component is slidably coupled to the body and includes a third cavity and a pair of ribs that extend into the third cavity, wherein the body includes a top flange and the pair of ribs are configured to engage the top flange received in the third cavity; wherein the pair of internal ribs are configured to apply a distally-directed force onto the top flange. In an embodiment of the invention, the blocking component is slidably coupled to the body and includes a pair of movable tabs that are configured to engage the body; and the pair of movable tabs are laterally deflectable upon receiving the body in the blocking component and are configured to apply a radially-inward directed force onto the body. In an embodiment of the invention, the blocking component further includes a pair of finger flanges, and each of the finger flanges includes a textured surface having a predefined pattern that increases a grip of the blocking component.

[000287]In an embodiment of the invention, the drug delivery device (DDD), includes:

- a body;
- a plunger rod having a distal end contacting a stopper inside the body, and a proximal end including an actuation portion with a thumb pad;
- a plurality of protrusions extending from the actuation portion; and
- a blocking component disposed on the body, the blocking component including a proximal collar having a plurality of slots,

wherein, when the protrusions and the slots are in a first configuration relative to one another, the blocking component restricts distal movement of the plunger rod to a first stopping point, and when the protrusions and the slots are in a second configuration, the blocking component restricts distal movement of the plunger rod to a second stopping point, wherein, in the second configuration, the slots are configured to receive the protrusions upon distal movement of the plunger rod. In an embodiment of the invention, the protrusions and the slots are movable from the first configuration to the second configuration by rotation of the actuation portion about a longitudinal axis in relation to the blocking component, and wherein when the protrusions and the slots are in the second configuration, the protrusions and the slots are not movable to the first configuration; and/or

a difference between the first stopping point and the second stopping point is equivalent to a distance that the stopper must travel to expel a predetermined volume of a drug product from a distal end of the body, and wherein the plunger rod is prevented from moving from the second stopping point to the first stopping point; and/or the plurality of protrusions includes two protrusions disposed symmetrically about the actuation portion; and/or the blocking component further comprises a pair of finger flanges; and/or the drug delivery device is a pre-filled syringe; and/or the drug delivery device is changeable: (a) from a pre-use state to a primed state, by longitudinally moving the plunger rod (*e.g.*, wherein the plunger rod includes a neck disposed distally from the actuation portion, wherein the neck interfaces with an opening in the blocking component to prevent proximal movement of the plunger rod, for example, wherein the neck further interfaces with the opening in the blocking component to prevent movement of the drug delivery device from the delivery state to the primed state) until the plunger rod reaches the first stopping point; (b) from the primed state to a delivery state by rotating the plunger rod in relation to the blocking component until the protrusions and the blocking component are in the second configuration; and (c) from a delivery state to a used state by longitudinally moving the plunger rod until the plunger reaches the second stopping point, wherein the drug delivery device is not changeable from the used state to the delivery state, from the delivery state to the primed state, or from the primed state to the pre-use state. In an embodiment of the invention, when the plunger rod is at the second stopping point, the stopper does not contact a distal end of the body.

[000288]In an embodiment of the invention, a drug delivery device, includes:

- a body;
- a plunger rod, including:
- a distal portion contacting a stopper inside the body;

- a proximal end including a generally cylindrical actuation portion disposed outside of the body; and
- two protrusions extending from opposite sides of the actuation portion in a symmetrical configuration; and
- a blocking component coupled to the body, the blocking component including: a collar configured to accept a distal part of the actuation portion; and two cavities in the collar having proximally-facing openings, wherein each cavity is configured to accept a distal portion of one of the two protrusions;

wherein the plunger rod is longitudinally movable and rotatable about a longitudinal axis relative to the blocking component, and

wherein, when the drug delivery device is in a pre-use state, the protrusions and the cavity openings are not longitudinally aligned, and when the drug delivery device is in a delivery state, the protrusions and the cavity openings are longitudinally aligned. In an embodiment of the invention, the blocking component further includes a finger flange, and further includes a ribbed surface on a side of the actuation portion. In an embodiment of the invention, the plunger rod further includes: two extensions protruding distally from the actuation portion; and a plurality of openings in the collar of the blocking component, wherein a portion of each extension is configured to be received by one of the plurality of openings upon distal movement of the plunger rod relative to the blocking component.

[000289]In an embodiment of the invention, a drug delivery device includes:

- a body;
- a stopper disposed inside the body;
- a sleeve having a proximal end and a distal end, the distal end being disposed inside the body, proximally from the stopper; and
- a plunger rod disposed at least partially inside the sleeve;

wherein, when the stopper is in a ready position, distal advancement of one of (a) only the sleeve, (b) only the plunger rod, or (c) both the sleeve and the plunger rod together, relative to the body advances the stopper to a primed position, and wherein, when the stopper is in the primed position, distal advancement of another of (a) only the sleeve, (b) only the plunger rod, or (c) both the sleeve and the plunger rod together, relative to the body advances the stopper to a dose completion position. For example, in an embodiment of the invention, a DDD further includes a removable blocking component (*e.g.*, wherein the blocking component is a clip removably secured around at least a portion of the sleeve) disposed between a proximal portion of the sleeve and a proximal end of the body, the blocking component obstructing distal

advancement of the sleeve relative to the body, wherein distal advancement of the sleeve relative to the body after removal of the blocking component advances the stopper to the primed position. In an embodiment of the invention, the DDD further includes a removable locking component (*e.g.*, a pin, a tab, or a bar) that couples the plunger rod to the sleeve, wherein distal advancement of both the sleeve and the plunger rod together relative to the body advances the stopper to the primed position, wherein distal advancement of only the plunger rod relative to the body after removal of the locking component advances the stopper to the dose completion position. In an embodiment of the invention, in the dose completion position, a proximal end of the plunger rod abuts against a distal end of the sleeve, such that the plunger rod is prevented from advancing distally any further relative to the body. In an embodiment of the invention, the DDD further includes a protrusion disposed on the plunger rod; and an inner protrusion disposed on an interior wall of the sleeve distally to the protrusion of the plunger rod, wherein distal advancement of only the plunger rod relative to the body advances the stopper to the primed position and causes the protrusion of the plunger rod to contact the inner protrusion of the sleeve, and wherein distal advancement of both the plunger rod and the sleeve relative to the body, after the protrusion of the plunger rod has contacted the inner protrusion of the sleeve, advances the stopper to the dose completion position. In an embodiment of the invention, the sleeve includes a finger flange. In an embodiment of the invention, the DDD further includes a stop disposed at a proximal end of the body, the stop sized to block distal advancement of the sleeve or the plunger rod once the stopper is in the completion position.

[000290]In an embodiment of the invention, a drug delivery device, includes:

- a body;
- a plunger rod having a distal portion disposed inside the body and a proximal portion disposed outside a proximal end of the body, the proximal portion having a width greater than a width of the distal portion; and
- an obstruction that, in an obstructing position relative to the plunger rod, prevents distal advancement of the plunger rod from a primed position to a dose completion position, wherein displacement of the obstruction from the obstructing position permits distal advancement of the plunger rod to the dose completion position, for example, further including a collar affixed to a proximal end portion of the body, the collar surrounding the proximal portion of the plunger rod; and a collar projection extending radially inward from the collar, wherein the proximal portion of the plunger rod includes a channel into which the collar projection protrudes, the channel including a circumferential path and an axial dose completion path, wherein the obstruction comprises the collar projection, which, when disposed in the circumferential path of

the channel, prevents distal advancement of the plunger rod to the dose completion position, and wherein displacement of the obstruction from the obstructing position comprises twisting the plunger rod about a longitudinal axis to align the collar projection with the axial dose completion path. For example, in an embodiment of the invention, the channel further includes an axial priming path offset from the axial dose completion path, and connected to the axial dose completion path by the circumferential path, and distal movement of the plunger rod such that the collar projection travels on the axial priming path advances the plunger rod to the primed position. In an embodiment of the invention, the DDD further includes a finger flange. In an embodiment of the invention, the proximal portion of the plunger rod includes a projection extending radially outward, and the drug delivery device further includes: a rotatable alignment component disposed in between the proximal portion of the plunger rod and the body, the alignment component including a channel, the channel sized and configured to accommodate the plunger rod projection, wherein the obstruction comprises a wall of the channel that blocks a distal axial path of the plunger rod projection when the plunger rod is in the primed position, and wherein displacement of the obstruction from the obstructing position comprises rotating the alignment component to remove the wall of the channel from the distal axial path of the plunger rod projection, *e.g.*, further including a finger flange coupled to a proximal end portion of the body, wherein the rotatable alignment component is disposed between the finger flange and the proximal portion of the plunger rod. In an embodiment of the invention, the DDD further includes a flange piece disposed at the proximal end of the body, wherein the obstruction includes a removable cap that, when in the obstructing position relative to the plunger rod, is disposed partially in between the proximal portion of the plunger rod and the flange piece. In an embodiment of the invention, removal of the cap allows the proximal portion of the plunger rod to advance to a dose completion position, wherein, in the dose completion position, the proximal portion of the plunger rod contacts the flange piece. In an embodiment of the invention, the removable cap covers the proximal portion of the plunger rod when in the obstructing position. In an embodiment of the invention, the DDD further includes a collar disposed between the proximal end of the body and the proximal portion of the plunger rod, the collar defining an opening sized to accommodate the proximal portion of the plunger rod upon distal advancement of the plunger rod beyond a primed position; wherein the obstruction comprises a tab protruding radially outward from the proximal portion of the plunger rod, the tab preventing the proximal portion of the plunger rod from fitting into the opening of the collar, and wherein a depth of the collar opening coincides with a distance the plunger rod must travel to advance distally to the dose completion position, *e.g.*, wherein displacement of the obstruction from the obstructing

position comprises either removing the tab or compressing the tab into a side of the proximal portion of the plunger rod; and/or wherein the tab is a first tab, and wherein the obstruction further comprises a second tab protruding radially outward from the proximal portion of the plunger rod in a direction opposite the protruding direction of the first tab; and/or wherein the obstruction comprises a tab that, when in the obstructing position, is disposed between the body and the proximal portion of the plunger rod, and wherein the plunger rod includes a geometry disposed proximally from the tab, wherein the geometry cannot advance distally past the tab when the tab is in the obstructing position. For example, displacement of the obstruction may include removing the tab from the drug delivery device by pulling the tab. In an embodiment of the invention, the DDD further includes a flange piece, wherein a portion of the tab is disposed inside a cavity of the flange piece. In an embodiment of the invention, displacement of the obstruction comprises removing the tab from the drug delivery device by breaking the tab. In an embodiment of the invention, the obstruction includes a flange piece that, in the obstructing position, is disposed proximally from the proximal end of the body, between the proximal portion of the plunger rod and the body, and is spaced from the proximal end of the body by a removable blocking component, and wherein displacement of the obstruction from the obstructing position comprises: removing the blocking component; and shifting the flange piece distally towards the proximal end of the body. In an embodiment of the invention, the plunger rod includes a projection extending radially outward, wherein the obstruction includes a lever having an end that, in the obstructing position, is located distally from the projection and blocks distal movement of the projection and thereby distal movement of the plunger rod, and wherein displacement of the obstruction from the obstructing position comprises actuating the lever to remove the end of the lever from its location distal from the projection. In an embodiment of the invention, distal advancement of the plunger rod beyond the dose completion position is prevented by contact between the proximal portion of the plunger rod and a portion of a flange piece coupled to the body.

[000291]In an embodiment of the invention, the drug delivery device, includes:

- a body;
- a sleeve affixed to the body, the sleeve including a proximal end, a distal end, and an opening disposed in a circumferential wall of the sleeve;
- a plunger rod passing through the sleeve, the plunger rod including a distal end portion disposed inside the body, and a radially-extending protrusion;

wherein the plunger rod may be distally advanced into the body from a ready position to a primed position, wherein, in the primed position, the protrusion of the plunger rod is disposed

inside the opening, and further distal advancement of the plunger rod is resisted by contact between the protrusion and a wall of the opening, and wherein pressure may be exerted on the protrusion to overcome the resistance to further distal advancement of the plunger rod. In an embodiment of the invention, the opening in the sleeve is a second opening, and the sleeve further includes a first opening disposed in the circumferential wall of the sleeve proximally from the second opening, and a third opening disposed in the circumferential wall of the sleeve distally from the second opening, wherein, in the ready position, the protrusion of the plunger rod is disposed in the first opening, and further distal advancement of the plunger rod is resisted by contact between the protrusion and a wall of the first opening, and wherein, after further distal advancement of the plunger rod past the primed position, the protrusion of the plunger rod is disposed in the third opening, and further distal advancement of the plunger rod is prevented. In an embodiment of the invention, the radially-extending protrusion is a first protrusion, and wherein the plunger rod further includes a second radially-extending protrusion opposite the first protrusion, and wherein squeezing the first and second protrusions towards one another while applying axial pressure in the distal direction on the plunger rod overcomes the resistance to further distal advancement of the plunger rod. In an embodiment of the invention, the protrusion includes a distally-tapering profile to aid in distal advancement of the plunger rod.

[000292]In an embodiment of the invention, a drug delivery device, includes:

- a body;
- a plunger rod including a distal end portion disposed inside the body and a rotatable element; and
- a sleeve affixed to the body, the sleeve including a proximal opening into which the plunger rod may be advanced,

wherein rotating the rotatable element causes distal advancement of the plunger rod to a primed position, and wherein once the plunger rod is in the primed position, further rotation of the rotatable element is resisted. In an embodiment of the invention, the DDD further includes a collar disposed at a proximal end of the body, an interior of the collar including a proximal threaded portion forming a proximal helical path, wherein the rotatable element comprises a proximal portion of the plunger rod including a protrusion, wherein the proximal portion of the plunger rod may be rotated about a longitudinal axis to cause the protrusion to travel distally along the proximal helical path, and wherein once the protrusion reaches the end of the proximal threaded portion of the collar, the plunger rod is in the primed position, *e.g.*, wherein once the plunger rod is in the primed position, the plunger rod may be depressed axially into the body to distally advance the plunger rod to a dose completion position; and/or wherein the

interior of the collar further includes a distal threaded portion, wherein threads of the distal threaded portion form a distal helical path offset from, and opposite to, the proximal helical path, wherein alignment of the protrusion with the distal helical path places the plunger rod in the primed position, and wherein rotation of the proximal portion of the plunger rod to cause the protrusion to travel distally along the distal helical path causes distal advancement of the plunger rod to a dose completion position.

[000293]A substance may be dispensed using such a DDD having a plunger rod and a body, may be done by a method including:

(a) advancing the plunger rod by a predetermined distance into the body until advancement of the plunger rod is resisted by a stop;

(b) rotating the plunger rod about a longitudinal axis; and

(c) actuating the plunger rod to dispense a predetermined volume of the substance,

wherein none of steps (a), (b), and (c) are reversible. In an embodiment of the invention, the DDD further includes a flange piece having a collar, and advancing the plunger rod and actuating the plunger rod comprise pressing an actuation portion of the plunger rod into the collar of the flange piece; for example, wherein the plunger rod comprises a protrusion, and wherein the collar of the flange piece abuts against the protrusion to resist advancement of the plunger rod. For example, in an embodiment of the invention, wherein rotating the plunger rod comprises twisting an actuation portion of the plunger rod relative to the flange piece, until a protrusion on the plunger rod becomes longitudinally aligned with a cavity in the collar of the flange piece, which may further include advancing the protrusion into the cavity until the protrusion abuts a distal side of the cavity, wherein the predetermined volume of the substance is dispensed when the protrusion abuts the distal side of the cavity.

See International patent application publication no. WO2020/247686.

[000294] Data from the PHOTON trial through week 48 are provided. Patient disposition data in the PHOTON trial are set forth in Figure 5 and baseline demographics data are in Figures 6 and Figure 7. The mean patient exposure to injections per week is summarized in Figure 8. Efficacy data with respect to changes in visual acuity (BCVA; Figure 9); durability (Figure 10); changes to DRSS (Figure 11); retinal fluid (Figure 12); and changes to central retinal thickness (CRT) (Figure 13) are also provided. In addition, safety data are set forth in Figure 14-Figure 24.

[000295] Data from the PULSAR trial through week 48 are provided. Patient disposition data in the PHOTON trial are set forth in Figure 45 and baseline demographics and study eye

characteristics data are in Figure 46 and Figure 47. The mean patient exposure to injections is summarized in Figure 48. Efficacy data with respect to changes in visual acuity (BCVA; Figure 49); durability (Figure 50); center subfield retinal fluid at weeks 16 and 48 (Figure 51 and Figure 52, respectively); and central retinal thickness (CRT) and changes to CRT (Figure 53) are also provided. In addition, safety data are set forth in Figure 54-Figure 64. Week 60 data with respect to absolute BCVA and change in BCVA over time are set forth in Figure 66. Durability is summarized in Figure 67 and the mean number of injections received in each group is summarized in Figure 68. Figure 69 summarizes central retinal thickness over time in the treatment groups.

EXAMPLES

[000296]The present invention includes methods for achieving any of the individual results or PK points, for example, by the period of time after treatment initiation that is indicated (*e.g.*, improvement in BCVA by X ETDRS letters by Y days after treatment initiation) as is set forth in the Examples section in a subject having nAMD, DR and/or DME by administering an HDq24, HDq12-20, HDq12, HDq16 or HDq20 treatment regimen to the subject.

Example 1: A Randomized, Double-Masked, Active-Controlled Phase 2/3 Study of the Efficacy and Safety of High-Dose Aflibercept in Patients with Diabetic Macular Edema (PHOTON) (clinicaltrials.gov ID. NCT04429503).

[000297] Data in these trials was previously presented in WO2023/177689. Additional data from PHOTON to week 96 or 100 is presented herein.

[000298]This is a phase 2/3, multi-center, randomized, double-masked study in patients with DME involving the center of the macula to investigate the efficacy and safety of HD versus 2 mg aflibercept. Approximately 640 eligible patients randomized into 3 treatment groups in a 1:2:1 ratio to the following 3 treatment groups:

1) **2q8**: 2 mg aflibercept every 8 weeks, following 5 initial monthly doses (n=160),
2) **HDq12**: HD aflibercept (8 mg) every 12 weeks, following 3 initial monthly doses (n=320),
3) **HDq16**: HD aflibercept (8 mg) every 16 weeks following 3 initial monthly doses (n=160).

(see Figure 1)

[000299]Approximately 24 patients will be included in a dense PK sub-study (n=8 per group, with half Japanese and half non-Japanese per group). In all patients, blood samples for measurement of drug concentrations (PK) and anti-drug antibody (ADA) will be obtained prior to the first treatment and at prespecified time points throughout the course of the study.

Dosing Schedule

[000300]The dosing schedule is set forth in Figure 3.

Primary Endpoints

[000301]The primary endpoint is the change from baseline in BCVA at week 48.

Secondary Endpoints

[000302]The key secondary efficacy endpoints are:

- Proportion of patients with a ≥2 step improvement in Diabetic Retinopathy Severity Scale (DRSS) at week 48
- Change from baseline in BCVA at week 60

[000303]The additional secondary efficacy endpoints are:

- Proportion of patients gaining ≥15 letters at week 48
- Proportion of patients with BCVA ≥69 letters at week 48
- Proportion of patients without fluid at foveal center at week 48
- Change from baseline in central retinal thickness (CRT) at week 48
- Proportion of patients without leakage on fluorescein angiography (FA) at week 48
- Change from baseline in National Eye Institute Visual Function Questionnaire (NEI-VFQ) total score at week 48
- Systemic pharmacokinetics of aflibercept as assessed from baseline through week 48
- Assessment of immunogenicity to aflibercept through end of study (EOS) week (week 96).

[000304]The secondary safety endpoint is:

- Safety evaluation by assessment of AEs and serious adverse events (SAEs) through weeks 48, 60, and 96

Exploratory Endpoints

[000305]The exploratory endpoints are:

- Proportion of patients without retinal fluid (total fluid, intraretinal fluid [IRF] and/or subretinal fluid [SRF]) at the foveal center and in center subfield at week 48 and week 96
- Time to fluid-free retina over 48 weeks and 96 weeks (total fluid, IRF and/or SRF at foveal center and in the center subfield)

- Proportion of patients with sustained fluid-free retina over 48 weeks and 96 weeks (total fluid, IRF and/or SRF at foveal center and in the center subfield)
- Proportion of patients without CSME (clinically significant macular edema) at week 48 and week 96
- Fluid on spectral domain optical coherence tomography (SD-OCT)
- Proportion of patients with a ≥3 step improvement in DRSS at week 48 and week 96
- Proportions of patients gaining and losing ≥5 or ≥10 letters at week 48 and week 96
- Proportion of patients losing ≥15 letters at week 48 and week 96
- Proportion of patients randomized to HDq16 maintaining q16 dosing interval or longer through weeks 48, 60, and 96
- Proportion of patients randomized to HDq12 maintaining q12 dosing interval or longer through weeks 48, 60 and 96
- Proportion of patients with an assigned injection interval of ≥16 or ≥20 weeks based on assessment at the last injection visit

In addition to those specified above, all primary, secondary, and exploratory endpoints may be analyzed in an exploratory manner at weeks 60 and 96.

Efficacy Variables

[000306]The efficacy variable relevant to the primary efficacy endpoint is visual acuity.

[000307]The efficacy variables relevant to the secondary endpoints are:

- BCVA
- Assessment of retinal fluid levels and retinal thickness on spectral domain optical coherence tomography (SD-OCT)
- Dosing interval
- Quality of life using the NEI VFQ-25
- Diabetic retinopathy severity level using the DRSS

[000308]The efficacy variables relevant to the exploratory endpoints are:

- Assessment of retinal fluid levels and retinal thickness on SD-OCT
- BCVA
- Dosing interval

Safety Variables

[000309]Safety will be evaluated by assessment of AEs and SAEs, ocular exams, IOP, vital signs (including BP, heart rate, and temperature), and clinical laboratory values.

Pharmacokinetic Variables

The PK variables are the concentrations of free, bound, adjusted bound, and total aflibercept in plasma at each time point.

Immunogenicity Variables

[000310]The immunogenicity variables are anti-drug antibody (ADA) status, titer, and neutralizing antibody (NAb) status at each study visit time point.

Number of Patients Planned

[000311]The study will enroll approximately 640 patients to be randomized 1:2:1 (160 patients each in the 2q8 and the HDq16 groups, and 320 patients in the HDq12 group).

Study Population

[000312]The study population will comprise patients with DME with central involvement.

Inclusion Criteria (See Figure 2)

[000313]A patient must meet the following criteria at both the screening and randomization visits (except where indicated) to be eligible for inclusion in the study:

1. Men or women ≥18 years of age (or country's legal age of adulthood if the legal age is >18 years) with type 1 or type 2 diabetes mellitus
2. DME with central involvement in the study eye with CRT ≥300µm (or ≥320 µm on Spectralis) as determined by the reading center at the screening visit
3. BCVA early treatment diabetic retinopathy study (ETDRS) letter score of 78 to 24 (approximate Snellen equivalent of 20/32 to 20/320) in the study eye with decreased vision determined to be primarily the result of DME
4. Willing and able to comply with clinic visits and study-related procedures
5. Provide informed consent signed by study patient or legally acceptable representative

Exclusion Criteria (See Figure 2)

[000314]Patients who meets any of the following criteria at either the screening or randomization visits will be excluded from the study:

1. Evidence of macular edema due to any cause other than diabetes mellitus in either eye
2. Active proliferative diabetic retinopathy in the study eye

3. Panretinal laser photocoagulation (PRP) or macular laser photocoagulation in the study eye within 12 weeks (84 days) of the screening visit
4. IVT anti-VEGF treatment (aflibercept, ranibizumab, bevacizumab, brolucizumab, pegaptanib sodium) in the study eye within 12 weeks (84 days) of the screening visit
5. Prior IVT investigational agents in either eye (*e.g.*, anti-ang-2/anti-VEGF bispecific monoclonal antibodies, gene therapy, etc.) at any time
6. Treatment with ocriplasmin (JETREA®) in the study eye at any time
7. Previous use of intraocular or periocular corticosteroids in the study eye within 16 weeks (112 days) of the screening visit, or ILUVIEN® or OZURDEX® IVT implants at any time
8. History of vitreoretinal surgery (including scleral buckle) in the study eye
9. Any other intraocular surgery within 12 weeks (84 days) before the screening visit
10. Yttrium-aluminum-garnet (YAG) laser capsulotomy in the study eye within 4 weeks (28 days) of the screening visit
11. IOP ≥25 mmHg in the study eye
12. History of glaucoma filtration surgery in the past, or likely to need filtration surgery in the future in the study eye
13. Evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye within 4 weeks (28 days) of the screening visit
14. Any intraocular inflammation/infection in either eye within 12 weeks (84 days) of the screening visit
15. History of idiopathic or autoimmune uveitis in the study eye
16. Vitreomacular traction or epiretinal membrane in the study eye evident on biomicroscopy or OCT that is thought to affect central vision
17. Preretinal fibrosis involving the macula in the study eye
18. Any history of macular hole of stage 2 and above in the study eye
19. Current iris neovascularization, vitreous hemorrhage, or tractional retinal detachment visible at the screening assessments in the study eye
20. History of corneal transplant or corneal dystrophy in study eye
21. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the patient beyond what is to be expected from standard procedures of IVT injections, or which otherwise may interfere with the injection procedure or with evaluation of efficacy or safety
22. Only 1 functional eye, even if that eye was otherwise eligible for the study (*e.g.*, BCVA of counting fingers or less in the eye with worse vision)

23. Structural damage to the center of the macula in the study eye that is likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia, or organized hard exudates
24. Ocular conditions with poorer prognosis in the fellow eye
25. Inability to obtain photographs, FA, or SD-OCT in the study eye, *e.g.*, due to media opacity, allergy to fluorescein dye, or lack of venous access
26. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect interpretation of the results of the study or render the patient at high risk for treatment complications
27. Any prior systemic (IV) anti-VEGF administration
28. Uncontrolled diabetes mellitus as defined by hemoglobin A1c (HbA1c) >12%
29. Uncontrolled blood pressure (defined as systolic >160 mmHg or diastolic >95 mmHg). Patients may be treated with up to 3 agents known to have anti-hypertensive effects for arterial hypertension to achieve adequate blood pressure control. This limit applies to drugs that could be used to treat hypertension even if their primary indication in the patient was not for blood pressure control. Any recent changes in medications known to affect blood must be stable for 12 weeks (84 days) prior to screening.
30. History of cerebrovascular accident or myocardial infarction within 24 weeks (168 days) of screening visit
31. Renal failure, dialysis, or history of renal transplant
32. Known sensitivity to any of the compounds of the study formulation
33. Participation in an investigational study within 30 days prior to screening visit that involved treatment with any drug (excluding vitamins and minerals) or device
34. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor
35. Pregnant or breastfeeding women
36. Men or women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 3 months after the last dose. Highly effective contraceptive measures include:
a. stable use of combined (estrogen and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal

contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
c. bilateral tubal ligation
d. vasectomy**
e. condom plus contraceptive sponge, foam, or jelly, or diaphragm plus contraceptive sponge, foam, or jelly
f. and/or sexual abstinence†, ‡.
*Postmenopausal women must be amenorrhoeic for at least 12 months without an alternative medical cause in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.
**Vasectomized partner or vasectomized study participant must have received medical assessment of the surgical success.
†Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
‡Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.
[000315]Additional Exclusion Criteria for the PK sub-study:
1. Prior treatment with IVT aflibercept in the fellow eye within 12 weeks (84 days) of the screening visit
2. Other IVT anti-VEGF treatment (ranibizumab, bevacizumab, brolucizumab, pegaptanib sodium) in the fellow eye within 4 weeks (28 days) of the screening visit
3. Patients with SBP >140 mmHg or diastolic blood pressure (DBP) >90 mmHg
4. Patients with known cardiac arrhythmia
5. Patients who, in the opinion of the investigator, are unlikely to have stable BP over the course of the study (*e.g.*, due to known or suspected non-compliance with medication)
6. Variation by more than 10% in the 3 pre-randomization BP measures recorded at the screening visits and at randomization

Investigational and Reference Treatments

[000316]The HD drug product will be supplied for this study as an aqueous solution in sterile, sealed, single-use vials for IVT administration at a concentration of 114.3 mg/mL aflibercept which will be delivered in an injection volume of 70 µl (0.07 mL). Intravitreal aflibercept injection 2 mg will be supplied for this study as an aqueous solution in sterile, sealed, single-use vials for IVT administration at a concentration of 40 mg/mL delivered in an injection volume of 50 µL (0.05 mL).

Study Assessments and Procedures

[000317]Study procedures and their timing are summarized in the following tables.

Table 1-1. Baseline to Week 48

Study Procedure	Screening Visit 1	Baseline Visit 2	Visit 3	Visit 4	Optional Visit 4.1[1]	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
Week		0	4	8		12	16	20	24	28	32	36	40	44	48
Day	-21 to -1	1	29	57	69-84	85	113	141	169	197	225	253	281	309	337
Window (day)			±5	±5		±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Screening/Baseline:															
Informed consent form(ICF)	X														
Dense PK substudy ICF[2]	X														
Genomic substudy ICF[3]	X														
Future Biomedical Research ICF[4]	X														
Inclusion/Exclusion	X	X													
Medical history	X														
Demographics	X														
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X													
Administer Study Drug[5]															
Study drug (active or sham)		X	X	X		X	X	X	X	X	X	X	X	X	X
DRM assessment							X[5]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
Ocular Efficacy and Safety (bilateral unless indicated):															
BCVA (ETDRS) and Refraction[7]	X	X	X	X		X	X	X	X	X	X	X	X	X	X
IOP[8]	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Slit lamp examination	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy[8]	X	X	X	X		X	X	X	X	X	X	X	X	X	X
FA, FP[9]	X					X			X			X			X
SD-OCT[10]	X	X	X	X		X	X	X	X	X	X	X	X	X	X

Table 1-2. Baseline to Week 48 (continued)

Study Procedure	Screening Visit 1	Baseline Visit 2	Visit 3	Visit 4	Optional Visit 4.1[1]	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
Week		0	4	8		12	16	20	24	28	32	36	40	44	48
Day	-21 to -1	1	29	57	60-84	85	113	141	169	197	225	253	281	309	337
Window (day)			±5	±5		±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
OCTA substudies[11]	X					X			X			X			X
NEI-VFQ-25	X								X						X
Nonocular Safety:															
Physical examination	X														
Vital signs[12]	X	X	X	X	X[1]	X	X	X	X	X	X	X	X	X	X
ECG	X														X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[13]															
Hematology	X														X
Blood chemistry	X														X
HbA1c	X														X
Pregnancy test (women of childbearing potential)[14]	X Serum	X Urine	X Urine	X Urine		X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine
Urinalysis/UPCR	X														X
Pharmacokinetics and Other Sampling															
PK samples (Dense)[15, 17]		See Schedule Below	X		X[1]	X				X					X
PK samples (Sparse)[16, 17]		X	X		X[2]	X				X					X
Genome DNA sample[3]		X													
Immunogenicity sample[16, 17]		X													X

Table 1-3. Week 52 to Week 96

Study Procedure	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 25	EOS Visit[19] 26
Week	52	56	60	64	68	72	76	80	84	88	92	96
Day	365	393	421	449	477	505	533	561	589	617	645	673
Window (day)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Screening Baseline:												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Administer Study Drug[3]												
Study Drug (active or sham)	X	X	X	X	X	X	X	X	X	X	X	
DRM assessment	X[5]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	
Ocular Efficacy and Safety (bilateral unless indicated):												
BCVA (ETDRS) and refraction[7]	X	X	X	X	X	X	X	X	X	X	X	X
IOP[8]	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp examination	X	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy[9]	X	X	X	X	X	X	X	X	X	X	X	X
FA, FP[10]			X			X			X			X
SD-OCT[10]	X	X	X	X	X	X	X	X	X	X	X	X
OCTA Substudies[11]			X			X			X			X
NEI VFQ-25			X									X
Nonocular Safety:												
Physical examination												
Vital signs[12]	X	X	X	X	X	X	X	X	X	X	X	X
ECG												X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[13]												
Hematology												X
Blood chemistry												X
HbA1c												X

Table 1-4. Study Procedure

Study Procedure	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 25	EOS Visit[18] 26
Week	52	56	60	64	68	72	76	80	84	88	92	96
Day	365	393	421	449	477	505	533	561	589	617	645	673
Pregnancy test (women of childbearing potential)[15]	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	
Urinalysis/UPCR												X
Pharmacokinetics and Other Sampling												
PK samples(Dense)[15,17]												
PK samples(Sparse)[15,17]												
Genomic DNA sample[3]												
Immunogenicity sample[16,17]												X

BCVA=Best corrected visual acuity, DRM = Dose regimen modification, ECG=electrocardiogram, ETDRS=Early Treatment Diabetic Retinopathy Study, FA=fluorescein angiography, FP=fundus photography, IOP=Intraocular pressure, OCTA = optical coherence tomography angiography, PK=pharmacokinetics, SD-OCT=spectral domain optical coherence tomography, UPCR=urine protein:creatinine ratio, UWFA = ultra-widefield fluorescein angiography.

Footnotes for Tables 1-1 to 1-3:

1. An optional visit for all patients on days 60 to 64 (after the third injection) to collect a PK sample and assess heart rate and BP (no temperature measures required) as well as concomitant medications and AEs
2. Signed only by patients participating in the dense PK sub-study and in addition to the study ICF
3. The optional genomic sub-study ICF should be presented to patients at the screening visit and may be signed at any subsequent visit at which the patient chooses to participate after screening. The genomic DNA sample should be collected on day 1/baseline (pre-dose) or at any study visit from patients who have signed the sub-study ICF.
4. The optional future biomedical research sub-study ICF should be presented to patients and signed at the screening visit.
5. Refer to pharmacy manual for study drug injection guidelines. Following study drug injection, patients will be observed for approximately 30 minutes.
6. Assessments for DRM criteria will occur in all patients at all visits for masking purposes beginning at week 16.
7. Patients enrolled at sites participating in the optional visual function sub-study may undergo additional visual function tests. See study procedure manual for details.
8. Intraocular pressure will be measured at all study visits (bilateral). On days when study drug is administered, IOP should be measured pre-dose (bilaterally) by the masked investigator (or designee) and approximately 30 minutes after administration of study drug (study eye only) by the unmasked investigator. IOP will be measured using Goldman applanation tonometry or Tono-pen™ and the same method of measurement must be used in each patient throughout the study.
9. Indirect ophthalmoscopy will be performed bilaterally at all visits by the masked investigator. On days when study drug is administered, it should also be performed immediately after administration of study drug (study eye only).
10. The same SD-OCT/FA/FP imaging system used at screening and day 1 must be used at all follow-up visits in each patient. Images will be taken in both eyes before dosing at each required visit. For FA, the study eye will be the transit eye and images should be collected using the widest field available. If available, sites should also submit an

optional ultra-widefield color photograph.
11. Details on an optional sub-study evaluating OCTA are provided in study procedure manual. Images will be collected at the same timepoints as FA/FP.
12. Vital signs (BP, heart rate, temperature) should be measured prior to injection and any blood sampling. When possible, timing of all BP assessments should be within 2 hours of clock time of dosing on day 1.
13. All samples collected for laboratory assessments should be obtained prior to administration of fluorescein and prior to administration of study drug.
14. For women of childbearing potential, a negative serum pregnancy test at screening is required for eligibility. A negative urine pregnancy test is required before treatment is administered at subsequent visits.
15. Dense PK sampling will be performed in approximately 24 patients (n=8/group) as indicated in Table 1-2. Additional samples will be drawn according to the dense PK sub-study schedule defined in Table 1-3. On dosing visits, PK sampling should be performed prior to the administration of study drug and within 2 hours of the clock time of dosing on day 1.
16. On dosing visits, PK and ADA sampling will be performed prior to dosing.
17. PK and ADA samples may also be drawn at any non-specified scheduled visit or any unscheduled visit if a patient experiences an unexpected SAE.
18. The EOS will also represent the early termination visit.

[000318]Schedule of events for the Dense PK sub-study are presented in Table 1-5, below.

Table 1-5. Schedule of Events for Dense PK sub-study

Visit	Dose	Assessment Day	Assessment Time (h)	PK Sample	Heart Rate and Blood Pressure[3]
Screening 2[1]		-20 to -1	±2h		X[2]
Visit 2		1	Predose[3]	X	X[3]
	X		4h ±30min	X	
			8h ±2h	X	
		2	±2h[3]	X	X[2]
		3	±2h[3]	X	X[2]
		5	±2h[3]	X	X[2]
		8	±2h[3]	X	X[2]
		15	±2h[3]	X	X[2]
		22	±2h[3]	X	X[3]

Footnotes for the Dense PK sub-study

1. Additional BP assessment to confirm eligibility for patients in the dense PK sub-study between screening and baseline
2. Timing of all BP assessments must be within 2 hours of the clock time of dosing on day 1. Blood pressure assessments for patients in the dense PK sub-study will be obtained prior to blood sample collection, using automated office blood pressure (AOBP) measurement with the Omron Model HEM 907XL (or comparable). Measures displayed by the device will be recorded in the electronic data capture (EDC). Detailed instructions can be found in the study procedure manual.
3. PK sampling is to be performed within ±2 hours of the clock time of dosing on day 1.

Ocular Procedures

[000319]The ocular study procedures (efficacy and safety) include the following.

[000320]*Intraocular Pressure.* Intraocular pressure of the study eye will be measured in both eyes at every visit using Goldmann applanation tonometry or Tono-pen®. The same method of IOP measurement must be used throughout the study for each individual patient. Intraocular pressure will be measured pre-dose (bilateral) by the masked physician (or designee), and at approximately 30 minutes post-dose (study eye) by the unmasked physician (or designee).

Slit Lamp Examination - Patients' anterior eye structure and ocular adnexa will be examined bilaterally pre-dose at each study visit using a slit lamp by the masked investigator.

[000321]*Indirect Ophthalmoscopy.* Patients' posterior pole and peripheral retina will be examined by indirect ophthalmoscopy at each study visit pre-dose (bilateral) by the masked investigator and post-dose (study eye) by the unmasked investigator. Post-dose evaluation must be performed immediately after injection.

[000322]*Fundus Photography/Fluorescein Angiography.* The anatomical state of the retinal vasculature, including the DRSS level, leakage, and perfusion status will be evaluated by FP and FA. Fundus photography and FA will be captured and transmitted to an independent reading center for both eyes. For FA, the study eye will be the transit eye and images should be collected using the widest field available. If available, sites should also submit an optional ultra-widefield color photograph. Fundus and angiographic images will be sent to an independent reading center where images will be read by masked readers.

[000323]*Spectral Domain Optical Coherence Tomography.* Retinal characteristics will be evaluated at each study visit using SD-OCT. Images will be captured and transmitted for both eyes. Images will be sent to an independent reading center where they will be read by masked readers.

[000324]*Best Corrected Visual Acuity.* Visual function of the study eye and the fellow eye will be assessed using the ETDRS protocol (Early Treatment Diabetic Retinopathy Study Research Group, 1985) at 4 meters at each study visit. Best corrected visual acuity should be assessed before any other ocular procedures are performed.

[000325]*Quality of Life Questionnaire* - Vision-related quality of life (QoL) will be assessed using the NEI VFQ-25 in the interviewer-administered format at visits.

Dosing Regimen Modifications/Rescue Regimen

[000326]For masking purposes, assessments for dose regimen modifications (DRMs) will be performed in all participants at all visits (through the IWRS) beginning at week 16. Based on these assessments, patients in the HD groups may have their treatment intervals shortened

(year 1 and year 2) or extended (year 2). The minimum interval between injections will be 8 weeks which is considered a rescue regimen for patients randomized to HD aflibercept and unable to tolerate a dosing interval greater than every 8 weeks. Patients in the aflibercept 2 mg group will remain on fixed q8 dosing throughout the study (*i.e.*, will not have modifications of their treatment intervals regardless of the outcomes of the DRM assessments).

Year 1: Baseline to Week *52*

[000327]Beginning at week 16, patients in the HD groups will have the dosing interval shortened (at the visits described below) if BOTH of the following criteria are met:

1. >10 letter loss in BCVA from week 12 in association with persistent or worsening DME; AND
2. >50 µm increase in CRT from week 12 (It should be noted that the change in CRT for these criteria will be assessed at the site.)

[000328]If a patient in the HDq12 group or the HDq16 group meets both criteria at week 16 or week 20, the patient will be dosed with 8 mg aflibercept at that visit and will continue on a rescue regimen (aflibercept 8 mg, every 8 weeks). If a patient in the HDq16 group who has not met the criteria at week 16 or 20 meets both criteria at week 24, the patient will be dosed with 8 mg aflibercept at that visit and will continue on q12 week dosing.

[000329]For patients whose interval was not shortened to q8 dosing at or before week 24, the interval will be shortened if the DRM criteria are met at a subsequent dosing visit. Patients in the HDq12 group who meet the criteria will receive the planned dose at that visit and will then continue on a rescue regimen (aflibercept 8 mg, every 8 weeks). Patients in the HDq16 group who meet these criteria will receive the planned dose at that visit and will then continue to be dosed every 12 weeks if they were on a 16-week interval, or switch to the rescue regimen (aflibercept 8mg, every 8 weeks) if they were previously shortened to a 12-week interval. Therefore, a patient randomized to HDq16 whose injection interval has been shortened to q12 will have their injection interval further shortened to q8 if these criteria are met at any subsequent dosing visit.

[000330] *Year 2:* Week *52 to* Week *96 (End of Study)*

[000331]From week 52 through the end of study (year 2), all patients in the HD groups will continue to have the interval shortened in 4-week intervals if the DRM criteria for shortening are met at dosing visits using the DRM criteria described above for year 1. As in year 1, the minimum dosing interval for patients in all treatment groups is every 8 weeks.

[000332]In addition to shortening of the interval, all patients in the HD groups (including patients whose interval was shortened during year 1) may be eligible for interval extension (by 4-week increments), if BOTH the following criteria are met at dosing visits in year 2:
1. <5 letter loss in BCVA from week 12; AND
2. CRT <300 µm for Cirrus SD-OCT (or <320 µm on Spectralis SD-OCT)
[000333]For patients who do not meet the criteria for shortening or extension of the interval, the dosing interval will be maintained.
[000334]As in year 1, all patients in all treatment groups (including the 2q8 group) will be evaluated against both DRM criteria at all visits through the IWRS for masking purposes. However, changes to dosing schedule will only be implemented as described above for those patients randomized to HDq12 or HDq16 treatment groups. No changes to the dosing schedule will be made to the 2q8 treatment group at any time.

[000335]The Full Analysis Set (FAS) included all randomized participants who received at least 1 dose of study drug; it was based on the treatment assigned to the participant at baseline (as randomized). The FAS was the primary analysis set for efficacy endpoints.
[000336]The Safety Analysis Set (SAF) included all randomized participants who received any study treatment; it was based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables were analyzed using the SAF.

Results at Week 48
[000337]Aflibercept HDq12 and HDq16 dosing regimens achieved the high bar of sustaining improvements in visual acuity and anatomic measures of retinal fluid across 48 weeks in patients with diabetic macular edema. The vast majority of patients did not require regimen modification. The data also support these regimens while maintaining a safety profile similar to EYLEA.
[000338] *Visual Outcomes.* Both HDq12 and HDq16 demonstrated non-inferiority to 2q8 with respect to the primary efficacy endpoint (change from baseline in BCVA at week 48) using the non-inferiority margin of 4 letters with LS_{mean} change from baseline in BCVA of 8.10 letters (HDq12) and 7.23 letters (HDq16) versus 8.67 letters in the 2q8 group (Table 1-6). The differences in LS_{mean} changes from baseline in BCVA (95% CI) were -0.57 (- 2.26, 1.13) and -1.44 (-3.27, 0.39) for HDq12 and HDq16, respectively compared to 2q8 (Table 1-6). The p-values for the non-inferiority test at a margin of 4 letters were <0.0001 for HDq12 vs. 2q8, and

0.0031 for HDq16 vs. 2q8. The lower confidence limits were greater than -4, allowing the conclusion of non-inferiority at week 48 timepoint.

Table 1-6. Primary Endpoint -- Change from Baseline in BCVA (ETDRS Letters) at Week 48 in the Study Eye, MMRM (Full Analysis Set)

Treatment	LSmean (SE) change from BL	Mean (SD) change form BL	BL mean	Number of patients with week 48 data	DF	Contrast [a]	t-value	1-sided NI p-value[b]	1-sided superiority p-value	Estimate for contrast and 2-sided 95% CI[c]
HDq12 (N=328)	8.10 (0.61)	8.77 (8.95)	63.63	277	351.5	HDq12 - 2q8	3.9881	<0.0001	0.7447	-0.57 (-2.26, 1.13)
HDq16 (N=163)	7.23 (0.71)	7.86 (8.38)	61.44	149	315.0	HDq16 - 2q8	2.7533	0.0031	0.9388	-1.44 (-3.27, 0.39)
2q8 (N=167)	8.67 (0.73)	9.21 (8.99)	61.47	150						

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; BCVA=Best corrected visual acuity; CRT=Central retinal thickness; DME=Diabetic macular edema; ETDRS=Early Treatment Diabetic Retinopathy Study; EDC=electronic data capture; BL=baseline; CI=confidence interval; DF=degrees of freedom; NI=non-inferiority; LS=least square; SAP=statistical analysis plan; SE=standard error; SD=standard deviation A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT from reading center [<400µm vs. ≥400µm], prior treatment for DME per EDC; [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom.
a The contrast also included the interaction term for treatment x visit.
b p-value for the 1-sided non-inferiority (NI) test at a margin of 4 letters.
c Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with 2-sided 95% CIs.

[000339]The mean values of BCVA score averaged from week 36 to week 48 were similar across treatment groups, and the change from baseline was similar across treatment groups (Table 1-7).

Table 1-7. Summary of Averaged BCVA Score: Week 36 to Week 48 (OC) (Full Analysis Set)

	Value at Visit	Change from Baseline

Treatment	Visit	n	Mean	SD	SE	Q1	Median	Q3	Min, Maxn	Mean	SD	SE	Q1	Median	Q3	Min, Max
2q8 (N=167)	BASELINE	167	61.5	11.22	0.87	54.0	63.0	70.0	24, 78							
WEEK 36 TO 48		155	70.5	11.75	0.94	64.0	73.0	79.0	23, 90 155	8.8	8.60	0.69	4.0	9.3	13.5	-26, 48
HDq12 (N=328)	BASELINE	328	63.6	10.10	0.56	57.0	65.0	72.0	27, 79							
WEEK 36 TO 48		286	71.8	11.35	0.67	65.3	73.9	80.0	22, 92 286	8.1	8.93	0.53	3.0	7.9	12.5	-50, 38
HDq16 (N=163)	BASELINE	163	61.4	11.76	0.92	55.0	64.0	71.0	29, 78							
WEEK 36 TO 48		154	69.1	12.77	1.03	62.5	72.6	78.3	21, 92 154	7.2	7.95	0.64	2.8	6.3	10.3	-12, 38

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals, HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals, ICE= intercurrent events; n= number; Q= quartile; SAP= statistical analysis plan; SD= standard deviation; SE= standard error; OC: observations after an intercurrent event (ICE) defined for the primary estimand were excluded.

[000340]The proportion of participants who gained ≥ 15 letters in BCVA from baseline to week 48 was 18.7% and 16.6% in the HDq12 and HDq16 groups, respectively, compared with 23.0% in the 2q8 group (Table 1-8).

[000341]Sensitivity analysis for the proportion of participants who gained ≥ 15 letters in BCVA from baseline at week 48 using OC was consistent with the LOCF analysis.

Table 1-8. Proportion of Participants who Gained ≥ 15 Letters in BCVA from Baseline at Week 48 (LOCF) (Full Analysis Set)

Treatment	Patients with ≥ 15 Letters gain in BCVA from baseline to Week 48, n (%)	Adjusted Difference (%) (95% CI)[a]	CMH test[b] p-value
HDq12 (N=328)	61/326 (18.7%)	-4.64 (-12.30 , 3.02)	0.2231
HDq16 (N=163)	27/163 (16.6%)	-7.14 (-15.45 , 1.17)	0.0960
2q8 (N=167)	38/165 (23.0%)		

Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12=High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16=High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. BCVA=best corrected visual acuity; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CRT= central retinal thickness (or, central subfield retinal thickness); DME= diabetic macular edema; ICE=intercurrent events; LOCF=last observation carried forward; N,n=number of patients; SAP= statistical analysis plan. LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute

subsequent and/or missing or non-gradable data. Missing data were not included in the denominator.
a Difference with CI was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]).
b Nominal p-value for the 2-sided CMH superiority test.

[000342]The proportion of participants who achieved ≥ 69 letters in BCVA (≥ 20/40 Snellen equivalent) at week 48 was similar across treatment groups (63.0 to 65.3% participants) (Table 1-9).

[000343]Sensitivity analyses for the proportion of participants who achieved ≥ 69 letters in BCVA at week 48 using OC were consistent with the LOCF analysis.

Table 1-9. Proportion of Participants with BCVA ≥ 69 letters at Week 48 (LOCF) (FAS)

Treatment	Patients with BCVA >= 69 letters at Week 48, n (%)	Adjusted Difference (%) (95% CI) [a]	CMH test [b] p-value
HDq12 (N=328)	213/326 (65.3%)	2.45 (-6.47 , 11.36)	0.5917
HDq16 (N=163)	102/163 (62.6%)	-0.67 (-11.16 , 9.82)	0.8998
2q8 (N=167)	104/165 (63.0%)		

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. BCVA: best corrected visual acuity; CMH=Cochran-Mantel-Haenszel; CRT= central retinal thickness (or, central subfield retinal thickness); DME= diabetic macular edema; FAS= Full analysis set; LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing data; N,n=number of patients.
a Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan])
b Nominal p-value for the 2-sided Cochran-Mantel-Haenszel

[000344]The proportion of participants who gained or lost ≥ 5, ≥ 10, or ≥ 15 letters from baseline through week 48 is presented in Table 1-10. Across all treatment groups, more participants gained letters, with the greatest proportion gaining ≥ 5 letters (approximately 65 to 71% across all treatment groups). A numerically lower proportion of participants in the HDq12 and HDq16 groups gained ≥ 10 letters or ≥ 15 letters compared to the 2q8 group. Few participants (approximately 1 to 6%) lost 5 or more letters through week 48 regardless of treatment group.

Table 1-10. Proportion of Participants who Gained or Lost ≥ 5, 10, or 15 Letters in BCVA from Baseline by Visit through Week 48 (LOCF) (Full Analysis Set)

Endpoint		2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)
Gained >= 5 letters	Week 48	113/165 (68.5%)	231/326 (70.9%)	107/163 (65.6%)
Gained >= 10 letters	Week 48	81/165 (49.1%)	132/326 (40.5%)	57/163 (35.0%)
Gained >= 15 letters	Week 48	38/165 (23.0%)	61/326 (18.7%)	27/163 (16.6%)
Lost >= 5 letters	Week 48	5/165 (3.0%)	21/326 (6.4%)	10/163 (6.1%)
Lost >= 10 letters	Week 48	2/165 (1.2%)	11/326 (3.4%)	2/163 (1.2%)
Lost >= 15 letters	Week 48	2/165 (1.2%)	7/326 (2.1%)	1/163 (0.6%)

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; BCVA= best corrected visual acuity; ICE=intercurrent events; LOCF=last observation carried forward; SAP=statistical analysis plan. LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing data. Missing data were not included in the denominator.

[000345]*DRSS.* The proportion of participants with a ≥ 3-step improvement in DRSS at week 48 was 11.9% and 9.2% in the HDq12 and HDq16 groups, respectively, compared with 14.6% in the 2q8 group (Table 1-11).

[000346]Sensitivity analyses for the proportion of participants with a ≥ 3-step improvement in DRSS score at week 48 using OC were consistent with the LOCF analysis.

Table 1-11. Proportion Analysis of Participants with a ≥ 3-step Improvement from Baseline in DRSS at Week 48 (LOCF) (Full Analysis Set)

Treatment	Patients with a ≥ 3-step improvement from baseline in DRSS at Week 48, n (%)	Adjusted Difference (%) (95% CI) [a]	CMH test [b] p-value
HDq12 (N=328)	37/310 (11.9%)	-2.79 (-9.50, 3.91)	0.3920
HDq16 (N=163)	14/153 (9.2%)	-5.59 (-12.88, 1.70)	0.1310
2q8 (N=167)	23/158 (14.6%)		

2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12=High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16=High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; DRSS=Diabetic Retinopathy Severity Scale; CRT=Central retinal thickness; DME=Diabetic macular edema. LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data.

Patients were considered as non-responders if all post-baseline measurements were missing or non-gradable. Missing or ungradable baseline was not included in the denominator.
a. Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan])
b. p-value for the two-sided Cochran-Mantel-Haenszel (CMH) superiority test

[000347]HDq12 was non-inferior to 2q8 with respect to this endpoint (≥2 step improvement in DRSS). However, this could not be shown for the HDq16 group. The non-inferiority margin was prespecified at 15%, however HDq12 also met a 10% NI margin. The proportion of participants with ≥ 2-step improvement in DRSS score was 25.7%, 24.7% and 20.7% at week 12 and 26.6%, 29.0%, and 19.6% at week 48 in the 2q8, HDq12, and HDq16 groups respectively. In Cochran-Mantel-Haenszel (CMH)-weighted estimates, the adjusted difference (95% CI) was 1.98% (-6.61, 10.57) for HDq12 and -7.52% (- 16.88, 1.84) for HDq16, respectively versus 2q8 (Table 1-12). Sensitivity analysis using observed cases (OC) was performed and was consistent with the primary analysis.

Table 1-12. Key Secondary Endpoint – Proportion of Participants with a ≥ 2-Step Improvement from Baseline in DRSS at Week 48 (LOCF) (Full Analysis Set)

Treatment	Patients with a ≥ 2-step Improvement From Baseline in DRSS, n (%)	Adjusted Difference (%) 2-sided (95% CI) [a]
HDq12 (N=328)	90/310 (29.0%)	1.98 (-6.61 , 10.57)
HDq16 (N=163)	30/153 (19.6%)	-7.52 (-16.88 , 1.84)
2q8 (N=167)	42/158 (26.6%)	

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. CI=confidence interval; CRT= central retinal thickness; DRSS=Diabetic Retinopathy Severity Scale; N,n=number of patients; SAP = statistical analysis plan Intercurrent events (ICE). LOCF= the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or nongradable data. Patients were considered as non-responders if all post-baseline measurements were missing or nongradable. a Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]). The non-inferiority margin was set at 15%. Missing or ungradable baseline was not included in the denominator.

[000348]As the tests for the primary endpoint and change from baseline in BCVA at Week 60 (key secondary endpoint) were significant for both HD groups, the test sequence could be continued with testing the key secondary efficacy endpoint, the proportion of participants with ≥

2-step improvement in DRSS score (as assessed by the central reading center) at week 48. HDq12 was non-inferior to 2q8 with respect to this endpoint. However, this could not be shown for the HDq16 group. The non-inferiority margin was prespecified at 15%, however HDq12 also met a 10% NI margin. The proportion of participants with ≥ 2-step improvement in DRSS score was 25.7%, 24.7% and 20.7% at week 12 and 26.6%, 29.0%, and 19.6% at week 48 in the 2q8, HDq12, and HDq16 groups respectively. In Cochran-Mantel-Haenszel (CMH)-weighted estimates, the adjusted difference (95% CI) was 1.98% (-6.61, 10.57) for HDq12 and 7.52% (-16.88, 1.84) for HDq16, respectively versus 2q8.

[000349] *Retinal Fluid.* The proportion of participants without fluid (no IRF and no SRF) at the foveal center (as assessed by the central reading center) at week 48 was 58.5% and 43.8% in the HDq12 and HDq16 groups, respectively, compared with 54.5% in the 2q8 group (Table 1-13).

[000350] Sensitivity analyses for the proportion of participants without fluid (no IRF and no SRF) at the foveal center at week 48 using OC were consistent with the LOCF analysis.

Table 1-13. Proportion of Participants without Fluid (no IRF and no SRF) at the Foveal Center at Week 48 (LOCF) (Full Analysis Set)

Treatment	Patients without fluid,- n(%)	Adjusted Difference (%) (95% CI)[a]	CMH test[b] p-value
HDq12 (N=328)	190/325 (58.5%)	4.32 (-4.72, 13.36)	0.3491
HDq16 (N=163)	71/162 (43.8%)	-9.73 (-20.34, 0.87)	0.0757
2q8 (N=167)	90/165 (54.5%)		

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
CI=confidence interval; CMH=Cochran-Mantel-Haenszel; DME= diabetic macular edema; ICE=intercurrent events; IRF=intraretinal fluid; LOCF=last observation carried forward; N=number of participants; SRF=subretinal fluid.
LOCF= the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data.
Missing or undetermined data were not included in the denominator.
a. Difference with CI was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]).
b. Nominal p-value for the 2-sided CMH superiority test.

[000351]The proportion of participants without fluid (no IRF and no SRF) in the center subfield at week 48 was 27.4% and 14.8% in the HDq12 and HDq16 groups, respectively, compared with 21.8% in the 2q8 group (Table 1-14).

[000352]Sensitivity analyses for the subset of participants without fluid (no IRF and no SRF) in the center subfield at week 48 using OC were consistent with the LOCF analysis.

Table 1-14. Proportion of Participants Without Fluid (no IRF and no SRF) at the Central Subfield at Week 48 (LOCF) (Full Analysis Set)

Treatment	Patients without fluid, n (%)	Adjusted Difference (%) (95% CI) [a]	CMH test [b] p-value
HDq12 (N=328)	89/325 (27.4%)	5.84 (-2.02 , 13.71)	0.1610
HDq16 (N=163)	24/162 (14.8%)	-6.75 (-14.94 , 1.44)	0.1110
2q8 (N=167)	36/165 (21.8%)		

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CRT = central retinal thickness; DME = diabetic macular edema; ICE= intercurrent events; IRF=intraretinal fluid; LOCF=last observation carried forward; N,n=number of patients; SAP = Statistical analysis plan; SRF=subretinal fluid. LOCF: the last observation prior to an ICE defined for the primary estimand was to be used to impute subsequent and/or missing data Missing or undetermined data were not included in the denominator.
a Difference with CI was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]).
b Nominal p-value for the 2-sided CMH superiority test.

[000353]*Anatomical Outcomes.* Overall, the LS_{mean} (SE) change from baseline in CRT (as assessed by the central reading center) at week 48 was -176.77 (5.73) and -148.84 (9.45) in the HDq12 and HDq16 groups, respectively, compared with -164.85 (8.79) in the 2q8 group (Table 1-15).

[000354]The mean changes from baseline in CRT using OC, are graphically displayed in Figure 26A; the corresponding LS_{mean} changes from baseline in CRT using MMRM in the FAS (full analysis set), are displayed in Figure 26B.

[000355]Sensitivity analyses for change from baseline in CRT at week 48 using LOCF were consistent with the MMRM analysis.

Table 1-15. Statistical Analysis of Change from Baseline in Central Retinal Thickness (microns) at Week 48 (MMRM)(FAS)

Treatment	LS_{mean} (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 48 data	DF	Contrast [a]	t-value	p-value [b]	Estimate for contrast and 2-sided 95% CI [c]
HDq12 (N=328)	-176.77 (5.73)	-171.65 (141.52)	449.15	276	254.9	HDq12 – 2q8	-1.2768	0.2028	-11.92 (-30.30, 6.47)
HDq16 (N=163)	-148.84 (9.45)	-148.30 (133.20)	460.32	149	295.3	HDq16 – 2q8	1.3386	0.1817	16.01 (-7.53, 39.54)
2q8 (N=167)	-164.85 (8.79)	-165.31 (140.22)	457.25	148					

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. CI = Confidence interval. CRT = Central retinal thickness. SE = Standard error. SD = Standard deviation. DF = Degrees of freedom. FAS = Full analysis set. LS = Least Square. BL = Baseline. MMRM = mixed model for repeated measurements. SAP = statistical analysis plan; DME=Diabetic macular edema; EDC=electronic data capture. A mixed model for repeated measurements (MMRM) was used with baseline CRT measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400µm vs. >=400µm], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject error.
a The contrast also included the interaction term for treatment x visit.
b Nominal p-value for the 2-sided superiority test
c Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with 2-sided 95% CIs.

Fluid Leakage

[000356]Overall, the proportion of participants without leakage on fluorescein angiography (as assessed by the central reading center) at week 48 (LOCF) was very low in all 3 treatment groups: 7.6% and 0.7% in the HDq12 and HDq16 groups, respectively, compared with 2.5% in the 2q8 group.

[000357]Sensitivity analyses for the proportion of participants without leakage on fluorescein angiography at week 48 using OC were consistent with the LOCF analysis.

[000358]A summary of the change from baseline in total area of fluorescein leakage within the ETDRS grid at week 48 is shown in Table 1-16.

Table 1-16. Summary of the Change from Baseline in Total Area of Fluorescein Leakage within ETDRS Grid (mm^2) at Week 48 (OC) (Full Analysis Set)

Statistic	2q8 N=167	HDq12 N=328	HDq16 N=163
Baseline n	164	319	153
Baseline mean (SD)	24.6 (13.20)	24.4 (13.22)	24.6 (11.73)
Week 48 n	131	224	129
Mean (SD) change from baseline at week 48	-9.2 (12.11)	-13.9 (13.91)	-9.4 (11.50)
Median change from baseline at week 48	-6.8	-13.3	-7.7
Min, Max	-85, 18	-88, 52	-39, 55

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; SAP=statistical analysis plan. ETDRS: Early Treatment Diabetic Retinopathy Study; OC: observations after an ICE defined for the primary estimand were excluded; SD; standard deviation.

[000359] *Patient Reported Outcomes.* Overall, the LS_{mean} change from baseline in NEI-VFQ-25 total score at week 48 was 4.06 and 2.94 in the HDq12, and HDq16 groups, respectively, compared with 2.82 in the 2q8 group (Table 1-17).

[000360] Sensitivity analyses for the change from baseline in NEI-VFQ-25 total score at week 48 using ANCOVA, LOCF and were consistent with the MMRM analysis.

Table 1-17. Change from Baseline in NEI-VFQ-25 Total Score at Week 48 (MMRM) (Full Analysis Set)

Treatment	LS_{mean} (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 48 data	DF	Contrast [a]	t-value	p-value [b]	Estimate for contrast and 2-sided 95% CI [c]
HDq12 (N=328)	4.06 (0.80)	5.64 (12.56)	76.79	276	251.4	HDq12 - 2q8	1.0515	0.2941	1.25 (-1.09, 3.58)
HDq16 (N=163)	2.94 (0.93)	4.16 (10.94)	77.86	149	261.8	HDq16 - 2q8	0.0995	0.9208	0.13 (-2.37, 2.62)
2q8 (N=167)	2.82 (1.10)	4.41 (13.84)	76.65	150					

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; CI = Confidence interval. SE = Standard error. SD = Standard deviation. DF = Degrees of freedom. LS = Least Square. BL = Baseline. MMRM = mixed model for repeated measurements. SAP = statistical analysis plan; DME = diabetic macular edema; EDC = electronic data capture A mixed model for repeated measurements

(MMRM) was used with baseline NEI-VFQ-25 total score measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400µm vs. >=400µm], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject error.
a The contrast also included the interaction term for treatment x visit
b Nominal p-value for the 2-sided superiority test
c Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with 2-sided 95% CIs.

[000361]*Safety.* Overall, a similar proportion of participants had TEAEs in the HD groups, 74.7% (245 participants; HDq12) and 77.3% (126 participants; HDq16), compared to 73.7% (123 participants) in the 2q8 group.

[000362]The proportions of participants with ocular TEAEs were similar across the groups and were 43.7% (73 participants), 44.8% (147 participants), and 44.8% (73 participants) in the 2q8, HDq12, and HDq16 groups, respectively. There were very few study-drug-related ocular and non-ocular TEAEs across all treatment groups. The proportion of participants with study conduct-related TEAEs and TEAEs related to 2 mg aflibercept in the fellow eye were minimally reported across groups (< 2.0% overall across groups). The proportion of participants with injection-procedure-related ocular TEAEs was similar across treatment groups (< 14% across groups).

[000363]The majority of serious AEs reported were non-ocular TEAEs (19.2% [32 participants], 18.6% [61 participants], and 16.6% [27 participants] in the 2q8, HDq12 and HDq16 groups, respectively). One injection-procedure-related ocular serious TEAE (Intraocular pressure increased) in the study eye was reported and occurred in the HDq12 group (0.3%). There were no reported study-drug-related serious TEAEs, study-conduct-related serious TEAEs, or serious TEAEs related to 2 mg aflibercept in the fellow eye.

[000364]Three (1.8%) participants in the 2q8 group, 9 (2.7%) participants in the HDq12 group, and 2 (1.2%) participants in the HDq16 group discontinued study drug due to TEAEs. Of these, 2 participants discontinued study drug due to ocular TEAEs (both in the HDq12 group).

[000365]Five deaths were reported in the 2q8 group (3.0%), 9 deaths in the HDq12 group (2.7%), and 4 deaths in the HDq16 group (2.5%). All deaths were considered unrelated to study treatment by the investigator.

[000366]The proportion of participants with treatment-emergent adjudicated Antiplatelet Trialists' Collaboration (APTC) events was low and generally similar across treatment groups:

3.6% (6 participants), 4.0% (13 participants), and 5.5% (9 participants) in the 2q8, HDq12, and HDq16 groups, respectively.

[000367]A slightly higher frequency of participants reported Hypertension in the HDq16 group (17.2%; 28 participants) compared to the 2q8 group (13.8%; 23 participants) and the HDq12 group (12.8%; 42 participants); however, this was not interpreted as clinically meaningful as there was no apparent dose relationship (ie, HDq16 versus HDq12).

[000368]There were no treatment-emergent nasal mucosal events reported through week 60.

[000369]Ocular TEAEs in the study eye were reported at similar frequencies in all 3 groups (29.3% [49 participants], 36.0% [118 participants], and 34.4% [56 participants] in the 2q8, HDq12, and HDq16 groups, respectively). No clinically meaningful differences were observed in type of TEAEs or their frequencies between the HD and 2q8 treatment groups, and reported events were consistent with the known safety profile of IVT aflibercept.

[000370]Overall, ocular TEAEs in the fellow eye were reported in 52 (31.1%) participants in the 2q8 group, 91 (27.7%) participants in the HDq12 group, and 52 (31.9%) participants in the HDq16 group.

[000371]All ocular TEAEs in the fellow eye were reported in < 6.0% of participants in each treatment group. The most frequent PTs were Cataract (4.2% [7 participants], 3.0% [10 participants], and 5.5% [9 participants] in the 2q8, HDq12, and HDq16 groups, respectively), Vitreous floaters (4.3%; 7 participants in the HDq16 group), Diabetic retinal oedema (3.4% [11 participants] in the HDq12 group), and Diabetic retinopathy (3.6% [6 participants] in the 2q8 group and 3.7% [6 participants] in the HDq16 group).

[000372]Ocular TEAEs were generally balanced across the 3 treatment groups.

[000373]Non-ocular TEAEs were reported in a similar proportion of participants in the 2q8 group (57.5%; 96 participants) and the Pooled HD group (60.9%; 299 participants). The majority of the TEAEs were in the SOC (system organ class) of Infections and infestations; however, the most common TEAE was Hypertension. A slightly higher frequency of participants reported Hypertension in the HDq16 group (15.3%; 25 participants) compared to the 2q8 group (10.8%; 18 participants) and the HDq12 group (9.1%; 30 participants); however, this was not interpreted as clinically meaningful as there was no apparent dose relationship (ie, HDq16 versus HDq12).

[000374]Other non-ocular TEAEs were reported ≤ 5.0% of participants in the 2q8 and the Pooled HD group except for COVID-19 (8.6%; 42 participants in the Pooled HD group).

[000375]Ocular study-drug-related TEAEs in the study eye were reported in 3 (1.8%) participants in the 2q8 group, 6 (1.8%) participants in the HDq12 group, and no participants in the HDq16 group.

[000376]Intraocular pressure increased was the only PT reported in more than 1 participant (3 [0.9%] participants in the HDq12 group).

[000377]All ocular study-drug-related TEAEs in the study eye were reported in < 1.0% of participants. There were no ocular study drug-related TEAEs in the fellow eye through week 60 reported in any treatment group.

[000378]One non-ocular study drug-related TEAE was reported through week 60: Lacunar infarction reported in 1 (0.6%) participant in the HDq16 group.

[000379]There were no non-ocular study-drug-related TEAEs reported through week 60 in the 2q8 or HDq12 groups.

[000380]Ocular IVT-injection-related TEAEs were reported in 16 (9.6%) participants in the 2q8 group, 42 (12.8%) participants in the HDq12 group, and 13 (8.0%) participants in the HDq16 group. Ocular IVT-injection-related TEAEs that were reported in > 2 participants in any of the 3 treatment groups included Conjunctival haemorrhage, Vitreous floaters, Eye pain, and Intraocularpressure increased which were reported in similar proportions of participants across the 3 treatment groups.

[000381]All other ocular IVT-injection-related TEAEs in the study eye were reported in ≤ 2 participants in each group. Ocular IVT-injection-related TEAEs in the fellow eye through week 60 were reported in 5 (3.0%) participants in the 2q8 group, 7 (2.1%) participants in the HDq

[000382]Non-ocular IVT-injection-related TEAEs through week 60 were reported in 3 (0.6%) participants in the Pooled HD group. The TEAEs reported in the HD groups included Nausea, Vomiting, and Headache. No participants reported non-ocular IVT-injection-related TEAEs in the 2q8 group.

[000383]Ocular and Non-ocular Study Conduct-Related TEAEs Through Week 60 The relationship of TEAEs to other study procedures were assessed by the masked investigator, and was a clinical decision based on all available information.

[000384]Study-conduct-related TEAEs were reported in 2 (0.6%) participants in the HDq12 group. These TEAEs were Conjunctival haemorrhage and Injection site irritation. No study-conduct-related TEAEs were reported in the 2q8 or HDq16 groups.

[000385]There were no ocular study-conduct-related TEAEs in the fellow eye through week 60 reported in any treatment group.

[000386]Non-ocular TEAEs Related to Study Conduct Non-ocular study-conduct-related TEAEs through week 60 were reported in 3 (1.8%) participants in the 2q8 group and 4 (0.8%) participants in the Pooled HD group. These TEAEs were Nausea, Vessel puncture site haematoma, Contrast media allergy, Post procedural pruritus, Rash, and Vein rupture

[000387]Ocular and Non-ocular TEAEs related to 2-mg Aflibercept in the Fellow Eye Once the fellow eye received 2-mg aflibercept treatment during the study, TEAEs and serious TEAEs were also assessed as related/not related to 2-mg aflibercept treatment in the fellow eye, assessed as related/not related to the study drug (delivered to the study eye), IVT injection, and other protocol-specified procedures.

[000388]No ocular TEAEs in the study eye related to 2-mg aflibercept in the fellow eye through week 60 were reported in any treatment group

[000389]Ocular TEAEs in the fellow eye related to 2-mg aflibercept in the fellow eye through week 60 were reported in few participants, 2 (1.2%) participants in the 2q8 group, 1 (0.3%) participant in the HDq12 group, and 2 (1.2%) participants in the HDq16 group. These TEAEs were Conjunctival haemorrhage, Halo vision, and Intraocular pressure increased.

[000390]One non-ocular TEAE related to 2-mg aflibercept in the fellow eye was reported through week 60: Lacunar infarction was reported in 1 (0.6%) participant in the HDq16 group. The same event was also considered to be related to study drug.

[000391]No non-ocular TEAEs related to 2-mg aflibercept in the fellow eye were reported through week 60 in the 2q8 or HDq12 groups.

[000392]Intensity of Ocular and Non-ocular TEAEs Through Week 60 'Intensity' is used in parallel and synonymously with 'severity' of AEs herein.

[000393]The majority of ocular TEAEs in the study eye were mild (22.8% [38 participants; 2q8 group], 26.2% [86 participants; HDq12 group], and 28.2% [46 participants; HDq16 group]) to moderate (6.0% [10 participants; 2q8 group], 9.1% [30 participants; HDq12 group], and 5.5% [9 participants; HDq16 group]).

[000394]Severe ocular TEAEs in the study eye were reported in few participants, 1 (0.6%) participant in the 2q8 group, 2 (0.6%) participants in the HDq12 group, and 1 (0.6%) participant in the HDq16 group. The ocular TEAEs that were reported as being severe in the study eye were Cataract nuclear and Cataract subcapsular (reported by 1 participant in the 2q8 group), Cataract subcapsular and Retinal vascular disorder (reported by 1 participant each in the HDq12 group), and Retinal detachment and Vitreous haemorrhage (reported by 1 participant in the HDq16 group).

[000395]The majority of ocular TEAEs in the fellow eye were mild (22.2% [37 participants; 2q8 group], 21.0% [69 participants; HDq12 group], and 22.1% [36 participants; HDq16 group]) to moderate (7.2% [12 participants; 2q8 group], 5.8% [19 participants; HDq12 group], and 9.8% [16 participants; HDq16 group]).

[000396]Severe ocular TEAEs in the fellow eye were reported in few participants, 3 (1.8%) participants in the 2q8 group, 3 (0.9%) participants in the HDq12 group, and no participants in the HDq16 group. Severe ocular TEAEs in the fellow eye reported by the 3 participants in the 2q8 group were Cataract subcapsular, Cataract nuclear, Diabetic retinopathy, and Retinal artery occlusion (reported by 1 participant each); Diabetic retinopathy (reported by 1 participant) and Vitreous haemorrhage (reported by 3 participants) in the HDq12 group.

[000397]The majority of non-ocular TEAEs were mild (25.7% [43 participants; 2q8 group] and 26.9% [132 participants; Pooled HD group]) to moderate (18.0% [30 participants; 2q8 group] and 21.6% [106 participants; Pooled HD group]). Severe non-ocular TEAEs were reported in 23 (13.8%) participants in the 2q8 group, and 61 (12.4%) participants in the Pooled HD group.

[000398]Ocular Serious TEAEs in the Study Eye Through Week 60 A total of 5 ocular serious TEAEs in the study eye were reported in 4 participants. Serious TEAEs in the study eye were Ulcerative keratitis (1 [0.6%] participant; 2q8 group), Cataract subcapsular, and Intraocular pressure increased (1 [0.3%] participant each; both in the HDq12 group), and Retinal detachment and Vitreous haemorrhage (1 [0.6%] participant; HDq16 group). None of the events were considered related to the study drug and 1 event (Intraocular pressure increased) was considered related to injection procedure.

[000399]A total of 11 ocular serious TEAEs of the fellow eye were reported in 9 participants. None of these events were considered related to the study drug. The majority of these TEAEs were reported in single participants only. Across the 2q8 and Pooled HD groups, the most frequent non-ocular serious TEAEs (reported in ≥3 participants) were Acute left ventricular failure (3 [1.8%] participants) in the 2q8 group; and Acute myocardial infarction (7 [1.4%] participants), Cardiac arrest (3 [0.6%] participants), Coronary artery disease (4 [0.8%] participants), Myocardial infarction (7 [1.4%] participants), COVID-19 (4 [0.8%] participants), Covid-19 pneumonia (3 [0.6%] participants), Pneumonia (4 [0.8%] participants), Hypoglycaemia (3 [0.6%] participants), Cerebrovascular accident (5 [1.0%] participants), Acute kidney injury (6 [1.2%] participants), and Acute respiratory failure (3 [0.6%] participants) in the Pooled HD group. None of these events were considered related to the study

[000400]There were no ocular TEAEs in the fellow eye reported resulting in the discontinuation of the study drug.

[000401]Non-ocular TEAEs reported that resulted in the discontinuation of the study drug for 3 (1.8%) participants in the 2q8 group and 9 (1.8%) participants in the Pooled HD group Non-ocular TEAEs leading to discontinuation of the study drug included Blood loss anaemia, Acute myocardial infarction, Cardiac arrest, Death, Multiple organ dysfunction syndrome, Cholecystitis

acute, Hip fracture, Endometrial cancer, Gastrointestinal neoplasm, Cerebrovascular accident, Encephalopathy, Acute kidney injury, Nephropathy toxic, and Aortic stenosis. No specific safety trend was observed, and most events were reported in single participants.

[000402]Ocular IVT-injection-related TEAEs in the fellow eye were generally balanced between the 3 treatment groups.

[000403]Through week 60, there were 18 deaths reported in this study, evenly distributed across the treatment groups, and all were associated with an SAE. None of the deaths were considered related to study drug or study procedure. Overall, the deaths reported were consistent with concurrent medical conditions and the complications of these conditions associated with an older population.

[000404]TEAEs related to Intraocular Inflammation were reported in 1 (0.6%) participant in the 2q8 group who reported Iridocyclitis, 4 (1.2%) participants in the HDq12 group who each reported 1 of the following: Iritis, Uveitis, Vitreal cells, and Vitritis, and 1 (0.6%) participant in the HDq16 group who reported Iridocyclitis. None of the events were serious.

[000405]Potential arterial thromboembolic events were evaluated by a masked adjudication committee according to criteria formerly applied and published by the APTC. Arterial thromboembolic events as defined by the APTC criteria include Nonfatal myocardial infarction, Nonfatal stroke (ischemic or hemorrhagic), or Death resulting from vascular or unknown causes. Low (< 6.0%) and similar proportions of participants reported adjudicated APTC events across the treatment groups.

[000406]Treatment-emergent hypertension events were reported in fewer than 20% of participants in any treatment group. A slightly higher portion of participants reported Hypertension in the HDq16 compared to the 2q8 group and the HDq12 group; however, this was not interpreted as clinically meaningful as there was no apparent dose relationship (ie, HDq16 versus HDq12). Approximately 76% of participants in all treatment groups had a medical history of Hypertension.

[000407]Due to findings from the preclinical toxicology studies for HD, an assessment was performed in the clinical program for events related to nasal mucosa. None of the participants experienced a TEAE consistent with Nasal mucosal findings.

[000408]Overall, the treatment-emergent ocular surgeries reported were consistent with the medical history and the concurrent clinical medical conditions of the population enrolled in this study. No specific safety concern was observed. Ocular treatment-emergent surgeries in the study eye were reported in 6 (3.6%) and 20 (4.1%) participants in the 2q8 and Pooled HD groups, respectively. The most frequent surgery was Cataract operation (3 [1.8%], 10 [3.0%],

and 2 [1.2%] participants in the 2q8, HDq12, and HDq16 groups, respectively). Fellow Eye Ocular treatment-emergent surgeries in the fellow eye were reported in 15 (9.0%) and 53 (10.8%) participants in the 2q8 and Pooled HD groups, respectively. The most frequent surgery across all treatment groups was Retinal laser coagulation (5 [3.0%], 15 [4.6%], and 7 [4.3%] participants in the 2q8, HDq12, and HDq16 groups, respectively).

[000409]Non-ocular Treatment-Emergent Surgeries Non-ocular treatment-emergent surgeries were reported in 38 (22.8%) and 72 (14.7%) participants in the 2q8 and Pooled HD groups, respectively (Post-text Table 14.3.3.3a). The most frequent treatment-emergent surgeries were Tooth extraction (4 [2.4%], 3 [0.9%], and 2 [1.2%] participants in the 2q8, HDq12, and HDq16 groups, respectively); Catheterisation cardiac (3 [1.8%], 4 [1.2%], and 0 participants in the 2q8, HDq12, and HDq16 groups, respectively); and Coronary artery bypass (3 [1.8%], 2 [0.6%], and 2 [1.2%] in the 2q8, HDq12, and HDq16 groups, respectively).

[000410]At 48 weeks, PHOTON met the primary endpoints of non-inferiority of aflibercept 8 mg to EYLEA, with BCVA improvements from baseline demonstrated across dosing groups (all $p=\leq 0.003$). The EYLEA outcomes in DME were consistent with previous clinical trial experience. In the every 16-week dosing regimen group, 89% of DME patients in PHOTON maintained this dosing interval with an average of 5 injections in the first year. In the every 12-week dosing regimen groups, 91% of DME patients in PHOTON maintained this dosing interval with an average of 6 injections in the first year. In a pooled analysis of aflibercept 8 mg dosing groups, 93% of DME patients in PHOTON maintained 12-week dosing or longer.

[000411]Key efficacy findings at 48 weeks are set forth in Table 1-18.

Table 1-18. Key Week 48 Efficacy Findings

	High-dose aflibercept 12-week regimen	**High-dose aflibercept 16-week regimen**	**EYLEA 8-week regimen**
PHOTON (DME)	**n=328**	**n=163**	**n=167**
Mean BCVA improvement, primary endpoint	8.8 letters	7.9 letters	9.2 letters
Non-inferiority p-value	<0.0001	0.0031	N/A
Absolute BCVA	72.6 letters	69.8 letters	71.0 letters
Patients maintained on dosing interval	91%	89%	N/A
Patients with ≥2-step DRSS, key secondary endpoint	29%*	20%*	27%

DRSS: diabetic retinopathy severity scale; N/A: not applicable
*the 12-week high-dose aflibercept group met the non-inferiority margin of 15%, while the 16-week group did not.

[000412]The safety of high-dose aflibercept was similar to EYLEA and consistent with the safety profile of EYLEA from previous clinical trials. There were no new safety signals for high-dose aflibercept and EYLEA, and no cases of retinal vasculitis, occlusive retinitis or endophthalmitis. Comparing pooled data for the 12- and 16-week high-dose aflibercept groups to the EYLEA groups, the following rates were observed:

- Serious ocular adverse events (AE): 0.6% versus 0.6% in PHOTON.
- Intraocular inflammation: 0.8% versus 0.6% in PHOTON.
- Patients meeting intraocular pressure criteria: 3.7% versus 2.4% in PHOTON.
- Serious non-ocular AEs: 14.7% versus 15.6% in PHOTON.

Results at Week 60

[000413]This study was conducted at 138 centers that randomized participants various countries. A total of 970 participants were screened; 310 of them were screen failures with failure to meet inclusion/exclusion criteria being the most frequent reason for screen failure. Overall, 660 participants were randomized as displayed in Table 1-19. Most participants in each of the 3 groups (2q8: 92.8%, HDq12: 87.8%, and HDq16: 92.7%) completed their week 60 analysis visit (Table 1-19). Numbers of participants who discontinued the study with reasons for discontinuation by treatment group are presented in Table 1-19. The most common reasons for discontinuation were death and withdrawal of consent by participant.

Table 1-19. Summary of Participant Disposition at Week 48 and Week 60 (All Randomized Participants)

	2q8 (N=167)	**HDq12 (N=329)**	**HDq16 (N=164)**	**All HD (N=493)**	**Total (N=660)**
Week 48 Number of patients who completed Week 48	157 (94.0%)	300 (91.2%)	156 (95.1%)	456 (92.5%)	613 (92.9%)
Number of patients who discontinued prior to Week 48	10 (6.0%)	29 (8.8%)	8 (4.9%)	37 (7.5%)	47 (7.1%)
Reasons for discontinuation prior to Week *48*					
Noncompliance with protocol by the subject	1 (0.6%)	0	0	0	1 (0.2%)
Adverse event	0	4 (1.2%)	1 (0.6%)	5 (1.0%)	5 (0.8%)

Decision by the investigator/sponsor	0	4 (1.2%)	1 (0.6%)	5 (1.0%)	5 (0.8%)
Withdrawal of consent by subject	4 (2.4%)	7 (2.1%)	2 (1.2%)	9 (1.8%)	13 (2.0%)
Lost to follow-up	1 (0.6%)	5 (1.5%)	1 (0.6%)	6 (1.2%)	7 (1.1%)
Death	4 (2.4%)	9 (2.7%)	3 (1.8%)	12 (2.4%)	16 (2.4%)
Due to COVID-19	0	0	0	0	0
Week 60 Number of patients who completed Week 60	155 (92.8%)	289 (87.8%)	152 (92.7%)	441 (89.5%)	596 (90.3%)
Number of patients who discontinued prior to Week 60	12 (7.2%)	40 (12.2%)	12 (7.3%)	52 (10.5%)	64 (9.7%)
Reasons for discontinuation prior to Week *60*					
Noncompliance with protocol by the subject	1 (0.6%)	1 (0.3%)	0	1 (0.2%)	2 (0.3%)
Adverse event	0	4 (1.2%)	2 (1.2%)	6 (1.2%)	6 (0.9%)
Decision by the investigator/sponsor	0	6 (1.8%)	2 (1.2%)	8 (1.6%)	8 (1.2%)
Withdrawal of consent by subject	4 (2.4%)	12 (3.6%)	2 (1.2%)	14 (2.8%)	18 (2.7%)
Lost to follow-up	2 (1.2%)	8 (2.4%)	2 (1.2%)	10 (2.0%)	12 (1.8%)
Death	5 (3.0%)	9 (2.7%)	4 (2.4%)	13 (2.6%)	18 (2.7%)
Due to COVID-19	0	0	0	0	0

Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12=High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16=High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; All HD=Pooled HDq12 and HDq16 groups; COVID-19=Coronavirus Disease 2019. The percentage was based on the number of patients in each treatment group as denominator. Definition of completed Week 48 = did not answer NO to the question "Did the subject complete the study?" on the "Study Completion" form prior to Week 48 visit. Definition of completed Week 60 = did not answer NO to the question "Did the subject complete the study?" on the "Study Completion" form prior to Week 60 visit.

[000414] *Protocol Deviations.* A summary of important protocol deviations by treatment group through week 48 is presented in Table 1-20. No additional important protocol deviations were identified between week 48 and week 60 database locks. Overall, there were 36 important protocol deviations reported for 36 participants. The proportion of participants with important deviations was similar across all treatment groups. The most common important protocol

deviation was initiation of study procedures without re-consenting participants to the amended informed consent form (ICF) (17 participants overall), followed by initiation of study procedures without consenting/prior to consenting of participants to the ICF (9 participants overall). All other important protocol deviations were reported in ≤ 5 participants in any treatment group and involved inclusion/exclusion criteria that were not met (Table 1-20).

Table 1-20. Summary of Important Protocol Deviations Through Week 48 (All Randomized Participants)

	2q8 (N=167)	HDq12 (N=329)	HDq16 (N=164)	All HD (N=493)	Total (N=660)
Number of Important Protocol Deviations	7	18	11	29	36
Patients with Any Important Protocol Deviation Type of Important Protocol Deviation	7 (4.2%)	18 (5.5%)	11 (6.7%)	29 (5.9%)	36 (5.5%)
Subject did not re-consent to amended ICF and study procedures initiated (never signed amended ICF or signed after procedure)	4 (2.4%)	6 (1.8%)	7 (4.3%)	13 (2.6%)	17 (2.6%)
Ex #07 met but subject randomized. [a]	3 (1.8%)	2 (0.6%)	0	2 (0.4%)	5 (0.8%)
Ex #08 met but subject randomized. [b]	0	1 (0.3%)	0	1 (0.2%)	1 (0.2%)
Inc #03 not met but subject randomized. [c]	0	3 (0.9%)	1 (0.6%)	4 (0.8%)	4 (0.6%)
Subject did not sign ICF and study procedures were initiated (never signed ICF or signed after procedure performed)	0	6 (1.8%)	3 (1.8%)	9 (1.8%)	9 (1.4%)

Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12=8 mg aflibercept administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16=8 mg aflibercept administered every 16 weeks after 3 initial injections at 4-week intervals; All HD=Pooled HDq12 and HDq16 groups; BCVA =best corrected visual acuity; DME= diabetic macular edema; ETDRS= Early Treatment Diabetic Retinopathy Study; Ex= exclusion criterion; ICF= informed consent form; Inc= inclusion criterion; IVT= intravitreal. The percentage for each analysis set was based on the number of randomized patients in each treatment group as denominator.
a Exclusion criterion #7: Prior use of intraocular or periocular corticosteroids in study eye within 16 weeks/112 days of screening or ILUVIEN® or OZURDEX® IVT implants at any time
b Exclusion criterion #8: History of vitreoretinal surgery (including scleral buckle) in the study eye
c Inclusion criterion #3: Subject didn't satisfy BCVA ETDRS score of 78-24 (Snellen equivalent of 20/32 - 20/320) in study eye with decreased vision determined to be result of DME

[000415]In addition to the above-mentioned important deviations, the following minor deviations regarding eligibility criteria were also reported:

- 1 participant in HDq16 met exclusion criterion #01- Evidence of macular edema due to any cause other than diabetes mellitus in the fellow eye;

- 5 participants met exclusion criterion #28- Uncontrolled diabetes mellitus as defined by HbA1c > 12% (3 in 2q8, 1 in HDq12, 1 in HDq16);
    - All 5 participants had values undetermined at baseline.
- 52 participants met exclusion criterion #29- Uncontrolled BP (systolic > 160 mmHg or diastolic > 95 mmHg); treated with up to 3 agents known to have anti-hypertensive effects for arterial hypertension to achieve adequate blood pressure control; changes in BP medications must be stable for 12 weeks (84 days prior to screening)
    - 26 participants were randomized despite having SBP or DBP above of the protocol specified range (3 in 2q8, 14 in HDq12, 9 in HDq16);
    - 25 participants were randomized despite being treated with > 3 BP medication (7 in 2q8, 10 in HDq12, 7 in HDq16);
    - 1 participant in 2q8 group was randomized despite having BP medication regimen changed within 12 weeks of screening

[000416]This study was not substantially impacted by the COVID-19 pandemic. A total of 18 visits in 17 participants were not performed, 1 visit was conducted as hybrid visit (partial face to face and remote visit) due to participants not being able to travel due to COVID-19 or participants/guardian under quarantine due to COVID-19. None of the participants withdrew due to COVID-19.

[000417] *Visual Outcomes.* Both HDq12 and HDq16 demonstrated non-inferiority to 2q8 with respect to this key secondary endpoint (change from baseline in BCVA at week 60) using the non-inferiority margin of 4 letters with LS_{mean} change from baseline in BCVA of 8.52 letters (HDq12) and 7.64 letters (HDq16) versus 9.40 letters in the 2q8 group (Table 1-21). The differences in LS_{mean} changes from baseline in BCVA (95% CI) were -0.88 (-2.67, 0.91) and -1.76 (-3.71, 0.19) for HDq12 and HDq16, respectively, compared to 2q8. The p-values for the non-inferiority test at a margin of 4 letters were 0.0003 for HDq12 vs. 2q8, and 0.0122 for HDq16 vs. 2q8. The lower confidence limits were greater than -4, allowing the conclusion of non-inferiority at the week 60 timepoint.

[000418]The mean changes from baseline in BCVA measured by the ETDRS letter score by visit using OC, are graphically displayed in Figure 25A (Full Analysis Set); the corresponding LS_{mean} changes from baseline in BCVA using MMRM in the FAS, are displayed in Figure 25B. The mean increases in BCVA over time were similar across all groups and minor numerical differences were not considered clinically relevant.

[000419]Results of the analysis in the PPS were consistent with the FAS and LS_{mean} change from baseline in BCVA by visit in the PPS was also consistent with the FAS.

Table 1-21. Key Secondary Endpoint -- Change from Baseline in BCVA (ETDRS Letters) at Week 60 in the Study Eye, MMRM (Full Analysis Set)

Treatment	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 60 data	DF	Contrast [a]	t-value	1-sided NI p-value [b]	1-sided superiority p-value	Estimate for contrast and 2-sided 95% CI [c]
HDq12 (N=328)	8.52 (0.63)	9.05 (9.27)	63.63	252	342.4	HDq12 - 2q8	3.4242	0.0003	0.8325	-0.88 (-2.67, 0.91)
HDq16 (N=163)	7.64 (0.75)	7.96 (9.14)	61.44	138	315.5	HDq16 - 2q8	2.2625	0.0122	0.9619	-1.76 (-3.71, 0.19)
2q8 (N=167)	9.40 (0.77)	9.62 (9.58)	61.47	133						

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
BL=baseline; CI=confidence interval; CRT= Central retinal thickness (or, central subfield retinal thickness); DF=degrees of freedom; DME=diabetic macular edema; NI=non-inferiority; LS=least square; SAP=statistical analysis plan; SE=standard error; SD=standard deviation
A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT from reading center [<400µm vs. ≥400µm], prior treatment for DME per EDC; [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom.
[a] The contrast also included the interaction term for treatment x visit.
[b] p-value for the 1-sided non-inferiority (NI) test at a margin of 4 letters.
[c] Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with 2-sided 95% CIs.

[000420]The proportion of participants who gained ≥ 15 letters in BCVA from baseline to week 60 was 21.5% and 16.0% in the HDq12 and HDq16 groups, respectively, compared with 26.1% in the 2q8 group (Table 1-22). The lower values observed for this parameter are potentially due to a ceiling effect created by inclusion of participants with baseline BCVA up to 78 letters. Although lower values were seen in the HDq16 group (16.0% compared to >20.0% in 2q8),

considering non-inferiority was achieved between HDq16 and 2q8 for the primary endpoint, the overall picture of letters gained/lost among the treatment groups must be taken into consideration.

[000421]Sensitivity analysis for the proportion of participants who gained ≥ 15 letters in BCVA from baseline at week 60 using OC was consistent with the LOCF analysis.

Table 1-22. Proportion of Participants who Gained ≥ 15 Letters in BCVA from Baseline at Week 60 (LOCF) (Full Analysis Set)

Treatment	Patients with ≥ 15 Letters gain in BCVA from baseline to Week 48, n (%)	Adjusted Difference (%) (95% CI)[a]	CMH test[b] p-value
HDq12 (N=328)	70/326 (21.5%)	-5.01 (-13.04 , 3.02)	0.2112
HDq16 (N=163)	26/163 (16.0%)	-10.78 (-19.27 , -2.29)	0.0143
2q8 (N=167)	43/165 (26.1%)		

Abbreviations: 2q8=Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12=High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16=High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
BCVA=best corrected visual acuity; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; ICE=intercurrent events; LOCF=last observation carried forward; N=number of participants.
LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data.
Missing data were not included in the denominator.
a. Difference with CI was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]).
b. Nominal p-value for the 2-sided CMH superiority test.

[000422]The proportion of participants who gained or lost ≥ 5, ≥ 10, or ≥ 15 letters from baseline through week 60 is presented in Table 1-23. Across all treatment groups, more participants gained letters, with the greatest proportion gaining ≥ 5 letters (approximately 64% to 72% across all treatment groups). A numerically lower proportion of participants in the HDq12 and HDq16 groups gained ≥ 10 letters or ≥ 15 letters compared to the 2q8 group. Few participants (approximately 3% to 6%) lost 5 or more letters through week 60 regardless of treatment group.

Table 1-23. Proportion of Participants who Gained or Lost ≥ 5, 10, or 15 Letters in BCVA from Baseline by Visit through Week 60 (LOCF) (Full Analysis Set)

	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)

Gained >= 5 letters	Week 60	119/165 (72.1%)	227/326 (69.6%)	105/163 (64.4%)
Gained >= 10 letters	Week 60	82/165 (49.7%)	133/326 (40.8%)	56/163 (34.4%)
Gained >= 15 letters	Week 60	43/165 (26.1%)	70/326 (21.5%)	26/163 (16.0%)
Lost >= 5 letters	Week 60	10/165 (6.1%)	21/326 (6.4%)	5/163 (3.1%)
Lost >= 10 letters	Week 60	4/165 (2.4%)	11/326 (3.4%)	2/163 (1.2%)
Lost >= 15 letters	Week 60	1/165 (0.6%)	7/326 (2.1%)	1/163 (0.6%)

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals;
HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals;
HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; BCVA=
best corrected visual acuity; ICE= intercurrent events; LOCF= last observation carried forward; SAP= statistical
analysis plan.
LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing data.
Missing data were not included in the denominator.

[000423]The proportion of participants who achieved ≥ 69 letters in BCVA (≥ 20/40 Snellen equivalent) at week 60 was similar across treatment groups (60.6 to 64.7% participants). Sensitivity analyses for the proportion of participants who achieved ≥ 69 letters in BCVA at week 60 using OC were consistent with the LOCF analysis. See Table 1-24.

Table 1-24. Proportion of Patients with BCVA ≥ 69 letters at Week 60 (LOCF) (FAS)

Treatment	Patients with BCVA >= 69 letters at Week 60, n (%)	Adjusted Difference (%) (95% CI) [a]	CMH test [b] p-value
HDq12 (N=328)	211/326 (64.7%)	4.34 (-4.72, 13.40)	0.3479
HDq16 (N=163)	101/163 (62.0%)	1.63 (-8.91, 12.17)	0.7620
2q8 (N=167)	100/165 (60.6%)		

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
BCVA: best corrected visual acuity; CMH=Cochran-Mantel-Haenszel ; DME= diabetic macular edema; FAS= Full analysis set; LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing data; N=number of participants.
a. Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan])
b. p-value for the two-sided Cochran-Mantel-Haenszel (CMH) superiority test.
Missing data were not included in the denominator.

[000424]The mean values of BCVA score averaged from week 48 to week 60 were similar across treatment groups, and the change from baseline was similar across treatment groups (Table 1-25).

[000425]Sensitivity analysis for the BCVA as measured by ETDRS letter score averaged over the period from week 48 to week 60 using LOCF analysis in the FAS was consistent with the OC analysis.

Table 1-25. Summary of Averaged BCVA Score: Week 48 to Week 60 (OC) (Full Analysis Set)

		Value at Visit								Change from Baseline							
Treatment	**Visit**	**n**	**Mean**	**SD**	**SE**	**Q1**	**Median**	**Q3**	**Min, Max**	**n**	**Mean**	**SD**	**SE**	**Q1**	**Median**	**Q3**	**Min, Max**
2q8 (N=167)	BASELINE	167	61.5	11.22	0.87	54.0	63.0	70.0	24, 78								
	WEEK 48 TO 60	150	71.2	11.71	0.96	65.0	72.0	79.8	20, 88	150	9.3	8.81	0.72	4.3	9.3	14.8	-30, 45
HDq12 (N=328)	BASELINE	328	63.6	10.10	0.56	57.0	65.0	72.0	27, 79								
	WEEK 48 TO 60	277	72.5	10.72	0.64	66.0	74.3	81.0	30, 94	277	8.7	8.61	0.52	3.8	8.0	13.0	-22, 40
HDq16 (N=163)	BASELINE	163	61.4	11.76	0.92	55.0	64.0	71.0	29, 78								
	WEEK 48 TO 60	149	69.5	12.95	1.06	62.5	73.3	79.3	20, 89	149	7.6	8.35	0.68	3.0	7.5	11.3	-14, 40

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals, HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals, ICE= intercurrent events; max= maximum; min= minimum; N,n= number of participants; Q1= quartile 1; Q3= quartile 3; SAP= statistical analysis plan; SD= standard deviation; SE= standard error OC: observations after an intercurrent event (ICE) defined for the primary estimand were excluded.

[000426] *Visual Outcomes Sub-group Analysis.* The treatment effects of HDq12 and HDq16 versus 2q8 on the primary endpoint, the mean change from baseline in best-corrected visual acuity (BCVA) at Week 48, were evaluated by baseline demographics (sex, age, race, and ethnicity).

[000427]Mean BCVA change from baseline at Week 48 with 2q8, HDq12, and HDq16, respectively, was +8.7, +8.4, and +8.3 letters in male patients (n=401); +9.8, +9.6, and +7.2 letters in female patients (n=257); +13.0, +10.2, and +11.1 letters in patients aged <55 years

(n=144); +10.3, +8.0, and +7.1 letters in patients aged ≥55-<65 years (n=225); +6.9, +9.2, and +7.0 letters in patients aged ≥65-<75 years (n=218). The results were generally comparable by race (White [n=471]: +9.3, +9.5, and +8.3 letters; Asian [n=101]: +7.3, +5.9, and +6.6 letters) and ethnicity (Hispanic or Latino [n=119]: +8.9, +8.3, and +7.6 letters; non-Hispanic or Latino [n=525]: +9.4, +8.8, and +7.9 letters). Select subgroups (≥75 years and Black or African American) could not be evaluated due to small sample size.

[000428]Aflibercept 8 mg achieved meaningful BCVA gains from baseline at Week 48 in patients with DME across evaluable subgroups of sex, age, race, and ethnicity.

[000429]*Diabetic Retinopathy Severity Score (DRSS).* The proportion of participants with ≥ 2-step improvement in DRSS score was 25.7%, 24.6%, and 20.7% at week 12 and 29.1%, 31.3%, and 22.2% at week 60 in the 2q8, HDq12, and HDq16 groups, respectively. In CMH-weighted estimates, the adjusted difference (95% CI) was 1.87(-6.88, 10.63) for HDq12 and -7.47 (-17.05, 2.12) for HDq16, respectively, versus 2q8 (Table 1-26). Sensitivity analysis using OC was performed and was consistent with the primary analysis.

Table 1-26. Exploratory Endpoint – Proportion of Participants with a ≥ 2-Step Improvement from Baseline in DRSS at Week 60 (LOCF) (Full Analysis Set)

Treatment	Patients with a ≥ 2-step Improvement From Baseline in DRSS, n (%)	Adjusted Difference (%) 2-sided (95% CI) [a]
HDq12 (N=328)	97/310 (31.3%)	1.87 (-6.88, 10.63)
HDq16 (N=163)	34/153 (22.2%)	-7.47 (-17.05, 2.12)
2q8 (N=167)	46/158 (29.1%)	

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
CI=confidence interval; CRT= central retinal thickness; DRSS=Diabetic Retinopathy Severity Scale; N=number of participants; SAP = Statistical analysis plan
LOCF= the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data. Participants were considered as non-responders if all post-baseline measurements were missing or non-gradable.
a. Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]). The non-inferiority margin was set at 15%.
Missing or ungradable baseline was not included in the denominator.

[000430]The proportion of participants with a ≥ 3-step improvement in DRSS at week 60 was 15.2% and 10.5% in the HDq12 and HDq16 groups, respectively, compared with 17.7% in the 2q8 group (Table 1-27).

[000431]Sensitivity analyses for the proportion of participants with a ≥ 3-step improvement in DRSS score at week 60 using OC were consistent with the LOCF analysis.

Table 1-27. Proportion Analysis of Participants with a ≥3-step Improvement from Baseline in DRSS at Week 60 (LOCF) (Full Analysis Set)

Treatment	Patients with a ≥ 3-step improvement from baseline in DRSS at Week 60, n (%)	Adjusted Difference (%) (95% CI) [a]	CMH test [b] p-value
HDq12 (N=328)	47/310 (15.2%)	-2.73 (-9.90, 4.44)	0.4412
HDq16 (N=163)	16/153 (10.5%)	-7.34 (-15.16, 0.47)	0.0660
2q8 (N=167)	28/158 (17.7%)		

2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; DRSS = Diabetic Retinopathy Severity Scale.
LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data. Patients were considered as non-responders if all post-baseline measurements were missing or non-gradable.
Missing or ungradable baseline was not included in the denominator.
a. Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan])
b. p-value for the two-sided Cochran-Mantel-Haenszel (CMH) superiority test

Retinal Fluid

[000432]The proportion of participants without fluid (no IRF and no SRF) at the foveal center (as assessed by the central reading center) at week 60 was 61.8% and 58.0% in the HDq12 and HDq16 groups, respectively, compared with 68.5% in the 2q8 group. Sensitivity analyses for the proportion of participants without fluid (no IRF and no SRF) at the foveal center at week 60 using OC were consistent with the LOCF analysis. See Table 1-28.

Table 1-28. Proportion of Participants without Fluid (no IRF and no SRF) at the Foveal Center at Week 60 (LOCF) (Full Analysis Set)

Treatment	Patients without fluid,- n(%)	Adjusted Difference (%) (95% CI)[a]	CMH test[b] p-value
HDq12 (N=328)	201/325 (61.8%)	-5.98 (-14.71 , 2.75)	0.1878
HDq16 (N=163)	94/162 (58.0%)	-9.88 (-20.31 , 0.56)	0.0647
2q8 (N=167)	113/165 (68.5%)		

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
CI=confidence interval; CMH=Cochran-Mantel-Haenszel; DME= diabetic macular edema; ICE=intercurrent events; IRF=intraretinal fluid; LOCF=last observation carried forward; N=number of participants; SRF=subretinal fluid.
LOCF= the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data.
Missing or undetermined data were not included in the denominator.
a. Difference with CI was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400 µm, ≥400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]).
b. Nominal p-value for the 2-sided CMH superiority test.

[000433]The proportion of participants without fluid (no IRF and no SRF) in the center subfield at week 60 was 23.1% and 15.4% in the HDq12 and HDq16 groups, respectively, compared with 29.7% in the 2q8 group (Table 1-29).

[000434]Sensitivity analyses for the subset of participants without fluid (no IRF and no SRF) in the center subfield at week 60 using OC were consistent with the LOCF analysis.

Table 1-29. Proportion of Participants without Fluid (no IRF and no SRF) at the Central Subfield at Week 60 (LOCF) (Full Analysis Set)

Treatment	Patients without fluid, n (%)	Adjusted Difference (%) (95% CI) [a]	CMH test [b] p-value
HDq12 (N=328)	75/325 (23.1%)	-6.45 (-14.78, 1.87)	0.1217
HDq16 (N=163)	25/162 (15.4%)	-14.19 (-23.03, -5.36)	0.0021
2q8 (N=167)	49/165 (29.7%)		

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals;
CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CRT = central retinal thickness; DME = diabetic macular edema; ICE= intercurrent events; IRF=intraretinal fluid; LOCF=last observation carried forward; N=number of participants; SAP = Statistical analysis plan; SRF=subretinal fluid.
LOCF: the last observation prior to an ICE defined for the primary estimand was to be used to impute subsequent and/or missing data
Missing or undetermined data were not included in the denominator.

a. Difference with CI was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]).
b. p-value for the two-sided CMH superiority test.

[000435]*Central Retinal Thickness (CRT).* Overall, the LS_{mean} (SE) change from baseline in CRT (as assessed by the central reading center) at week 60 was -181.95 (6.09) and -166.26 (8.56) in the HDq12 and HDq16 groups, respectively, compared with -194.16 (7.15) in the 2q8 group (Table 1-30).

[000436]The mean changes from baseline in CRT using OC are graphically displayed in Figure 26A; the corresponding LS_{mean} changes from baseline in CRT using MMRM in the FAS are displayed in Figure 26B. Both the mean and LS_{mean} changes in CRT over time were similar across all groups. Although reductions from baseline in CRT were consistently observed at all timepoints, some fluctuation in mean CRT was seen in all treatment groups with attenuation in magnitude over the course of 60 weeks. The small fluctuations that are observed in all treatment groups over time are not considered to be clinically relevant given the demonstration of the non-inferiority in visual acuity.

[000437]Sensitivity analyses for change from baseline in CRT at week 60 using LOCF were consistent with the MMRM analysis.

Table 1-30. Statistical Analysis of Change from Baseline in Central Retinal Thickness (microns) at Week 60 (MMRM)(FAS)

	LS_{mean} (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 60 data	DF	Contrast [a]	t-value	p-value [b]	Estimate for contrast and 2-sided 95% CI [c]
HDq12 (N=328)	-181.95 (6.09)	-176.24 (144.71)	449.15	251	346.8	HDq12 - 2q8	1.5051	0.1332	12.21 (-3.74, 28.16)
HDq16 (N=163)	-166.26 (8.56)	-167.18 (127.18)	460.32	137	283.4	HDq16 - 2q8	2.7685	0.0060	27.90 (8.06, 47.74)
2q8 (N=167)	-194.16 (7.15)	-191.31 (142.00)	457.25	131					

2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
CI = Confidence interval. CRT = Central retinal thickness. SE = Standard error. SD = Standard deviation. DF = Degrees of freedom. FAS = Full analysis set. LS = Least Square. BL = Baseline. MMRM = mixed model for repeated measurements. SAP = statistical analysis plan

A mixed model for repeated measurements (MMRM) was used with baseline CRT measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400µm vs. >=400µm], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject error.
a. The contrast also included the interaction term for treatment x visit.
b. p-value for the two-sided superiority test
c. Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

[000438] *Fluid Leakage.* Overall, the proportion of participants without leakage on fluorescein angiography (as assessed by the central reading center) at week 60 (LOCF) was very low in all 3 treatment groups: 7.9% and 2.0% in the HDq12 and HDq16 groups, respectively, compared with 4.3% in the 2q8 group.

[000439] Sensitivity analyses for the proportion of participants without leakage on fluorescein angiography at week 60 using OC were consistent with the LOCF analysis.

[000440] A summary of the change from baseline in total area of fluorescein leakage within the ETDRS grid at week 60 is shown in Table 1-31.

Table 1-31. Summary of the Change from Baseline in Total Area of Fluorescein Leakage within ETDRS Grid (mm^2) at Week 60 (OC) (Full Analysis Set)

Statistic	2q8 N=167	HDq12 N=328	HDq16 N=163
Baseline n	164	319	153
Baseline mean (SD)	24.6 (13.20)	24.4 (13.22)	24.6 (11.73)
Week 60 n	112	202	110
Mean (SD) change from baseline at week 60	-14.4 (12.89)	-13.9 (13.54)	-12.0 (13.26)
Median change from baseline at week 60	-12.3	-13.6	-12.6
Min, Max	-86, 4	-80, 57	-37, 68

2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. ETDRS: Early Treatment Diabetic Retinopathy Study; OC: observations after an ICE defined for the primary estimand were excluded; SD; standard deviation.

[000441] *Safety.* Overall, a similar proportion of participants had TEAEs in the HD groups, 74.7% (245 participants; HDq12) and 77.3% (126 participants; HDq16), compared to 73.7% (123 participants) in the 2q8 group. The proportions of participants with ocular TEAEs were similar across the groups and were 43.7% (73 participants), 44.8% (147 participants), and

44.8% (73 participants) in the 2q8, HDq12, and HDq16 groups, respectively. There were very few study-drug-related ocular and non-ocular TEAEs across all treatment groups. The proportion of participants with study conduct-related TEAEs and TEAEs related to 2 mg aflibercept in the fellow eye were minimally reported across groups (< 2.0% overall across groups). The proportion of participants with injection-procedure-related ocular TEAEs was similar across treatment groups (< 14% across groups). The majority of serious AEs reported were non-ocular TEAEs (19.2% [32 participants], 18.6% [61 participants], and 16.6% [27 participants] in the 2q8, HDq12 and HDq16 groups, respectively). One injection-procedure-related ocular serious TEAE (Intraocular pressure increased) in the study eye was reported and occurred in the HDq12 group (0.3%). There were no reported study-drug-related serious TEAEs, study-conduct-related serious TEAEs, or serious TEAEs related to 2 mg aflibercept in the fellow eye. Three (1.8%) participants in the 2q8 group, 9 (2.7%) participants in the HDq12 group, and 2 (1.2%) participants in the HDq16 group discontinued study drug due to TEAEs. Of these, 2 participants discontinued study drug due to ocular TEAEs (both in the HDq12 group).

[000442]Five deaths were reported in the 2q8 group (3.0%), 9 deaths in the HDq12 group (2.7%), and 4 deaths in the HDq16 group (2.5%). All deaths were considered unrelated to study treatment by the investigator.

[000443]The proportion of participants with treatment-emergent adjudicated Antiplatelet Trialists' Collaboration (APTC) events was low and generally similar across treatment groups: 3.6% (6 participants), 4.0% (13 participants), and 5.5% (9 participants) in the 2q8, HDq12, and HDq16 groups, respectively. A slightly higher frequency of participants reported Hypertension in the HDq16 group (17.2%; 28 participants) compared to the 2q8 group (13.8%; 23 participants) and the HDq12 group (12.8%; 42 participants); however, this was not interpreted as clinically meaningful as there was no apparent dose relationship (i.e., HDq16 versus HDq12).

[000444]There were no treatment-emergent nasal mucosal events reported through week 60.

[000445]Ocular TEAEs in the study eye were reported at similar frequencies in all 3 groups (29.3% [49 participants], 36.0% [118 participants], and 34.4% [56 participants] in the 2q8, HDq12, and HDq16 groups, respectively). No clinically meaningful differences were observed in type of TEAEs or their frequencies between the HD and 2q8 treatment groups, and reported events were consistent with the known safety profile of IVT aflibercept. Overall, ocular TEAEs in the fellow eye were reported in 52 (31.1%) participants in the 2q8 group, 91 (27.7%) participants in the HDq12 group, and 52 (31.9%) participants in the HDq16 group. All ocular TEAEs in the fellow eye were reported in < 6.0% of participants in each treatment group. The most frequent PTs were Cataract (4.2% [7 participants], 3.0% [10 participants], and 5.5% [9

participants] in the 2q8, HDq12, and HDq16 groups, respectively), Vitreous floaters (4.3%; 7 participants in the HDq16 group), Diabetic retinal oedema (3.4% [11 participants] in the HDq12 group), and Diabetic retinopathy (3.6% [6 participants] in the 2q8 group and 3.7% [6 participants] in the HDq16 group). Ocular TEAEs were generally balanced across the 3 treatment groups.

[000446]Non-ocular TEAEs were reported in a similar proportion of participants in the 2q8 group (57.5%; 96 participants) and the Pooled HD group (60.9%; 299 participants). The majority of the TEAEs were in the SOC of Infections and infestations; however, the most common TEAE was Hypertension. A slightly higher frequency of participants reported Hypertension in the HDq16 group (15.3%; 25 participants) compared to the 2q8 group (10.8%; 18 participants) and the HDq12 group (9.1%; 30 participants); however, this was not interpreted as clinically meaningful as there was no apparent dose relationship (*i.e.*, HDq16 versus HDq12).

[000447]Other non-ocular TEAEs were reported ≤ 5.0% of participants in the 2q8 and the Pooled HD group except for COVID-19 (8.6%; 42 participants in the Pooled HD group)

[000448]Ocular study-drug-related TEAEs in the study eye were reported in 3 (1.8%) participants in the 2q8 group, 6 (1.8%) participants in the HDq12 group, and no participants in the HDq16 group. Intraocular pressure increased was the only PT (Preferred term) reported in more than 1 participant (3 [0.9%] participants in the HDq12 group). All ocular study-drug-related TEAEs in the study eye were reported in < 1.0% of participants. One non-ocular study drug-related TEAE was reported through week 60: Lacunar infarction reported in 1 (0.6%) participant in the HDq16 group. There were no non-ocular study-drug-related TEAEs reported through week 60 in the 2q8 or HDq12 groups.

[000449]Ocular IVT-injection-related TEAEs were reported in 16 (9.6%) participants in the 2q8 group, 42 (12.8%) participants in the HDq12 group, and 13 (8.0%) participants in the HDq16 group. Ocular IVT-injection-related TEAEs that were reported in > 2 participants in any of the 3 treatment groups included Conjunctival haemorrhage, Vitreous floaters, Eye pain, and Intraocularpressure increased which were reported in similar proportions of participants across the 3 treatment groups. All other ocular IVT-injection-related TEAEs in the study eye were reported in ≤ 2 participants in each group. Ocular IVT-injection-related TEAEs in the fellow eye through week 60 were reported in 5 (3.0%) participants in the 2q8 group, 7 (2.1%) participants in the HDq12 group, and 5 (3.1%) participants in the HDq16 group. Ocular IVT-injection-related TEAEs in the fellow eye were generally balanced between the 3 treatment groups.

[000450]Non-ocular IVT-injection-related TEAEs through week 60 were reported in 3 (0.6%) participants in the Pooled HD group. The TEAEs reported in the HD groups included Nausea,

Vomiting, and Headache. No participants reported non-ocular IVT-injection-related TEAEs in the 2q8 group

[000451]The relationship of TEAEs to other study procedures were assessed by the masked investigator, and was a clinical decision based on all available information.

[000452]Study-conduct-related TEAEs were reported in 2 (0.6%) participants in the HDq12 group. These TEAEs were Conjunctival haemorrhage and Injection site irritation. No study-conduct-related TEAEs were reported in the 2q8 or HDq16 groups.

[000453]There were no ocular study-conduct-related TEAEs in the fellow eye through week 60 reported in any treatment group.

[000454]Non-ocular study-conduct-related TEAEs through week 60 were reported in 3 (1.8%) participants in the 2q8 group and 4 (0.8%) participants in the Pooled HD group. These TEAEs were Nausea, Vessel puncture site haematoma, Contrast media allergy, Post procedural pruritus, Rash, and Vein.

[000455]Once the fellow eye received 2-mg aflibercept treatment during the study, TEAEs and serious TEAEs were also assessed as related/not related to 2-mg aflibercept treatment in the fellow eye, assessed as related/not related to the study drug (delivered to the study eye), IVT injection, and other protocol-specified procedures.

[000456]No ocular TEAEs in the study eye related to 2-mg aflibercept in the fellow eye through week 60 were reported in any treatment group.

[000457]Ocular TEAEs in the fellow eye related to 2-mg aflibercept in the fellow eye through week 60 were reported in few participants, 2 (1.2%) participants in the 2q8 group, 1 (0.3%) participant in the HDq12 group, and 2 (1.2%) participants in the HDq16 group. These TEAEs were Conjunctival haemorrhage, Halo vision, and Intraocular pressure increased.

[000458]One non-ocular TEAE related to 2-mg aflibercept in the fellow eye was reported through week 60: Lacunar infarction was reported in 1 (0.6%) participant in the HDq16 group. The same event was also considered to be related to study drug.

[000459]No non-ocular TEAEs related to 2-mg aflibercept in the fellow eye were reported through week 60 in the 2q8 or HDq12 groups.

[000460]The majority of ocular TEAEs in the study eye were mild (22.8% [38 participants; 2q8 group], 26.2% [86 participants; HDq12 group], and 28.2% [46 participants; HDq16 group]) to moderate (6.0% [10 participants; 2q8 group], 9.1% [30 participants; HDq12 group], and 5.5% [9 participants; HDq16 group]). Severe ocular TEAEs in the study eye were reported in few participants, 1 (0.6%) participant in the 2q8 group, 2 (0.6%) participants in the HDq12 group, and 1 (0.6%) participant in the HDq16 group. The ocular TEAEs that were reported as being

severe in the study eye were Cataract nuclear and Cataract subcapsular (reported by 1 participant in the 2q8 group), Cataract subcapsular and Retinal vascular disorder (reported by 1 participant each in the HDq12 group), and Retinal detachment and Vitreous haemorrhage (reported by 1 participant in the HDq16 group).

[000461]The majority of ocular TEAEs in the fellow eye were mild (22.2% [37 participants; 2q8 group], 21.0% [69 participants; HDq12 group], and 22.1% [36 participants; HDq16 group]) to moderate (7.2% [12 participants; 2q8 group], 5.8% [19 participants; HDq12 group], and 9.8% [16 participants; HDq16 group]). Severe ocular TEAEs in the fellow eye were reported in few participants, 3 (1.8%) participants in the 2q8 group, 3 (0.9%) participants in the HDq12 group, and no participants in the HDq16 group.

[000462]Severe ocular TEAEs in the fellow eye reported by the 3 participants in the 2q8 group were Cataract subcapsular, Cataract nuclear, Diabetic retinopathy, and Retinal artery occlusion (reported by 1 participant each); Diabetic retinopathy (reported by 1 participant) and Vitreous haemorrhage (reported by 3 participants) in the HDq12 group.

[000463]The majority of non-ocular TEAEs were mild (25.7% [43 participants; 2q8 group] and 26.9% [132 participants; Pooled HD group]) to moderate (18.0% [30 participants; 2q8 group] and 21.6% [106 participants; Pooled HD group]).

[000464]Severe non-ocular TEAEs were reported in 23 (13.8%) participants in the 2q8 group, and 61 (12.4%) participants in the Pooled HD group. Severe non-ocular TEAEs were primarily reported in the SOC of Cardiac disorders.

[000465]A total of 5 ocular serious TEAEs in the study eye were reported in 4 participants. Serious TEAEs in the study eye were Ulcerative keratitis (1 [0.6%] participant; 2q8 group), Cataract subcapsular, and Intraocular pressure increased (1 [0.3%] participant each; both in the HDq12 group), and Retinal detachment and Vitreous haemorrhage (1 [0.6%] participant; HDq16 group). None of the events were considered related to the study drug and 1 event (Intraocular pressure increased) was considered related to injection procedure

[000466] A total of 11 ocular serious TEAEs of the fellow eye were reported in 9 participants. None of these events were considered related to the study drug

[000467]The majority of these Non-ocular Serious TEAEs Through Week 60 were reported in single participants only. Across the 2q8 and Pooled HD groups, the most frequent non-ocular serious TEAEs (reported in ≥3 participants) were Acute left ventricular failure (3 [1.8%] participants) in the 2q8 group; and Acute myocardial infarction (7 [1.4%] participants), Cardiac arrest (3 [0.6%] participants), Coronary artery disease (4 [0.8%] participants), Myocardial infarction (7 [1.4%] participants), COVID-19 (4 [0.8%] participants), Covid-19 pneumonia (3

[0.6%] participants), Pneumonia (4 [0.8%] participants), Hypoglycaemia (3 [0.6%] participants), Cerebrovascular accident (5 [1.0%] participants), Acute kidney injury (6 [1.2%] participants), and Acute respiratory failure (3 [0.6%] participants) in the Pooled HD group. None of these events were considered related to the study drug.

[000468]Ocular TEAEs in the study eye leading to discontinuation of the study drug were Iritis and Visual impairment. There were no ocular TEAEs in the fellow eye reported resulting in the discontinuation of the study drug.

[000469]Non-ocular TEAEs reported that resulted in the discontinuation of the study drug for 3 (1.8%) participants in the 2q8 group and 9 (1.8%) participants in the Pooled HD group. Non-ocular TEAEs leading to discontinuation of the study drug included Blood loss anaemia, Acute myocardial infarction, Cardiac arrest, Death, Multiple organ dysfunction syndrome, Cholecystitis acute, Hip fracture, Endometrial cancer, Gastrointestinal neoplasm, Cerebrovascular accident, Encephalopathy, Acute kidney injury, Nephropathy toxic, and Aortic stenosis. No specific safety trend was observed, and most events were reported in single participants.

[000470]Through week 60, there were 18 deaths reported in this study, evenly distributed across the treatment groups, and all were associated with an SAE. None of the deaths were considered related to study drug or study procedure. Overall, the deaths reported were consistent with concurrent medical conditions and the complications of these conditions associated with an older population.

[000471]TEAEs related to Intraocular Inflammation were reported in 1 (0.6%) participant in the 2q8 group who reported Iridocyclitis, 4 (1.2%) participants in the HDq12 group who each reported 1 of the following: Iritis, Uveitis, Vitreal cells, and Vitritis, and 1 (0.6%) participant in the HDq16 group who reported Iridocyclitis. None of the events were serious.

[000472]Potential arterial thromboembolic events were evaluated by a masked adjudication committee according to criteria formerly applied and published by the APTC. Arterial thromboembolic events as defined by the APTC criteria include Nonfatal myocardial infarction, Nonfatal stroke (ischemic or hemorrhagic), or Death resulting from vascular or unknown causes.

[000473]Low (< 6.0%) and similar proportions of participants reported adjudicated APTC events across the treatment groups.

[000474]Treatment-emergent hypertension events were reported in fewer than 20% of participants in any treatment group. A slightly higher portion of participants reported Hypertension in the HDq16 compared to the 2q8 group and the HDq12 group; however, this was not interpreted as clinically meaningful as there was no apparent dose relationship (i.e.,

HDq16 versus HDq12). Approximately 76% of participants in all treatment groups had a medical history of Hypertension.

[000475]Due to findings from the preclinical toxicology studies for HD, an assessment was performed in the clinical program for events related to nasal mucosa. None of the participants experienced a TEAE consistent with Nasal mucosal findings.

[000476]Overall, the treatment-emergent ocular surgeries reported were consistent with the medical history and the concurrent clinical medical conditions of the population enrolled in this study. No specific safety concern was observed.

Results at week 96

[000477]Reducing the treatment burden in patients with diabetic macular edema is a critical unmet need. The results presented herein show that patients with diabetic macular edema were able to rapidly achieve extended dosing intervals without sacrifice of vision gains over about two years, thus providing a tremendous benefit in the treatment of these patients. In summary, see Table 1-32 below:

Table 1-32. Summary of Visual Outcomes at Week 48 and 96

	Week 48 (one year)				Week 96 (two years)		
	EYLEA 8-week regimen	**EYLEA HD 12-week regimen**	**EYLEA HD 16-week regimen**		**EYLEA 8-week regimen**	**EYLEA HD 12-week regimen**	**EYLEA HD 16-week regimen**
Mean number of injections	7.9	6.0	5.0		13.8	9.5	7.8
Mean observed BCVA improvement	9.2 letters	8.8 letters	7.9 letters		8.4 letters	8.8 letters	7.5 letters
LS mean (SE) change from baseline	8.7 (0.7)	8.1 (0.6)	7.2 (0.7)		7.7 (0.9)	8.2 (0.6)	6.6 (0.8)
Difference in LS mean (95% CI)		-0.6* (-2.3, 1.1)	-1.4† (-3.3, 0.4)			+0.5‡ (-1.6, 2.4)	-1.11§ (-3.3, 1.1)
Proportion of patients losing ≥15 letters, per LOCF	1.2%	2.1%	0.6%		3.6%	3.4%	1.2%

BCVA: best corrected visual acuity; LS: least squares; SE: standard error; LOCF: last observation carried forward
*Non-inferiority p-value: p<0.0001
†Non-inferiority p-value: p=0.0031
‡Nominal non-inferiority p-value: p<0.0001
§Nominal non-inferiority p-value: p=0.0044

[000478]These data demonstrated that 43% and 27% of patients met the criteria for ≥20- and 24-week dosing intervals, respectively. Also, 89% of all patients receiving the 8 mg doses maintained ≥12-week dosing intervals through two years, compared to 93% through one year. The safety of 8 mg regimens also continues to be similar to EYLEA in the PHOTON study, and remains consistent with the known safety profile of EYLEA from previous clinical trials. There were no cases of retinal vasculitis, occlusive retinitis or endophthalmitis. The rate of intraocular inflammation was 1.2% for both EYLEA and the 8 mg regimens.
[000479]Patients in the PHOTON clinical trial were dosed according to the timeline set forth in Table 1-33. By week 96 of the trial, the disposition of the patients in each of the 2q8, HDq12 and HDq16 arms are shown in Table 1-34A. Baseline demographics and characteristics of patients in the trial are summarized in Table 1-34B. Patients in the 2q8, 8q12 and 8q16 arms received an average of 12.9, 8.6 and 7.5 injections, respectively, by week 96. Among those in each of the 2q8, 8q12 and 8q16 arms who completed week 96 received an average of 13.8, 9.5 and 7.8 injections, respectively. See Table 1-35.

Table 1-33. PHOTON: Dosing Schedule to Week 96

	Day 1*	Wk 4*	Wk 8*	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
2q8	X	X	X	X	X	o	X	o	X	o	X	o	X
8q12	X	X	X		o	X	o	o	X	o	o	X	o
8q16	X	X	X		o	o	X	o	o	o	X	o	o

	Wk 52	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96
2q8	o	X	o	X	o	X	o	X	o	X	O	

8q12	o	**X**	o	o	**X**	o	o	**X**	o	o	**X**	
8q16	o	**X**	o	o	o	**X**	o	o	o	**X**	o	

*= initial treatment phase; X=active injection; o=sham injections; Note: Table does not reflect all dosing options once a patient is shortened. No extension of interval was allowed in Year 1.
CRT, central retinal thickness; DRM, dose regimen modifications; OCT, optical coherence tomography; Wk, week.
DRM: Weeks 16 or 20: 8q12/8q16 can be shortened to q8; Week 24: 8q16 can be shortened to q12; Up to Wk 48: Intervals may be shortened by 4 weeks (min. interval 8 wk); From Wk 52: Intervals may be shortened (min. q8) or extended by 4 weeks (max q20).
DRM criteria for shortening of dosing interval: >10-letter loss in BCVA from Week 12 BCVA due to persistent or worsening DME + >50 µm increase in CRT from Week 12
DRM criteria for extension of dosing interval: <5-letter loss from Week 12 BCVA + CRT <300 µm on SD-OCT

Table 1-34A. Patient Disposition at Week 96

	2q8	**HDq12**	**HDq16**	**Total**
# Randomized	167	329	164	660
# Completing Week 48	157 (94.0%)	300 (91.2%)	156 (95.1%)	613 (92.9%)
# Completing Week 96	139 (83.2%)	256 (77.8%)	139 (84.8%)	534 (80.9%)
# Discontinued before Week 96	28 (16.8%)	73 (22.2%)	25 (15.2%)	126 (19.1%)
Reasons for Discontinuation				
Noncompliance with protocol	2 (1.2%)	1 (0.3%)	0	3 (0.5%)
Adverse event	1 (0.6%)	9 (2.7%)	2 (1.2%)	12 (1.8%)
Decision by the investigator	2 (1.2%)	9 (2.7%)	3 (1.8%)	14 (2.1%)
Withdrawal by subject	9 (5.4%)	17 (5.2%)	8 (4.9%)	34 (5.2%)
Lost to follow-up	5 (3.0%)	19 (5.8%)	7 (4.3%)	31 (4.7%)

Death	9 (5.4%)	18 (5.5%)	5 (3.0%)	32 (4.8%)

Table 1-34B. Baseline Demographics and Characteristics

	2q8	**8q12**	**8q16**	**Total**
N (FAS/SAF)	167	328	163	658
Completion rate at Week 48 (%)	94.0	91.2	95.1	92.9
Completion rate at Week 96 (%)	83.2	77.8	84.8	80.9
Age (years)	63.0 (9.8)	62.1 (11.1)	61.9 (9.5)	62.3 (10.4)
Female (%)	44.9	36.0	39.3	39.1
Race (%)				
White	67.1	70.4	78.5	71.6
Asian	18.0	14.6	14.1	15.3
Black or African American	10.8	10.7	5.5	9.4
Other*	2.4	3.0	0.6	2.4
Not reported	1.8	1.2	1.2	1.4
Ethnicity (%)				
Hispanic or Latino	18.6	16.5	20.9	18.1
Duration of diabetes (years)	15.9 (10.0)	15.1 (10.0)	15.7 (10.7)	15.5 (10.2)
Hemoglobin A_{1c} (%)	8.1 (1.5)	7.9 (1.5)	7.8 (1.5)	8.0 (1.5)

BMI (kg/m^2)	29.9 (6.5)	30.4 (6.2)	31.0 (6.1)	30.5 (6.2)
BCVA (ETDRS letters)	61.5 (11.2)	63.6 (10.1)	61.4 (11.8)	62.5 (10.9)
CST (µm)	457.2 (144.0)	449.1 (127.4)	460.3 (117.8)	454.0 (129.5)
Prior treatment for DME (%)	44.3	43.6	43.6	43.8

Data are mean (SD) unless otherwise indicated. FAS: all randomized patients who received ≥1 study treatment. SAF: all patients who received study treatment. *Other includes patients who were American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and multiracial. BCVA, best corrected visual acuity; BMI, body mass index; CST, central subfield thickness; DME, diabetic macular edema; ETDRS, Early Treatment of Diabetic Retinopathy Study; FAS, full analysis set; SAF, safety analysis set.

Table 1-35. Mean Number of Injections at Week 96

	2q8	**HDq12**	**HDq16**
Week 96	12.9 (out of 14)	8.6 (out of 10)	7.5 (out of 8)
Week 96 (completers#)	13.8 (out of 14)	9.5 (out of 10)	7.8 (out of 8)

FAS:2q8 n=167; HDq12 n=328; HDq16 n=163 (at baseline)

Patients that completed the week 96 visit

[000480]At each visit, patients were evaluated for suitability to extend or shorten the maintenance dosing interval by ±4 weeks. Patients who achieved the last intended dosing interval of q8w, q12w, q16w, q20w or q24w by week 96 in each treatment arm are set forth in Table 1-36 and 1-38.

[000481]In the 8q12 and 8q16 arms, 24% and 32% of patients, respectively, achieved a last intended or assigned interval of 24 weeks (26 or 27% of all patients receiving 8 mg combined). The percentage of patients maintaining at least q12w and q16w dosing intervals, by week 96, in each group is set forth in Table 1-37 and 1-38. As set forth in Table 1-36, about 92% of the pateints in the 8q12 group achieved a last assigned dosing interval of ≥q12w; about 47% of patients in the 8q16 group achieved a last assigned dosing interval of ≥q20w and about 88% of patients in the 8q16 group achieved a last assigned dosing interval of ≥q16w. Of the 8 mg combined arms, about 44% and 72% achieved a last assigned dosing interval of ≥q20w and

≥q16w, respectively. The proportion of Patients who maintained or extended intervals through week 96 is summarized graphically in Figure 73.

Table 1-36. Last Intended or Assigned Dosing Interval at Week 96

	Intended				
	q8 (%)	**q12 (%)**	**q16 (%)**	**q20 (%)**	**q24 (%)**
8q12 n=256^	11	27	20	18	24
8q16 n=139^	9	6	39	14	32
All 8 mg n=395^	10	20	27	16	26
Assigned					
8q12 n=256	8	28	21	19	24#
8q16 n=139	5	7	41	14	32#
All 8 mg n=395	7	21	28	17	27#
Completed					
8q12 $n=256_c$	5	6	48	41	n/a
8q16 $n=139^c$	9	31	31	30	n/a

[c]Patients completing Week 96
*Patients shortened/extended based on DRM assessments at some point through week 96
^Patients completing week 96
Patients were assigned to 24-week dosing intervals if they continued to meet extension criteria but there was not sufficient time to complete the interval within the 96-week study period
Values may not add up to 100% due to rounding.

Table 1-37. % Patients Maintaining ≥Q12 and ≥Q16 Week Intervals through Week 96

	≥q12 (%)	**≥q16 (%)**	**q8 (%)**	**q12 (%)**
8q12 n=256^	88		13*	
8q16 n=139^		84	7*	9*
All 8 mg n=395^	89		11*	

*Patients shortened based on DRM assessments at some point through week 96
^Patients completing week 96
Values may not add up to 100 due to rounding.

Table 1-38. Summary of Treatment Exposure in Study Eye through Week 96 (Safety Analysis Set Completing Week 96)

	2q8 (N=139)	HDq12 (N=256)	HDq16 (N=139)	All HD (N=395)
Treatment duration (weeks) [a]				
n	139	256	139	395
Mean (SD)	96.95 (2.548)	96.73 (2.447)	96.85 (2.246)	96.77 (2.376)
Median	96.10	96.10	96.30	96.10
Q1 : Q3	96.00 : 96.90	96.00 : 97.05	96.00 : 97.00	96.00 : 97.00
Min : Max	92.0 : 116.7	78.0 : 112.9	92.0 : 114.1	78.0 : 114.1
Patients maintained with q12 or longer dosing interval, n (%)	0	224 (87.5%)	129 (92.8%)	353 (89.4%)
Patients maintained with q16 or longer dosing interval, n (%)	0	0	116 (83.5%)	116 (29.4%)
Patients maintained and extended to q24 dosing interval, n (%)	0	61 (23.8%)	45 (32.4%)	106 (26.8%)
Patients with q12 or longer dosing interval as the last [b] intended dosing interval, n (%)	0	229 (89.5%)	127 (91.4%)	356 (90.1%)
Patients with q16 or longer dosing interval as the last [b] intended dosing interval, n (%)	0	159 (62.1%)	118 (84.9%)	277 (70.1%)
Patients with q20 or longer dosing interval as the last [b] intended dosing interval, n (%)	0	108 (42.2%)	63 (45.3%)	171 (43.3%)
Patients with q24 dosing interval as the last [b] intended dosing interval, n (%)	0	61 (23.8%)	44 (31.7%)	105 (26.6%)
Patients shortened to q8 dosing interval at week 16, n (%)	0	3 (1.2%)	1 (0.7%)	4 (1.0%)
Patients shortened to q8 dosing interval at week 20, n (%)	0	11 (4.3%)	2 (1.4%)	13 (3.3%)
Patients with a shortened dosing interval anytime, n (%)	0	36 (14.1%)	24 (17.3%)	60 (15.2%)
Patients shortened to q8 dosing interval anytime, n (%)	0	32 (12.5%)	10 (7.2%)	42 (10.6%)
Patients shortened to q12 dosing interval anytime (without shortening to q8), n (%)	0	0	22 (15.8%)	22 (5.6%)
Patients never extended dosing interval, n (%)	139 (100%)	81 (31.6%)	65 (46.8%)	146 (37.0%)
Patients with an extended dosing interval anytime, n (%)	0	175 (68.4%)	74 (53.2%)	249 (63.0%)
Patients extended to q20 dosing interval anytime, n (%)	0	111 (43.4%)	66 (47.5%)	177 (44.8%)
Patients extended to q20 dosing interval and shortened back to q16, n (%)	0	1 (0.4%)	1 (0.7%)	2 (0.5%)
Patients extended to q20 dosing interval and maintained at q20, n (%)	0	49 (19.1%)	20 (14.4%)	69 (17.5%)

Patients extended to q20 dosing interval and extended to q24, n (%)	0	61 (23.8%)	45 (32.4%)	106 (26.8%)

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
The percentage is based on the number of patients in each treatment group as denominator.
[a] Treatment Duration = (Last study treatment [active or sham] date - First study treatment [active or sham] date + 28 days)/7.
[b] Last means at Week 96.
Study interventions given at Week 96 or beyond are not included in this table.
Summary of dosing interval is based on assigned dose level from IWRS. Missing doses or make-up dose are not considered in the summary.

[000482]Patients achieved excellent improvements in vision by week 96. Patients in the 8q12 and 8q16 arms achieved average BCVA improvements of 8.8 and 7.5 letters, respectively, by week 96. See Table 1-39.

Table 1-39. Mean Change in Best Corrected Visual Acuity (ETDRS letters)

Week	2q8	8q12	8q16
0	0.0	0.0	0.0
4	5.3	4.5	4.4
8	6.9	6	5.9
12	7.3	6.7	6.2
16	7.5	6.8	7
20	7.9	6.4	6.3
24	7.6	7.3	5.8
28	8.4	7.6	7.8
32	8.2	7.1	7.5
36	8.9	8	6.7
40	8.4	8.4	6.8
44	8.6	8.3	7.7
48	9.2	8.8	7.9
52	9.6	8.8	7.4
56	9	8.2	6.8
60	9.6	9.1	8
64	9.7	8.9	7.8
68	9.9	8.3	7.5
72	9	8.3	5.9
76	10	8.3	6.6
80	8.8	8.1	7.5
84	9.2	8.3	7.7
88	8.2	8.5	7.1
92	9.2	8.7	7.1
96	8.4	8.8	7.5

Primary EP: Mean change in BCVA at week 96
p-value for the one-sided non-inferiority (NI) test at a margin of 4 letters (based on adjusted means derived using an MMRM):
p < 0.0001 HDq12 vs. 2q8 95% CI (-1.55, 2.45)
p = 0.0044 HDq16 vs. 2q8 95% CI (-3.27, 1.05)
Observed values (censoring data post ICE); FAS:2q8 n=167; HDq12 n=328; HDq16 n=163 (at baseline)

[000483]By week 96, average BCVA scores achieved by the patients in the 8q12 and 8q16 arms were 73.0 (average change of 8.8 from baseline) and 69.0 (average change of 7.5 from baseline), respectively (2q8 average BCVA at week 96: 70.9; average change of 8.4 from baseline). See Table 1-40. The Least Squares Mean change in BCVA are set forth in Table 1-41.

Table 1-40. Best Corrected Visual Acuity Over Time (ETDRS letters)

Week	2q8	8q12	8q16
0	61.5	63.6	61.4
4	66.9	68.2	65.8
8	68.2	69.7	67.4
12	68.7	70.4	67.8
16	68.9	70.6	68.6
20	69.5	70.1	68
24	69	71.1	67.4
28	70	71.5	69.8
32	69.8	70.9	69.5
36	70.8	71.4	68.3
40	70.2	72	68.9
44	70.8	71.9	69.9
48	71	72.6	69.8
52	71.5	72.7	69.3
56	70.8	72	68.7
60	71.5	73	69.5
64	71.5	73	69.8
68	71.8	72.3	69.4
72	70.8	72.5	67.9
76	71.9	72.5	68.2
80	71	72.3	69.1
84	71.6	72.4	69.7
88	70.4	72.6	68.7
92	71.6	72.8	68.7
96	70.9	73	69

Primary EP: Mean change in BCVA at week 96
p-value for the one-sided non-inferiority (NI) test at a margin of 4 letters (based on adjusted means derived using an MMRM):
p < 0.0001 HDq12 vs. 2q8 95% CI (-1.55, 2.45)
p = 0.0044 HDq16 vs. 2q8 95% CI (-3.27, 1.05)
Observed values (censoring data post ICE); FAS:2q8 n=167; HDq12 n=328; HDq16 n=163 (at baseline)

[000484]Although exploratory, both HDq12 and HDq16 demonstrated non-inferiority to 2q8 at week 96 using the non-inferiority margin of 4 letters with LS_{mean} change from baseline in BCVA of 8.15 letters (HDq12) and 6.59 letters (HDq16) versus 7.70 letters in the 2q8 group (Table 1-41). The differences in LS_{mean} changes from baseline in BCVA (95% CI) were 0.45 (-1.55, 2.45) (nominal p value: 0.3282) and -1.11 (-3.27, 1.05) (nominal p value: 0.8431) for HDq12 and HDq16, respectively compared to 2q8 (Table 1-41). The nominal p-values for the non-inferiority test at a margin of 4 letters were < 0.0001 for HDq12 vs. 2q8, and 0.0044 for HDq16 vs. 2q8. The lower confidence limits were greater than -4, allowing the conclusion of non-inferiority at week 96 timepoint.

Table 1-41. LS_{Mean} Change in Best Corrected Visual Acuity (OC; ETDRS letters) (Full Analysis Set)

2q8 (N=167)										
	n	mean	SD	SE	Q1	Median	Q3	Min, max	LS_{mean} (SE)	95% CI
WEEK 4	163	5.3	6.62	0.52	0.0	5.0	9.0	-12, 28	4.6 (0.7)	(3.3, 5.9)
WEEK 8	163	6.9	7.31	0.57	2.0	6.0	12.0	-10, 38	6.1 (0.7)	(4.7, 7.4)
WEEK 12	165	7.3	7.70	0.60	2.0	7.0	12.0	-12, 40	6.5 (0.7)	(5.1, 7.9)
WEEK 16	163	7.5	8.77	0.69	2.0	8.0	12.0	-36, 38	6.8 (0.8)	(5.2, 8.3)
WEEK 20	147	7.9	9.22	0.76	3.0	8.0	13.0	-37, 46	7.3 (0.8)	(5.8, 8.8)
WEEK 24	160	7.6	9.41	0.74	2.0	8.0	13.0	-33, 43	6.8 (0.8)	(5.3, 8.3)
WEEK 28	150	8.4	9.07	0.74	3.0	8.5	14.0	-30, 47	7.5 (0.7)	(6.2, 8.9)
WEEK 32	159	8.2	9.64	0.76	3.0	8.0	14.0	-38, 48	7.3 (0.7)	(5.9, 8.8)
WEEK 36	142	8.9	9.31	0.78	4.0	9.0	15.0	-31, 48	8.0 (0.7)	(6.6, 9.4)
WEEK 40	152	8.4	8.84	0.72	3.0	9.0	13.0	-24, 48	7.6 (0.7)	(6.2, 8.9)
WEEK 44	141	8.6	9.43	0.79	2.0	10.0	14.0	-27, 48	8.2 (0.7)	(6.7, 9.6)
WEEK 48	150	9.2	8.99	0.73	4.0	9.5	14.0	-25, 48	8.4 (0.7)	(7.0, 9.8)
WEEK 52	144	9.6	9.65	0.80	3.0	10.0	15.0	-36, 47	8.7 (0.7)	(7.2, 10.1)
WEEK 56	144	9.0	9.66	0.80	3.0	9.5	15.0	-34, 43	8.2 (0.8)	(6.6, 9.7)
WEEK 60	133	9.6	9.58	0.83	4.0	10.0	15.0	-25, 43	9.0 (0.7)	(7.5, 10.5)
WEEK 64	136	9.7	9.07	0.78	4.0	9.0	14.0	-21, 48	9.0 (0.7)	(7.6, 10.4)
WEEK 68	128	9.9	9.37	0.83	5.0	10.0	15.0	-24, 43	9.2 (0.8)	(7.7, 10.6)
WEEK 72	133	9.0	9.54	0.83	3.0	9.0	14.0	-20, 36	8.3 (0.8)	(6.8, 9.8)
WEEK 76	124	10.0	9.07	0.81	4.0	9.0	16.0	-15, 46	9.2 (0.7)	(7.8, 10.6)
WEEK 80	127	8.8	9.80	0.87	4.0	10.0	14.0	-23, 43	8.2 (0.8)	(6.7, 9.7)
WEEK 84	124	9.2	10.19	0.92	4.0	10.0	15.0	-23, 47	8.6 (0.8)	(7.0, 10.2)
WEEK 88	125	8.2	10.36	0.93	3.0	9.0	15.0	-27, 43	7.6 (0.8)	(6.1, 9.2)

WEEK 92	124	9.2	10.56	0.95	3.5	10.0	16.0	-24, 43	8.6 (0.8)	(6.9, 10.2)
WEEK 96	124	8.4	11.10	1.00	3.0	10.0	15.0	-24, 43	7.7 (0.9)	(5.9, 9.5)
HDq12 (N=328)										
WEEK 4	326	4.5	6.21	0.34	1.0	4.0	9.0	-28, 25	4.0 (0.5)	(3.0, 5.0)
WEEK 8	317	6.0	7.34	0.41	1.0	6.0	10.0	-50, 33	5.5 (0.6)	(4.4, 6.6)
WEEK 12	314	6.7	8.30	0.47	2.0	7.0	11.0	-42, 37	6.2 (0.6)	(5.0, 7.4)
WEEK 16	299	6.8	8.02	0.46	2.0	7.0	11.0	-42, 38	6.4 (0.6)	(5.3, 7.6)
WEEK 20	304	6.4	8.69	0.50	2.0	6.0	10.0	-41, 39	5.9 (0.6)	(4.7, 7.1)
WEEK 24	272	7.3	9.53	0.58	2.5	7.0	12.0	-48, 37	6.7 (0.6)	(5.5, 7.9)
WEEK 28	285	7.6	8.88	0.53	3.0	7.0	12.0	-41, 39	7.1 (0.6)	(5.9, 8.2)
WEEK 32	287	7.1	8.68	0.51	2.0	7.0	12.0	-41, 35	6.4 (0.6)	(5.3, 7.5)
WEEK 36	271	8.0	9.08	0.55	3.0	8.0	13.0	-42, 41	7.2 (0.6)	(6.0, 8.3)
WEEK 40	267	8.4	9.39	0.57	4.0	8.0	13.0	-57, 39	7.4 (0.6)	(6.3, 8.6)
WEEK 44	280	8.3	8.63	0.52	3.0	8.0	13.5	-29, 40	7.5 (0.6)	(6.4, 8.6)
WEEK 48	277	8.8	8.95	0.54	4.0	9.0	13.0	-33, 41	8.0 (0.6)	(6.9, 9.1)
WEEK 52	255	8.8	8.81	0.55	3.0	9.0	14.0	-17, 40	8.0 (0.6)	(6.9, 9.1)
WEEK 56	266	8.2	9.26	0.57	2.0	8.0	13.0	-31, 41	7.4 (0.6)	(6.3, 8.5)
WEEK 60	252	9.1	9.27	0.58	4.0	8.0	14.0	-33, 40	8.2 (0.6)	(7.1, 9.4)
WEEK 64	245	8.9	9.24	0.59	5.0	9.0	14.0	-38, 38	8.1 (0.6)	(7.0, 9.2)
WEEK 68	248	8.3	9.70	0.62	3.0	8.0	13.0	-46, 41	7.6 (0.6)	(6.5, 8.8)
WEEK 72	246	8.3	9.43	0.60	3.0	8.0	14.0	-57, 41	7.4 (0.6)	(6.2, 8.7)
WEEK 76	232	8.3	10.47	0.69	4.0	8.5	14.0	-56, 47	7.6 (0.7)	(6.3, 8.9)
WEEK 80	234	8.1	11.49	0.75	3.0	9.0	13.0	-68, 47	7.3 (0.7)	(5.9, 8.8)
WEEK 84	232	8.3	11.09	0.73	3.0	8.0	13.0	-69, 45	7.3 (0.7)	(6.0, 8.7)
WEEK 88	230	8.5	9.82	0.65	3.0	8.0	14.0	-46, 45	7.5 (0.7)	(6.2, 8.8)
WEEK 92	228	8.7	9.75	0.65	3.0	8.0	13.0	-42, 47	7.8 (0.6)	(6.5, 9.0)
WEEK 96	222	8.8	9.93	0.67	4.0	8.5	14.0	-40, 47	8.1 (0.6)	(6.9, 9.4)
HDq16 (N=163)										
WEEK 4	163	4.4	6.08	0.48	0.0	4.0	8.0	-17, 28	3.6 (0.6)	(2.4, 4.7)
WEEK 8	161	5.9	6.88	0.54	1.0	5.0	11.0	-10, 32	5.0 (0.7)	(3.7, 6.3)
WEEK 12	160	6.2	7.16	0.57	1.0	5.5	10.0	-13, 31	5.4 (0.7)	(4.1, 6.7)
WEEK 16	159	7.0	7.40	0.59	2.0	6.0	11.0	-8, 39	6.1 (0.7)	(4.8, 7.4)
WEEK 20	152	6.3	6.64	0.54	1.0	6.0	11.0	-10, 25	5.7 (0.6)	(4.5, 7.0)
WEEK 24	155	5.8	8.01	0.64	0.0	6.0	11.0	-21, 34	4.9 (0.7)	(3.5, 6.4)
WEEK 28	144	7.8	8.14	0.68	2.0	7.0	13.0	-12, 39	6.6 (0.7)	(5.2, 8.0)
WEEK 32	149	7.5	8.21	0.67	2.0	7.0	12.0	-24, 36	6.7 (0.7)	(5.3, 8.1)
WEEK 36	146	6.7	8.95	0.74	2.0	6.0	11.0	-19, 44	5.9 (0.8)	(4.4, 7.4)
WEEK 40	151	6.8	8.43	0.69	1.0	6.0	11.0	-13, 34	5.9 (0.7)	(4.6, 7.3)
WEEK 44	145	7.7	8.40	0.70	3.0	7.0	12.0	-15, 32	6.8 (0.7)	(5.5, 8.2)
WEEK 48	149	7.9	8.38	0.69	3.0	7.0	12.0	-17, 40	7.0 (0.7)	(5.6, 8.3)
WEEK 52	137	7.4	9.12	0.78	3.0	7.0	11.0	-27, 41	6.7 (0.7)	(5.3, 8.2)
WEEK 56	142	6.8	9.57	0.80	1.0	7.0	12.0	-20, 39	5.9 (0.8)	(4.4, 7.5)
WEEK 60	138	8.0	9.14	0.78	2.0	7.0	12.0	-15, 40	7.2 (0.7)	(5.8, 8.6)
WEEK 64	134	7.8	8.95	0.77	2.0	7.0	11.0	-15, 36	7.1 (0.7)	(5.7, 8.4)
WEEK 68	133	7.5	9.43	0.82	1.0	7.0	12.0	-17, 40	6.7 (0.7)	(5.3, 8.2)
WEEK 72	131	5.9	10.95	0.96	0.0	6.0	11.0	-36, 37	5.2 (0.9)	(3.5, 6.9)
WEEK 76	125	6.6	11.83	1.06	0.0	6.0	13.0	-62, 41	5.6 (0.9)	(3.8, 7.4)
WEEK 80	127	7.5	10.17	0.90	2.0	7.0	12.0	-30, 43	6.5 (0.8)	(5.0, 8.1)
WEEK 84	120	7.7	10.39	0.95	2.0	7.0	12.0	-30, 41	6.4 (0.8)	(4.9, 8.0)
WEEK 88	124	7.1	9.72	0.87	1.5	7.0	12.5	-13, 45	6.1 (0.8)	(4.6, 7.6)
WEEK 92	126	7.1	9.99	0.89	1.0	6.0	11.0	-32, 39	6.3 (0.8)	(4.8, 7.8)
WEEK 96	127	7.5	9.86	0.88	1.0	7.0	13.0	-15, 39	6.6 (0.8)	(5.1, 8.1)

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
OC: observations after an ICE defined for the primary estimand were excluded.
Least square mean (LSM) was generated from a mixed model for repeated measurements (MMRM), with baseline BCVA measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400µm vs. >=400µm], prior treatment for DME (per EDC) [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. Heterogeneous Toeplitz covariance structure was used to model the within-subject error

[000485]The proportion of participants who gained or lost ≥ 5, ≥ 10, or ≥ 15 letters from baseline at week 96 is presented in Table 1-42. Across all treatment groups, more participants gained rather than lost letters, with the greatest proportion gaining ≥ 5 letters (approximately 62% to 70% across all treatment groups). A lower proportion of participants in the HDq12 and HDq16 groups gained ≥5 letters, ≥ 10 letters, or ≥ 15 letters compared to the 2q8 group. Few participants lost ≥ 5 letters, ≥ 10 letters, or ≥15 letters through week 96 regardless of treatment group (Table 1-42). A lower proportion of participants in the HDq12 group lost ≥ 5 letters compared with the HDq16 and 2q8 groups, and a lower proportion of participants in the HDq12 and HDq16 groups lost ≥ 10 letters or ≥ 15 letters compared to the 2q8 group. These data were consistent with prior results. Sensitivity analysis for the proportion of participants who gained or lost ≥ 5 letters, ≥ 10 letters, or ≥ 15 letters in BCVA from baseline at week 96 using OC was consistent with the LOCF analysis.

Table 1-42. Proportion of Patients who Gained or Lost >= 5, 10, or 15 Letters in BCVA from Baseline by Visit through Week 96 (LOCF) (Full Analysis Set)

Endpoint	Visit	2q8	HDq12	HDq16
Gained >= 5 letters	Week 4	85/163 (52.1%)	154/326 (47.2%)	73/163 (44.8%)
	Week 8	94/165 (57.0%)	187/326 (57.4%)	81/163 (49.7%)
	Week 12	104/165 (63.0%)	199/326 (61.0%)	90/163 (55.2%)
	Week 16	113/165 (68.5%)	202/326 (62.0%)	103/163 (63.2%)
	Week 20	105/165 (63.6%)	201/326 (61.7%)	101/163 (62.0%)
	Week 24	105/165 (63.6%)	212/326 (65.0%)	91/163 (55.8%)
	Week 28	113/165 (68.5%)	216/326 (66.3%)	104/163 (63.8%)
	Week 32	110/165 (66.7%)	198/326 (60.7%)	104/163 (63.8%)
	Week 36	114/165 (69.1%)	212/326 (65.0%)	102/163 (62.6%)
	Week 40	112/165 (67.9%)	217/326 (66.6%)	96/163 (58.9%)
	Week 44	114/165 (69.1%)	216/326 (66.3%)	105/163 (64.4%)

	Week 48	113/165 (68.5%)	231/326 (70.9%)	107/163 (65.6%)
	Week 52	115/165 (69.7%)	220/326 (67.5%)	109/163 (66.9%)
	Week 56	111/165 (67.3%)	211/326 (64.7%)	101/163 (62.0%)
	Week 60	119/165 (72.1%)	227/326 (69.6%)	105/163 (64.4%)
	Week 64	117/165 (70.9%)	229/326 (70.2%)	104/163 (63.8%)
	Week 68	125/165 (75.8%)	223/326 (68.4%)	100/163 (61.3%)
	Week 72	112/165 (67.9%)	215/326 (66.0%)	99/163 (60.7%)
	Week 76	116/165 (70.3%)	223/326 (68.4%)	95/163 (58.3%)
	Week 80	115/165 (69.7%)	220/326 (67.5%)	103/163 (63.2%)
	Week 84	113/165 (68.5%)	218/326 (66.9%)	106/163 (65.0%)
	Week 88	111/165 (67.3%)	217/326 (66.6%)	102/163 (62.6%)
	Week 92	117/165 (70.9%)	223/326 (68.4%)	98/163 (60.1%)
	Week 96	116/165 (70.3%)	222/326 (68.1%)	101/163 (62.0%)
Gained >= 10 letters	Week 4	36/163 (22.1%)	65/326 (19.9%)	28/163 (17.2%)
	Week 8	55/165 (33.3%)	90/326 (27.6%)	45/163 (27.6%)
	Week 12	55/165 (33.3%)	109/326 (33.4%)	45/163 (27.6%)
	Week 16	63/165 (38.2%)	103/326 (31.6%)	50/163 (30.7%)
	Week 20	72/165 (43.6%)	89/326 (27.3%)	51/163 (31.3%)
	Week 24	71/165 (43.0%)	114/326 (35.0%)	50/163 (30.7%)
	Week 28	70/165 (42.4%)	118/326 (36.2%)	58/163 (35.6%)
	Week 32	75/165 (45.5%)	115/326 (35.3%)	55/163 (33.7%)
	Week 36	77/165 (46.7%)	117/326 (35.9%)	51/163 (31.3%)
	Week 40	79/165 (47.9%)	125/326 (38.3%)	52/163 (31.9%)
	Week 44	85/165 (51.5%)	118/326 (36.2%)	53/163 (32.5%)
	Week 48	81/165 (49.1%)	132/326 (40.5%)	57/163 (35.0%)
	Week 52	82/165 (49.7%)	132/326 (40.5%)	57/163 (35.0%)
	Week 56	80/165 (48.5%)	132/326 (40.5%)	58/163 (35.6%)
	Week 60	82/165 (49.7%)	133/326 (40.8%)	56/163 (34.4%)
	Week 64	81/165 (49.1%)	135/326 (41.4%)	54/163 (33.1%)
	Week 68	84/165 (50.9%)	134/326 (41.1%)	54/163 (33.1%)
	Week 72	81/165 (49.1%)	136/326 (41.7%)	55/163 (33.7%)
	Week 76	78/165 (47.3%)	140/326 (42.9%)	55/163 (33.7%)
	Week 80	86/165 (52.1%)	144/326 (44.2%)	59/163 (36.2%)
	Week 84	87/165 (52.7%)	140/326 (42.9%)	52/163 (31.9%)
	Week 88	81/165 (49.1%)	138/326 (42.3%)	52/163 (31.9%)
	Week 92	86/165 (52.1%)	138/326 (42.3%)	55/163 (33.7%)
	Week 96	86/165 (52.1%)	139/326 (42.6%)	54/163 (33.1%)
Gained >= 15 letters	Week 4	14/163 (8.6%)	20/326 (6.1%)	8/163 (4.9%)
	Week 8	24/165 (14.5%)	39/326 (12.0%)	16/163 (9.8%)
	Week 12	27/165 (16.4%)	45/326 (13.8%)	20/163 (12.3%)
	Week 16	33/165 (20.0%)	45/326 (13.8%)	22/163 (13.5%)
	Week 20	35/165 (21.2%)	42/326 (12.9%)	21/163 (12.9%)
	Week 24	38/165 (23.0%)	52/326 (16.0%)	15/163 (9.2%)
	Week 28	37/165 (22.4%)	52/326 (16.0%)	29/163 (17.8%)

	Week 32	38/165 (23.0%)	43/326 (13.2%)	27/163 (16.6%)
	Week 36	42/165 (25.5%)	57/326 (17.5%)	26/163 (16.0%)
	Week 40	30/165 (18.2%)	60/326 (18.4%)	22/163 (13.5%)
	Week 44	39/165 (23.6%)	67/326 (20.6%)	26/163 (16.0%)
	Week 48	38/165 (23.0%)	61/326 (18.7%)	27/163 (16.6%)
	Week 52	46/165 (27.9%)	68/326 (20.9%)	26/163 (16.0%)
	Week 56	41/165 (24.8%)	69/326 (21.2%)	24/163 (14.7%)
	Week 60	43/165 (26.1%)	70/326 (21.5%)	26/163 (16.0%)
	Week 64	38/165 (23.0%)	69/326 (21.2%)	31/163 (19.0%)
	Week 68	41/165 (24.8%)	67/326 (20.6%)	28/163 (17.2%)
	Week 72	39/165 (23.6%)	68/326 (20.9%)	30/163 (18.4%)
	Week 76	46/165 (27.9%)	73/326 (22.4%)	28/163 (17.2%)
	Week 80	41/165 (24.8%)	68/326 (20.9%)	31/163 (19.0%)
	Week 84	44/165 (26.7%)	69/326 (21.2%)	27/163 (16.6%)
	Week 88	43/165 (26.1%)	73/326 (22.4%)	29/163 (17.8%)
	Week 92	50/165 (30.3%)	69/326 (21.2%)	31/163 (19.0%)
	Week 96	43/165 (26.1%)	80/326 (24.5%)	32/163 (19.6%)
Lost >= 5 letters	Week 4	6/163 (3.7%)	21/326 (6.4%)	5/163 (3.1%)
	Week 8	6/165 (3.6%)	9/326 (2.8%)	7/163 (4.3%)
	Week 12	5/165 (3.0%)	19/326 (5.8%)	7/163 (4.3%)
	Week 16	5/165 (3.0%)	16/326 (4.9%)	10/163 (6.1%)
	Week 20	5/165 (3.0%)	15/326 (4.6%)	5/163 (3.1%)
	Week 24	8/165 (4.8%)	17/326 (5.2%)	13/163 (8.0%)
	Week 28	7/165 (4.2%)	16/326 (4.9%)	11/163 (6.7%)
	Week 32	9/165 (5.5%)	18/326 (5.5%)	8/163 (4.9%)
	Week 36	5/165 (3.0%)	20/326 (6.1%)	12/163 (7.4%)
	Week 40	6/165 (3.6%)	19/326 (5.8%)	11/163 (6.7%)
	Week 44	8/165 (4.8%)	20/326 (6.1%)	11/163 (6.7%)
	Week 48	5/165 (3.0%)	21/326 (6.4%)	10/163 (6.1%)
	Week 52	7/165 (4.2%)	24/326 (7.4%)	11/163 (6.7%)
	Week 56	11/165 (6.7%)	24/326 (7.4%)	13/163 (8.0%)
	Week 60	10/165 (6.1%)	21/326 (6.4%)	5/163 (3.1%)
	Week 64	6/165 (3.6%)	23/326 (7.1%)	10/163 (6.1%)
	Week 68	9/165 (5.5%)	28/326 (8.6%)	9/163 (5.5%)
	Week 72	10/165 (6.1%)	23/326 (7.1%)	18/163 (11.0%)
	Week 76	7/165 (4.2%)	28/326 (8.6%)	14/163 (8.6%)
	Week 80	13/165 (7.9%)	28/326 (8.6%)	14/163 (8.6%)
	Week 84	10/165 (6.1%)	28/326 (8.6%)	12/163 (7.4%)
	Week 88	11/165 (6.7%)	23/326 (7.1%)	17/163 (10.4%)
	Week 92	13/165 (7.9%)	25/326 (7.7%)	14/163 (8.6%)
	Week 96	15/165 (9.1%)	26/326 (8.0%)	16/163 (9.8%)
Lost >= 10 letters	Week 4	2/163 (1.2%)	5/326 (1.5%)	2/163 (1.2%)
	Week 8	2/165 (1.2%)	4/326 (1.2%)	1/163 (0.6%)
	Week 12	3/165 (1.8%)	7/326 (2.1%)	2/163 (1.2%)
	Week 16	3/165 (1.8%)	5/326 (1.5%)	0/163

	Week 20	3/165 (1.8%)	8/326 (2.5%)	1/163 (0.6%)
	Week 24	6/165 (3.6%)	10/326 (3.1%)	2/163 (1.2%)
	Week 28	3/165 (1.8%)	8/326 (2.5%)	2/163 (1.2%)
	Week 32	3/165 (1.8%)	10/326 (3.1%)	3/163 (1.8%)
	Week 36	3/165 (1.8%)	10/326 (3.1%)	6/163 (3.7%)
	Week 40	3/165 (1.8%)	11/326 (3.4%)	1/163 (0.6%)
	Week 44	4/165 (2.4%)	10/326 (3.1%)	2/163 (1.2%)
	Week 48	2/165 (1.2%)	11/326 (3.4%)	2/163 (1.2%)
	Week 52	2/165 (1.2%)	13/326 (4.0%)	5/163 (3.1%)
	Week 56	3/165 (1.8%)	10/326 (3.1%)	6/163 (3.7%)
	Week 60	4/165 (2.4%)	11/326 (3.4%)	2/163 (1.2%)
	Week 64	1/165 (0.6%)	10/326 (3.1%)	3/163 (1.8%)
	Week 68	3/165 (1.8%)	12/326 (3.7%)	3/163 (1.8%)
	Week 72	5/165 (3.0%)	14/326 (4.3%)	6/163 (3.7%)
	Week 76	3/165 (1.8%)	16/326 (4.9%)	7/163 (4.3%)
	Week 80	5/165 (3.0%)	16/326 (4.9%)	8/163 (4.9%)
	Week 84	5/165 (3.0%)	15/326 (4.6%)	7/163 (4.3%)
	Week 88	8/165 (4.8%)	14/326 (4.3%)	8/163 (4.9%)
	Week 92	6/165 (3.6%)	16/326 (4.9%)	4/163 (2.5%)
	Week 96	9/165 (5.5%)	16/326 (4.9%)	4/163 (2.5%)
Lost >= 15 letters	Week 4	0/163	1/326 (0.3%)	1/163 (0.6%)
	Week 8	0/165	2/326 (0.6%)	0/163
	Week 12	0/165	4/326 (1.2%)	0/163
	Week 16	2/165 (1.2%)	4/326 (1.2%)	0/163
	Week 20	2/165 (1.2%)	5/326 (1.5%)	0/163
	Week 24	4/165 (2.4%)	5/326 (1.5%)	2/163 (1.2%)
	Week 28	3/165 (1.8%)	6/326 (1.8%)	1/163 (0.6%)
	Week 32	3/165 (1.8%)	9/326 (2.8%)	2/163 (1.2%)
	Week 36	3/165 (1.8%)	7/326 (2.1%)	2/163 (1.2%)
	Week 40	2/165 (1.2%)	9/326 (2.8%)	0/163
	Week 44	2/165 (1.2%)	7/326 (2.1%)	1/163 (0.6%)
	Week 48	2/165 (1.2%)	7/326 (2.1%)	1/163 (0.6%)
	Week 52	1/165 (0.6%)	8/326 (2.5%)	2/163 (1.2%)
	Week 56	1/165 (0.6%)	7/326 (2.1%)	3/163 (1.8%)
	Week 60	1/165 (0.6%)	7/326 (2.1%)	1/163 (0.6%)
	Week 64	1/165 (0.6%)	7/326 (2.1%)	1/163 (0.6%)
	Week 68	1/165 (0.6%)	8/326 (2.5%)	2/163 (1.2%)
	Week 72	2/165 (1.2%)	10/326 (3.1%)	4/163 (2.5%)
	Week 76	1/165 (0.6%)	10/326 (3.1%)	3/163 (1.8%)
	Week 80	3/165 (1.8%)	11/326 (3.4%)	3/163 (1.8%)
	Week 84	3/165 (1.8%)	11/326 (3.4%)	2/163 (1.2%)
	Week 88	4/165 (2.4%)	11/326 (3.4%)	1/163 (0.6%)
	Week 92	4/165 (2.4%)	11/326 (3.4%)	3/163 (1.8%)
	Week 96	6/165 (3.6%)	11/326 (3.4%)	2/163 (1.2%)

[000486]The proportion of participants who achieved an ETDRS letter score of ≥ 69 letters in BCVA (≥ 20/40 Snellen equivalent) at week 96 was similar across treatment groups (Table 1-43). The small numerical differences across the treatment groups were not clinically meaningful. These data were consistent with prior results. Sensitivity analyses for the proportion of participants who achieved ≥ 69 letters in BCVA at week 96 using OC were consistent with the LOCF analysis .

Table 1-43. Proportion of Participants with BCVA ≥ 69 letters at Week 96 (LOCF) (FAS)

Table 14: Proportion of Participants with BCVA ≥ 69 letters at Week 96 (LOCF) (FAS) Treatment	**Patients with BCVA ≥ 69 letters at Week 96, n (%)**
HDq12 (N=328)	218/326 (66.9%)
HDq16 (N=163)	100/163 (61.3%)
2q8 (N=167)	104/165 (63.0%)

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing data. BCVA=best corrected visual acuity; CMH=Cochran-Mantel-Haenszel; CRT=central retinal thickness (or, central subfield retinal thickness); DME=diabetic macular edema; FAS=Full analysis set; LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing data; N=number of patients. ICE defined for the primary estimand was used to

impute subsequent and/or missing data; N=number of patients.

[000487]The proportion of patients gaining or losing ≥15 letters at week 96 are set forth below in Table 1-44 and Table 1-45, respectively.

Table 1-44. % Patients Gaining ≥ 15 Letters at Week 96

	≥15 Letters
2q8	26%
HDq12	25%
HDq16	20%

LOCF (censoring data post ICE); FAS: 2q8 n=167; HDq12 n=328; HDq16 n=163

Table 1-45. % Patients Losing ≥15 Letters at Week 96

	≥15 Letters
2q8	4%
HDq12	3%
HDq16	1%

LOCF (censoring data post ICE); FAS: 2q8 n=167; HDq12 n=328; HDq16 n=163

[000488]A key secondary endpoint was the proportion of participants with a ≥ 2-step improvement from baseline in DRSS score at week 48. This endpoint was met at week 48 for the HDq12 group (non-inferiority to 2q8), but non-inferiority was not met in the HDq16 group (week 48). The proportion of participants with ≥ 2-step or ≥ 3-step improvement from baseline in DRSS score at week 96 is reported in Table 1-46 and 1-47. At week 96, a ≥ 2-step improvement in DRSS scores from baseline was observed in 31.0%, 33.9%, and 22.2% of participants in the 2q8, HDq12, and HDq16 groups, respectively. In CMH-weighted estimates, the adjusted difference (95% CI) was 2.64 (-6.22, 11.50) for HDq12 and -9.31 (-18.95, 0.34) for HDq16, versus 2q8. Fewer participants had a ≥ 3-step improvement than a ≥ 2-step

improvement from baseline in DRSS score, regardless of treatment group. These data were consistent with prior results.

[000489]Sensitivity analysis using OC was performed and was consistent with the primary analysis for ≥ 2-step improvement in DRSS score.

Table 1-46. % Patients with ≥2-step Improvement in DRSS

	2q8	HDq12	HDq16
Week 48	26.6%	29.0%	19.6%
Week 96	31.0%	33.9%	22.2%

LOCF (censoring data post ICE); FAS: 2q8 n=167; HDq12 n=328; HDq16 n=163
At Week 48: *HDq12 vs. 2q8 95% CI (-6.61, 10.57); ^HDq16 vs. 2q8 95% CI (-16.88, 1.84)
(NI margin set at 15%)

Table 1-47. Proportion of Participants with a ≥ 3-Step Improvement from Baseline in DRSS Score at Week 96 (LOCF) (FAS)

Improvement in DRSS Score from Baseline	Number of Participants with Improvement From Baseline in DRSS, n (%)	Adjusted Difference (%) 2-sided (95% CI)[a]
HDq12 (N=328)	46/310 (14.8%)	-3.02 (-10.15 , 4.11)
HDq16 (N=163)	18/153 (11.8%)	-6.16 (-14.05 , 1.73)
2q8 (N=167)	28/158 (17.7%)	

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data. Patients were considered as non-responders if all post-baseline measurements were missing or non-gradable. CI=confidence interval; CRT=central retinal thickness; DME=diabetic macular edema; DRSS=Diabetic Retinopathy Severity Scale; FAS=Full analysis set; LOCF=last observation carried forward; N,n=number of participants; SAP=Statistical analysis plan a Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted for stratification factors (baseline CRT (from reading center) [<400µm, >=400 µm], prior DME treatment [yes, no], geographical region [Rest of world, Japan]). The non-inferiority margin was set at 15%.

[000490]Overall, the LS_{mean} (SE) change from baseline in CRT (as assessed by the central reading center) at week 96 was -193.99 (6.09) and -158.39 (9.67) in the HDq12 and HDq16 groups, respectively, compared with -191.26 (9.12) in the 2q8 group (Table 1-48). Both the mean and LS_{mean} changes in CRT over time were similar across all groups. Although reductions from baseline in CRT were consistently observed at all timepoints, some fluctuation in mean CRT was seen in all treatment groups with attenuation in magnitude over the course of 96

weeks. The small fluctuations that are observed in all treatment groups over time are not considered to be clinically relevant given the demonstration of the non-inferiority in visual acuity. These data were consistent with prior results. Sensitivity analyses for change from baseline in CRT at week 96 using LOCF were consistent with the MMRM analysis. See also Table 1-49 and Table 1-50.

Table 1-48. Statistical Analysis of Change from Baseline in Central Retinal Thickness (microns) at Week 96 (MMRM)(FAS)

	LS Mean (SE) change from BL	Mean (SD) change from BL	BL Mean	Number of patients with Week 96 data	Contrast a
HDq12 (N=328)	-193.99 (6.09)	-185.28 (146.49)	449.15	215	HDq12 - 2q8
HDq16 (N=163)	-158.39 (9.67)	-154.98 (144.92)	460.32	124	HDq16 - 2q8
2q8 (N=167)	-191.26 (9.12)	-186.95 (146.28)	457.25	122	

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. BL=Baseline, FAS=Full analysis set; LS=Least Square, SE=Standard error, SD=Standard deviation. A mixed model for repeated measurements (MMRM) was used with baseline CRT measurement as a covariate, treatment group and the stratification variables (geographic region [Japan vs. Rest of World]; baseline CRT (from reading center) [<400µm vs. >=400µm], prior treatment for DME [yes vs. no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. Heterogeneous Toeplitz covariance structure was used to model the within-subject error.

Table 1-49. Mean Change in Central Retinal Thickness (micrometers)

Week	2q8	HDq12	HDq16
0	0	0	0.0
4	-121.2	-118.3	-126.7
8	-135.6	-137.4	-139.6
12	-150.1	-150.1	-152.7
16	-164.2	-139.4	-145.5
20	-168.5	-116.7	-112.5
24	-148.5	-158.1	-103.8
28	-169.8	-146.7	-162.3
32	-152.1	-132	-145
36	-176.7	-168.1	-124.7
40	-160.6	-162.6	-123
44	-178.6	-147.3	-164.1

48	-165.3	-171.7	-148.3
52	-191.6	-165.6	-148.8
56	-170.1	-154.2	-128.8
60	-191.3	-176.2	-167.2
64	-185.1	-173.4	-164.3
68	-212.8	-159.4	-153.9
72	-181.6	-166.6	-134.2
76	-217.1	-181.1	-160.8
80	-184.7	-168.9	-164
84	-204.3	-177.5	-150.2
88	-190.7	-171.2	-144.3
92	-205.5	-166.7	-155.5
96	-187	-185.3	-155

Observed values (censoring data post ICE); FAS: 2q8 n=167; HDq12 n=328; HDq16 n=163 (at baseline)

Table 1-50. Central Retinal Thickness (micrometers)

Week	2q8	HDq12	HDq16
0	457.2	449.1	460.3
4	333.6	331.5	333.4
8	319.9	312	319.9
12	304.6	299.4	305.9
16	295.3	312.7	312.9
20	291.9	333.3	344.4
24	309	293.4	351.9
28	292.8	302.8	294.2
32	305.6	318.5	305.4
36	283.9	285	331.1
40	299.2	289.5	332.7
44	280.2	303.2	291.7
48	295.8	279.4	305.9
52	272.2	283.4	309
56	291.7	296	328.3
60	268	275.5	289.5
64	282.5	279.4	289.6
68	258.5	294.5	305.3
72	286.1	284.2	327.2
76	256.6	270.6	302
80	279.5	284.6	293.5
84	258.8	274.7	310.8
88	274.4	283.7	312.3
92	256.9	285.7	301.8

96	274.9	267.5	304.2

Observed values (censoring data post ICE); FAS: 2q8 n=167; HDq12 n=328; HDq16 n=163 (at baseline)

[000491]The proportion of participants without fluid (no IRF and no SRF) at the foveal center (as assessed by the central reading center) at week 96 was 66.5% and 54.0% in the HDq12 and HDq16 groups, respectively, compared with 73.3% in the 2q8 group (Table 1-51). These data were consistent with prior results.

[000492]Sensitivity analyses for the proportion of participants without fluid (no IRF and no SRF) at the foveal center at week 96 using OC were consistent with the LOCF analysis.

Table 1-51. Proportion of Patients without Fluid (no IRF and no SRF) at the Foveal Center by Visit through Week 96 (LOCF & OC)

Visit	Fluid status	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)
Baseline (LOCF)	Dry	11/167 (6.6%)	17/327 (5.2%)	5/161 (3.1%)
	Not Dry	156/167 (93.4%)	310/327 (94.8%)	156/161 (96.9%)
	IRF only	101/167 (60.5%)	219/327 (67.0%)	118/161 (73.3%)
	SRF only	6/167 (3.6%)	12/327 (3.7%)	2/161 (1.2%)
	IRF and SRF	49/167 (29.3%)	79/327 (24.2%)	36/161 (22.4%)
	Missing or undetermined	0	1	2
	IRF missing or undetermined	0	1	1
	SRF missing or undetermined	0	0	0
	Both missing or undetermined	0	0	1
Week 96 (LOCF)	Dry	121/165 (73.3%)	216/325 (66.5%)	88/163 (54.0%)
	Not Dry	44/165 (26.7%)	109/325 (33.5%)	75/163 (46.0%)
	IRF only	42/165 (25.5%)	104/325 (32.0%)	69/163 (42.3%)
	SRF only	0/165	2/325 (0.6%)	0/163
	IRF and SRF	2/165 (1.2%)	3/325 (0.9%)	6/163 (3.7%)
	Missing or undetermined	0	0	0
	IRF missing or undetermined	0	0	0
	SRF missing or undetermined	0	0	0
	Both missing or undetermined	0	0	0
Baseline (OC)	Dry	11/167 (6.6%)	17/327 (5.2%)	5/161 (3.1%)
	Not Dry	156/167 (93.4%)	310/327 (94.8%)	156/161 (96.9%)

	IRF only	101/167 (60.5%)	219/327 (67.0%)	118/161 (73.3%)
	SRF only	6/167 (3.6%)	12/327 (3.7%)	2/161 (1.2%)
	IRF and SRF	49/167 (29.3%)	79/327 (24.2%)	36/161 (22.4%)
	Missing or undetermined	0	1	2
	IRF missing or undetermined	0	1	1
	SRF missing or undetermined	0	0	0
	Both missing or undetermined	0	0	1
Week 96 (OC)	Dry	87/122 (71.3%)	157/215 (73.0%)	66/125 (52.8%)
	Not Dry	35/122 (28.7%)	58/215 (27.0%)	59/125 (47.2%)
	IRF only	33/122 (27.0%)	55/215 (25.6%)	55/125 (44.0%)
	SRF only	0/122	2/215 (0.9%)	0/125
	IRF and SRF	2/122 (1.6%)	1/215 (0.5%)	4/125 (3.2%)
	Missing or undetermined	2	3	2
	IRF missing or undetermined	0	1	0
	SRF missing or undetermined	0	0	0
	Both missing or undetermined	2	2	2

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals.
IRF = Intraretinal fluid; SRF = Subretinal fluid
LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data.
OC: observations after an ICE defined for the primary estimand were excluded
Missing/undetermined data were not included in the denominator

[000493]The proportion of participants without fluid (no IRF and no SRF) in the center subfield at week 96 was 23.1% and 15.4% in the HDq12 and HDq16 groups, respectively, compared with 29.7% in the 2q8 group (Table 1-52). These data were consistent with prior results. Sensitivity analyses for the subset of participants without fluid (no IRF and no SRF) in the center subfield at week 96 using OC were consistent with the LOCF analysis.

Table 1-52. Proportion of Participants Without Fluid (no IRF and no SRF) in Center Subfield at Week 96 (LOCF) (FAS)

Treatment	Patients without Fluid at Week 96, n (%)
HDq12 (N=328)	107/325 (32.9%)
HDq16 (N=163)	37/163 (22.7%)
2q8 (N=167)	60/165 (36.4%)

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. CMH=Cochran-Mantel-Haenszel; CRT=central retinal thickness; DME=diabetic macular edema; FAS=Full analysis set; ICE=intercurrent events; IRF=intraretinal fluid; LOCF=last observation carried forward; N,n=number of patients; SAP=Statistical analysis plan; SRF=subretinal fluid. LOCF: the last observation prior to an ICE defined for the primary estimand will be used to impute subsequent and/or missing data. Missing/undetermined data were not included in the denominator.

[000494]Overall, the proportion of participants without leakage on fluorescein angiography (as assessed by the central reading center) at week 96 (LOCF) was very low in all 3 treatment groups: 5.6% and 1.3% in the HDq12 and HDq16 groups, respectively, compared to 3.1% in the 2q8 group (Table 1-53). Reductions in the total area of fluorescein leakage within the ETDRS grid were observed in all treatment groups from baseline to week 96 by -9.4 to -12.8 mm^2. (Table 1-54) These data were consistent with prior results. Sensitivity analyses for the proportion of participants without leakage on fluorescein angiography and total area of fluorescein leakage within the ETDRS grid at week 96 using OC were consistent with the LOCF analyses.

Table 1-53. Proportion of Participants Without Leakage on Fluorescein Angiography at Week 96 (LOCF) (FAS)

Treatment	Patients without Leakage on Fluorescein Angiography at Week 96, n (%)
HDq12 (N=328)	17/304 (5.6%)
HDq16 (N=163)	2/152 (1.3%)
2q8 (N=167)	5/162 (3.1%)

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; FAS=Full analysis set; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals. LOCF: the last observation prior to an ICE

defined for the primary estimand was used to impute subsequent and/or missing or non-gradable data. Missing/undetermined data were not included in the denominator.

Table 1-54. Summary of the Change from Baseline in Total Area of Fluorescein Leakage within ETDRS Grid (mm^2) at Week 96 (OC) (FAS)

Statistic	2q8 N=167	HDq12 N=328	HDq16 N=163
Baseline n	163	316	153
Baseline mean (SD)	24.2 (13.20)	23.8 (11.67)	24.6 (11.73)
Week 96 n	102	194	104
Mean (SD) change from baseline at week 96	-11.9 (11.26)	-12.8 (10.98)	-9.4 (10.61)
Median change from baseline at week 96	-8.5	-11.7	-8.4
Min, Max	-39, 8	-36, 18	-39, 16

2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; FAS=Full analysis set; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; ETDRS: Early Treatment Diabetic Retinopathy Study; SD; standard deviation. OC: observations after an ICE defined for the primary estimand were excluded.

[000495]At week 96, the proportion of participants without clinically significant macular edema was 49.3% and 46.8% in the HDq12 and HDq16 groups, respectively, compared to 48.8% in the 2q8 group (Table 1-55). Sensitivity analyses for the proportion of participants without clinically significant macular edema at week 48 and week 96 using OC were consistent with the LOCF analysis.

Table 1-55. Proportion of Participants without Clinically Significant Macular Edema at Week 48 and Week 96 (LOCF) (FAS)

Treatment	Patients without Clinically Significant Macular Edema, n (%)
Week 48[a]	
HDq12 (N=328)	66/217 (30.4%)
HDq16 (N=163)	45/119 (37.8%)
2q8 (N=167)	42/122 (34.4%)
Week 96	
HDq12 (N=328)	112/227 (49.3%)
HDq16 (N=163)	58/124 (46.8%)
2q8 (N=167)	61/125 (48.8%)

2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; FAS=Full analysis set; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3

initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; SAP=Statistical Analysis Plan.
[a]Week 48 data were not presented in previous reports, as the data from the reading center were not available at the week 48 database lock. LOCF: the last observation prior to an ICE defined for the primary estimand was used to impute subsequent and/or missing data. Missing data were not included in the denominator.

[000496]Improvements in mean change from baseline in NEI-VFQ-25 total score at week 96 were observed in all treatment groups from baseline to week 96 by 3.1 to 6.4 points (Table 1-56). These data were consistent with prior results. Sensitivity analyses for the change from baseline in NEI-VFQ-25 total score at week 96 using LOCF and were consistent with the OC analysis.

Table 1-56. Summary of the Change from Baseline in NEI-VFQ-25 Total Score at Week 96 (OC) (FAS)

Statistic	2q8 N=167	HDq12 N=328	HDq16 N=163
Baseline n	166	326	163
Baseline mean (SD)	76.7 (15.89)	76.8 (17.32)	77.9 (15.58)
Week 96 n	123	219	125
Mean (SD) change from baseline at week 96	6.4 (11.74)	5.5 (13.23)	3.1 (11.67)
Median change from baseline at week 96	14.8	12.1	9.2
Min, Max	-24, 35	-44, 45	-49, 36

2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; FAS=Full analysis set; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; ETDRS: Early Treatment Diabetic Retinopathy Study; SD; standard deviation. OC: observations after an intercurrent event (ICE) defined for the primary estimand were excluded.

[000497] The safety of aflibercept 8 mg, at week 96, remained consistent with the established profile of EYLEA® (aflibercept) 2 mg Injection. Ocular serious TEAEs; Intraocular inflammation; mean change in intraocular pressure; treatment emergent hypertension events; APTC events; and deaths, through week 96, are summarized below in Tables 1-57 - 1-60.

Table 1-57. Safety Through Week 96

	2q8	8q12	8q16	All 8 mg

N (SAF)	167	328	163	491
Ocular safety (study eye)				
Patients with ≥1 ocular AE (%)[a]	37.1	43.9	45.4	44.4
Patients with ≥1 IOI AE (%)[a]	1.2	1.5	0.6	1.2
Patients with IOP ≥35 mmHg pre- or post-injection (%)[b]	1.2	0.6	0	0.4
Non-ocular safety				
APTC events (%)[a]	7.2	6.7	6.7	6.7
Hypertension events (%)[a]	16.2	15.5	20.9	17.3
Non-ocular SAEs (%)[a]	25.1	22.9	23.9	23.2
Deaths (%)[c]	5.4	5.5	3.1	4.7

aTreatment-emergent. bIOP was measured in the study eye. cAll events. AE, adverse event; APTC, Anti-Platelet Trialists' Collaboration; IOI, intraocular inflammation; IOP, intraocular pressure; SAE, serious adverse event; SAF, safety analysis set.

Table 1-58. Ocular Serious TEAEs in the Study Eye Through Week 96

	2q8	**8q12**	**8q16**	**All 8 mg**
N (SAF)	167	328	163	491
Patients with ≥ 1 AE (%)*	2 (1.2%)	3 (0.9%)	3 (1.8%)	6 (1.2%)
Cataract	1 (0.6%)	0	1 (0.6%)	1 (0.2%)
Cataract nuclear	0	1 (0.3%)	0	1 (0.2%)
Cataract subcapsular	0	1 (0.3%)	0	1 (0.2%)
Retinal detachment	0	0	1 (0.6%)	1 (0.2%)

Retinal neovascularisation	0	0	1 (0.6%)	1 (0.2%)
Ulcerative keratitis	1 (0.6%)	0	0	0
Vitreous haemorrhage	0	0	2 (1.2%)	2 (0.4%)
Intraocular pressure increased	0	1 (0.3%)	0	1 (0.2%)

[000498]The proportion of participants with TEAEs related to intraocular inflammation in the study eye was low and similar among the treatment groups (Table 1-59). None of the events were serious.

Table 1-59. Intraocular Inflammation in the Study Eye through Week 96

	2q8	**8q12**	**8q16**	**All 8 mg**
N (SAF)	167	328	163	491
Patients with ≥ 1 IOI AE (%)*	2 (1.2%)	5 (1.5%)	1 (0.6%)	6 (1.2%)
Anterior chamber cell	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Iridocyclitis	1 (0.6%)	0	1 (0.6%)	1 (0.2%)
Iritis	0	1 (0.3%)	0	1 (0.2%)
Uveitis	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Vitreal cells	0	1 (0.3%)	0	1 (0.2%)
Vitritis	0	1 (0.3%)	0	1 (0.2%)

*treatment-emerging events

Table 1-60. Mean Change in Pre-dose Intraocular Pressure in the Study Eye

Week	2q8	HDq12	HDq16
0	0.0	0.0	0.0
4	-0.7	-0.2	0.3
8	-0.5	-0.3	0.2

12	-0.1	0	0.7
16	-0.7	0	0
20	-0.3	-0.5	0
24	-0.3	-0.7	0
28	-0.6	-0.5	0
32	-0.4	-0.4	0.2
36	-0.4	-0.3	0.4
40	-0.3	-0.5	0.1
44	-0.3	-0.3	0
48	-0.1	-0.2	-0.1
52	-0.6	-0.3	-0.2
56	-0.6	-0.5	-0.4
60	-0.6	-0.6	0.3
64	-0.5	-0.7	0.1
68	-0.5	-0.3	-0.2
72	-0.4	-0.6	0.4
76	-1	-0.7	0.2
80	-0.6	-0.9	-0.2
84	-0.7	-0.6	-0.4
88	-0.8	-0.6	-0.1
92	-0.8	-0.7	-0.5
96	-0.5	-0.6	0

SAF: 2q8 n=167; HDq12 n=328; HDq16 n=163

[000499]Treatment-emergent hypertension events were reported in fewer than 21% of participants in any treatment group. A slightly higher portion of participants reported Hypertension in the HDq16 compared to the 2q8 group and the HDq12 group (Table 1-61); however, this was not interpreted as clinically meaningful as there was no apparent dose relationship (*i.e.*, HDq16 versus HDq12). Approximately 76% of participants in all treatment groups had a medical history of Hypertension.

Table 1-61. Summary of Treatment-Emergent Hypertension Events Through Week 96 (SAS)

Primary System Organ Class	**2q8 (N=167)**	**HDq12 (N=328)**	**HDq16 (N=163)**	**All HD (N=491)**
Preferred Term				
Number of Patients with at	27 (16.2%)	51 (15.5%)	34 (20.9%)	85 (17.3%)

Least One Such TEAE, n (%)				
Investigations	4 (2.4%)	14 (4.3%)	6 (3.7%)	20 (4.1%)
Blood pressure increased	4 (2.4%)	12 (3.7%)	6 (3.7%)	18 (3.7%)
Blood pressure systolic increased	0	2 (0.6%)	0	2 (0.4%)
Vascular disorders	23 (13.8%)	40 (12.2%)	32 (19.6%)	72 (14.7%)
Hypertension	22 (13.2%)	36 (11.0%)	31 (19.0%)	67 (13.6%)
Hypertensive crisis	1 (0.6%)	0	1 (0.6%)	1 (0.2%)
Hypertensive emergency	1 (0.6%)	2 (0.6%)	0	2 (0.4%)
Hypertensive urgency	1 (0.6%)	0	1 (0.6%)	1 (0.2%)
Labile hypertension	0	1 (0.3%)	0	1 (0.2%)
Orthostatic hypertension	0	1 (0.3%)	0	1 (0.2%)
White coat hypertension	0	0	1 (0.6%)	1 (0.2%)

[000500]Potential ATEs (arterial thromboembolic events) were evaluated by a masked adjudication committee according to criteria formerly applied and published by the APTC(Antithrombotic Trialists' Collaboration, 2002; Antithrombotic Trialists' Collaboration, 1994). ATEs as defined by the APTC criteria include Nonfatal myocardial infarction, Nonfatal stroke (ischemic or hemorrhagic), or Death resulting from vascular or unknown causes. Low (< 7.2%) and similar proportions of participants reported adjudicated APTC events across the treatment groups (Table 1-62).

Table 1-62. Summary of Adjudicated Treatment-Emergent APTC Arterial Thromboembolic Events by Category of APTC Event, Preferred Term, and Treatment Through Week 96 (SAS)

APTC Category	**2q8 (N=167)**	**HDq12 (N=328)**	**HDq16 (N=163)**	**All HD (N=491)**
Preferred Term				
Number of Patients with at Least One Such TEAE, n (%)	12 (7.2%)	22 (6.7%)	11 (6.7%)	33 (6.7%)

Non-fatal myocardial infarction	5 (3.0%)	10 (3.0%)	3 (1.8%)	13 (2.6%)
Acute myocardial infarction	2 (1.2%)	6 (1.8%)	2 (1.2%)	8 (1.6%)
Blood creatine phosphokinase increased	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
Chest pain	1 (0.6%)	0	0	0
Coronary artery disease	0	2 (0.6%)	0	2 (0.4%)
Myocardial infarction	2 (1.2%)	4 (1.2%)	2 (1.2%)	6 (1.2%)
Non-fatal stroke	2 (1.2%)	5 (1.5%)	6 (3.7%)	11 (2.0%)
Cerebral infarction	0	0	1 (0.6%)	1 (0.2%)
Cerebrovascular accident	1 (0.6%)	3 (0.9%)	4 (2.5%)	7 (1.4%)
Dysarthria	0	0	1 (0.6%)	1 (0.2%)
Embolic stroke	1 (0.6%)	0	0	0
Hemiplegia	0	0	1 (0.6%)	1 (0.2%)
Intraventricular haemorrhage	0	1 (0.3%)	0	1 (0.2%)
Ischaemic stroke	1 (0.6%)	0	0	0
Lacunar infarction	0	0	1 (0.6%)	1 (0.2%)
Precerebral arteriosclerosis	0	0	1 (0.6%)	1 (0.2%)
Thalamus haemorrhage	0	1 (0.3%)	0	1 (0.2%)
Transient ischaemic attack	0	1 (0.3%)	0	1 (0.2%)
Vascular death	5 (3.0%)	7 (2.1%)	2 (1.2%)	9 (1.8%)
Acute myocardial infarction	0	4 (1.2%)	0	4 (0.8%)
Cardiac arrest	3 (1.8%)	0	0	0
Coronary artery stenosis	0	1 (0.3%)	0	1 (0.2%)
Death	1 (0.6%)	2 (0.6%)	0	2 (0.4%)
Myocardial infarction	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
Sudden death	0	0	1 (0.6%)	1 (0.2%)

MedDRA (Medical Dictionary for Regulatory Activities) (Version 26.0) coding dictionary applied.
2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals;
HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-

week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; All HD: Pooled HDq12 and HDq16 groups; SAS=Safety analysis set. The percentage is based on the number of patients in each treatment group as denominator. A treatment-emergent adverse event (TEAE) is an AE starting after the first dose of study drug to the last dose of study drug (active or sham) plus 30 days. Additionally, for patients who are still participating in the study (ie, have not been withdrawn) as of the Week 96 visit all AEs up through the date of the last visit will be considered treatment-emergent.

[000501]Through week 96, 32 deaths were reported in this study and were evenly distributed across the treatment groups (Table 1-63). All were associated with an SAE. None of the deaths were considered related to study drug or study procedure. Overall, the deaths reported were consistent with concurrent medical conditions and the complications of these conditions associated with an older population.

Table 1-63. Summary of Adverse Events With Fatal Outcomes by Primary System Organ Class and Preferred Term Occurring in Participants in any Treatment Group Through Week 96 (SAS)

Primary System Organ Class	2q8 (N=167)	HDq12 (N=328)	HDq16 (N=163)	All HD (N=491)
Preferred Term				
Number of Patients with at Least One Such AE, n (%)	9 (5.4%)	18 (5.5%)	5 (3.1%)	23 (4.7%)
Cardiac disorders	4 (2.4%)	7 (2.1%)	3 (1.8%)	10 (2.0%)
Acute myocardial infarction	0	4 (1.2%)	0	4 (0.8%)
Cardiac arrest	3 (1.8%)	2 (0.6%)	0	2 (0.4%)
Cardio-respiratory arrest	0	0	1 (0.6%)	1 (0.2%)
Left ventricular failure	0	0	1 (0.6%)	1 (0.2%)
Myocardial infarction	1 (0.6%)	1 (0.3%)	1 (0.6%)	2 (0.4%)
General disorders and administration site conditions	2 (1.2%)	3 (0.9%)	1 (0.6%)	4 (0.8%)
Death	1 (0.6%)	3 (0.9%)	0	3 (0.6%)
Multiple organ dysfunction syndrome	1 (0.6%)	0	0	0
Sudden death	0	0	1 (0.6%)	1 (0.2%)
Infections and infestations	1 (0.6%)	4 (1.2%)	0	4 (0.8%)
COVID-19	0	2 (0.6%)	0	2 (0.4%)
Pneumonia	0	1 (0.3%)	0	1 (0.2%)

Septic shock	0	1 (0.3%)	0	1 (0.2%)
Urosepsis	1 (0.6%)	0	0	0
Metabolism and nutrition disorders	1 (0.6%)	0	0	0
Diabetic metabolic decompensation	1 (0.6%)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.3%)	0	1 (0.2%)
Endometrial cancer	0	1 (0.3%)	0	1 (0.2%)
Renal and urinary disorders	1 (0.6%)	3 (0.9%)	0	3 (0.6%)
Acute kidney injury	1 (0.6%)	1 (0.3%)	0	1 (0.2%)
End stage renal disease	0	1 (0.3%)	0	1 (0.2%)
Renal failure	0	1 (0.3%)	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.6%)	1 (0.2%)
Pulmonary embolism	0	0	1 (0.6%)	1 (0.2%)

MedDRA (Version 26.0) coding dictionary applied.
2q8: Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12: High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16: High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; All HD: Pooled HDq12 and HDq16 groups; SAS=Safety analysis set. The percentage is based on the number of patients in each treatment group as denominator.

Case Report

[000502]A 55-year-old, treatment-naïve, male patient with DME was randomized to the PHOTON HDq16 group, and he had a BCVA of 45 letters and a CRT of 611 microns at baseline. The patient maintained improvements in BCVA and CRT through week 96.

[000503]Through Week 12, he gained 12 letters and experienced a CRT reduction of 418 microns following 3 initial monthly injections from baseline to Week 8. Through Year 1, the patient maintained a Q16 dosing interval. At Week 56, the first visit for DRM assessment in Year 2, he gained 9 letters compared with Week 12 and had a CRT of 192 microns. He therefore qualified for interval extension to Q20. The criteria for interval extension in the PHOTON trial was less than 5-letter loss in BCVA from Week 12 and CRT of less than 300 microns, or less than 320 microns on Spectralis. The patient continued to maintain visual and anatomic improvements through Week 76, and at this visit, he qualified for interval extension to 24 weeks. At the end of the trial at Week 96, there were visual and anatomic improvements

maintained 20 weeks after his last injection. From baseline through Week 96, he gained 19 letters and experienced a CRT reduction of 437 microns. See Figure 76. At week 100, his BCVA was 68 letters and his CRT was 191 micrometers.

[000504]These data demonstrate that after a 24 week interval between 8 mg doses of aflibercept, from week 76 to 100, the patient maintained BCVA and CRT.

Pharmacokinetics- observed systemic concentration-time profiles and associated PK parameters

[000505]Choice of Dose and Dosing Regimen. Prior to the conduct of the HD aflibercept phase 2 and 3 studies, the choice of dose and dosing regimens was supported by an empirical modeling approach (Eissing *et al.*, Durability of VEGF Suppression with Intravitreal Aflibercept and Brolucizumab: Using Pharmacokinetic Modeling to Understand Clinical Outcomes, Transl Vis Sci Technol. 2021 Apr 1;10(4):9). PK simulations, based on the simple linear 1-compartment model, predicted that an 8 mg IVT dose of aflibercept may provide up to 20 days longer duration of pharmacological effect than a 2 mg IVT dose of aflibercept. However, the observed clinical data from the phase 2 CANDELA and phase 3 (PULSAR, PHOTON) studies indicate a longer than expected duration of pharmacological effect for HD aflibercept than that based on this initial empirical model.

[000506]Initiation of the HD aflibercept clinical program was based on the continuing need for patients with proliferative neovascular eye disease who are currently being treated with, or indicated for, anti-VEGF therapy to have treatment options with less frequent IVT dosing without inferior efficacy. Given the well-characterized and favorable risk/benefit profile of 2 mg aflibercept, a higher dose of aflibercept able to extend the treatment interval was proposed. A novel drug product (High Dose Aflibercept [HD aflibercept]) able to deliver via IVT 8 mg of aflibercept was developed. Pharmacokinetic simulations of free aflibercept concentration-time profiles in human vitreous using a 1-compartment ocular model demonstrate 8 mg IVT dose of aflibercept extending the dosing interval by approximately 20 days (two half-lives) relative to a 2 mg IVT dose.

[000507]Summaries of free and adjusted bound aflibercept concentrations in plasma for participants in the dense PK analysis set (DPKS) are presented by treatment in Table 1-64 and Table 1-65. Mean (SD) concentrations of free and adjusted bound aflibercept are presented by nominal time for participants in the DPKS in Figure 27 and Figure 28 (log scale). After the initial IVT aflibercept dose of 2 mg or pooled HD aflibercept (HDq12+HDq16 aflibercept, referred to in this section as 8 mg aflibercept), the concentration-time profiles of free aflibercept were

characterized by an initial phase of increasing concentrations as the drug moved from the ocular space into systemic circulation followed by a mono-exponential elimination phase (Figure 27). The concentration-time profiles of adjusted bound aflibercept in plasma was characterized by a slower attainment of peak concentration (C_{max}) compared to free aflibercept. Following attainment of C_{max}, a sustained plateau of the concentration-time profiles of adjusted bound aflibercept in plasma was observed until approximately the end of the dosing interval for both dose groups (Figure 28).

[000508]For participants enrolled in the dense PK sub-study who received 2 mg aflibercept (n = 12), concentrations of free aflibercept were detectable in 4 participants at day 7 and were undetectable in all participants by day 14. Adjusted bound aflibercept concentrations were undetectable by day 28 in 1 participant in the 2 mg aflibercept treatment (n = 12). For the 8 mg aflibercept treatment (n = 21), free aflibercept concentrations were undetectable in 4 participants at day 28, and adjusted bound aflibercept concentrations were undetectable in 1 participant at day 28 (Table 1-64, Table 1-65).

[000509]After the initial aflibercept dose of 2 mg or 8 mg aflibercept, the concentration-time profiles for free aflibercept in plasma were similar for Japanese and non-Japanese populations in participants enrolled in the dense PK sub-study.

[000510]Following the third initial monthly IVT dose of aflibercept, based on the ratio of aflibercept concentration in plasma at week 12 to week 4 (C_{week12}/C_{week4}), the accumulation of free aflibercept was 2.0 and 1.8 for HDq12 and HDq16. The accumulation of free aflibercept could not be determined for 2q8 since all aflibercept concentration values at week 12 were below the limit of quantitation (BLQ). The accumulation of adjusted bound aflibercept was 1.7 for 2q8 and 1.5 for both HDq12 and HDq16.

[000511]For the participants in the PKAS, the concentrations of free and adjusted bound aflibercept in plasma were, on average, higher for the HDq12 and HDq16 treatment groups than the 2q8 treatment group (Figure 29 and Figure 30).

[000512]The impact of fellow eye treatment with 2 mg aflibercept and DRMs on free and adjusted bound aflibercept concentrations was assessed by comparing the mean concentrations over time for all participants in PKAS with the mean concentrations over time from participants in the PKAS who only received unilateral aflibercept injections without DRMs through week 48. Concentrations of free and adjusted bound aflibercept were lower in participants who received unilateral aflibercept injections with no DRMs than in the overall

population. Of note, the dosing interval was only allowed to be shortened in the first year of treatment.

Table 1-64. Summary of Concentrations of Free Aflibercept in Plasma by Time and Treatment in Participants with DME with Unilateral Treatment in the Dense PK Sampling Sub-study

	Concentrations of Free Aflibercept in Plasma (mg/L)			
	2q8 (N=12)		HDq12+HDq16 (N=23)	
Sampling Time Post First Dose (Days)	n	Mean (SD)	n	Mean (SD)
0	11	0 (0)	23	0 (0)
0.1667	12	0.00834 (0.0154)	22	0.149 (0.249)
0.3333	11	0.0147 (0.0229)	22	0.205 (0.250)
1	12	0.0229 (0.0324)	22	0.266 (0.211)
2	12	0.0146 (0.0171)	22	0.218 (0.145)
4	12	0.00858 (0.0107)	22	0.140 (0.0741)
7	12	0.00713 (0.0114)	19	0.0767 (0.0436)
14	12	0 (0)	21	0.0309 (0.0241)
21	12	0 (0)	21	0.0171 (0.0171)
28	12	0 (0)	21	0.00730 (0.0113)

Abbreviations: N,n=Number of patients; SD=Standard deviation; DME=Diabetic macular edema; 2q8=2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12=High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses; HDq16=High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses; DPKS=Dense PK Sampling Substudy Note: HDq12+HDq16 = combined data from treatment groups HDq12 and HDq16. Patients in the dense PK substudy only received aflibercept injections unilaterally.

Table 1-65. Summary of Concentrations of Adjusted Bound Aflibercept in Plasma by Time and Treatment in Participants with DME with Unilateral Treatment in the Dense PK Sampling Sub-study (Study VGFTe-HD-DME-1934, [DPKS])

	Concentrations of Adjusted Bound Aflibercept in Plasma (mg/L)			
	2q8 (N=12)		HDq12+HDq16 (N=23)	
Sampling Time Post First Dose (Days)	n	Mean (SD)	n	Mean (SD)
0	11	0.00451 (0.0150)	23	0.00583 (0.0280)
0.1667	12	0.00452 (0.0156)	22	0.00698 (0.0276)
0.3333	11	0.00426 (0.0141)	22	0.00731 (0.0279)
1	12	0.0131 (0.0260)	22	0.0678 (0.0486)
2	12	0.0452 (0.0357)	22	0.138 (0.0618)
4	12	0.0765 (0.0412)	22	0.259 (0.126)
7	12	0.0885 (0.0392)	19	0.346 (0.151)
14	12	0.105 (0.0414)	21	0.374 (0.110)
21	12	0.101 (0.0423)	21	0.343 (0.128)
28	12	0.0873 (0.0506)	21	0.269 (0.149)

Abbreviations: N,n=Number of patients; SD=Standard deviation; DME=Diabetic macular edema; 2q8=2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12=High-

dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses; HDq16 = High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses. Note: Adjusted bound aflibercept = 0.717*bound aflibercept. HDq12+HDq16 = combined data from treatment groups HDq12 and HDq16. Patients in the dense PK substudy only received aflibercept injections unilaterally.

[000513]Summaries of PK parameters from observed free and adjusted bound aflibercept concentrations for participants in the DPKS are presented by treatment in Table 1-66 and Table 1-67. After the initial monthly aflibercept dose of 2 mg (2q8) or 8 mg, free aflibercept median time to peak concentration (t_{max}) was 0.268 and 0.965 days for the 2 mg and 8 mg aflibercept treatments, respectively. The attainment of t_{max} for adjusted bound aflibercept concentrations was slower when compared to free aflibercept. For adjusted bound aflibercept, the median t_{max} was 14 days for the 2 mg and 8 mg aflibercept treatments. As the IVT dose of aflibercept increased from 2 mg to 8 mg (a 4-fold increase in dose), the mean peak concentration (C_{max}) and mean area under the concentration-time curve from time zero to the time of the last measurable concentration (AUC_{last}) for free aflibercept increased in a greater than dose-proportional manner (approximately 12 to 14 fold). Conversely, for adjusted bound aflibercept, mean AUC_{last} and C_{max} increased slightly less than to dose proportionally (approximately 3 to 4-fold). These results are consistent with historical data and the known nonlinear kinetics of aflibercept (Table 1-66 and Table 1-67).

Table 1-66. Summary of Pharmacokinetic Parameters Calculated from Concentrations of Free Aflibercept in Plasma by Treatment in Participants with DME with Unilateral Treatment in the Dense PK Sampling Substudy (Study VGFTe-HD-DME-1934, [DPKS])

		2q8 (N=12)				HDq12+HDq16 (N=23)			
PK Parameters	Unit	n	Mean (SD)	Median	Min : Max	n	Mean (SD)	Median	Min : Max
AUC_{inf}	day*mg/L	0				13	2.26 (0.714)	2.29	1.14 : 3.36
AUC_{inf}/Dose	day*mg/L/mg	0				13	0.283 (0.0892)	0.287	0.143 : 0.420
AUC_{last}	day*mg/L	7	0.126 (0.0660)	0.146	0.0244 : 0.202	21	1.71 (0.816)	1.85	0.230 : 2.82
AUC_{last}/Dose	day*mg/L/mg	7	0.0628 (0.0330)	0.0732	0.0122 : 0.101	21	0.214 (0.102)	0.232	0.0287 : 0.352
AUC_{0-28}	day*mg/L	6	0.170 (0.124)	0.162	0 : 0.358	19	1.86 (0.840)	1.97	0 : 2.89
C_{max}	mg/L	12	0.0266 (0.0333)	0.0198	0 : 0.109	23	0.310 (0.263)	0.245	0 : 1.08
C_{max}/Dose	mg/L/mg	12	0.0133 (0.0167)	0.00990	0 : 0.0545	23	0.0388 (0.0328)	0.0306	0 : 0.135
C_{last}	mg/L	7	0.0217 (0.00619)	0.0195	0.0157 : 0.0335	21	0.0390 (0.0399)	0.0223	0.0158 : 0.169

$C_{trough28}$	mg/L	12	0 (0)	0	0 : 0	21	0.00730 (0.0113)	0	0 : 0.0371
$t_{1/2}$	day	1	NR[1]	NR[1]	NR[1]	15	8.43 (4.55)	8.48	1.41 : 20.4
t_{max}	day	12	--	0.268	0 : 7.04	23	--	0.965	0 : 4.01
t_{last}	day	7	--	6.94	1.98 : 7.04	21	--	20.9	2.00 : 32.0

PK=Pharmacokinetic; N=Number of patients; n=Number of patients contributing to each PK parameter; SD=Standard deviation; DME=Diabetic macular edema; 2q8=2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12=High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses; HDq16=High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses
Note: HDq12+HDq16=combined data from treatment groups HDq12 and HDq16. Patients in the dense PK sub-study only received aflibercept injections unilaterally. Data presented were collected during the dense PK sub-study (from pre-dose Day 0 through Day 28).
1 NR = not reported; N=1 participant had a reportable $t_{1/2}$ value of 17.3 days.

Table 1-67. Summary of Pharmacokinetic Parameters Calculated from Concentrations of Adjusted Bound Aflibercept in Plasma by Treatment in Participants with DME with Unilateral Treatment in the Dense PK Sampling Substudy (Study VGFTe-HD-DME-1934, [DPKS])

		2q8 (N=12)				HDq12+HDq16 (N=23)			
Parameters	**Unit**	**n**	**Mean (SD)**	**Median**	**Min : Max**	**n**	**Mean (SD)**	**Median**	**Min : Max**
AUCinf	day*mg/L	0				0			
AUCinf/Dose	day*mg/L/mg	0				0			
AUClast	day*mg/L	11	2.48 (0.607)	2.52	1.33 : 3.67	23	8.30 (3.05)	8.03	4.07 : 17.6
AUClast/Dose	day*mg/L/mg	11	1.24 (0.303)	1.26	0.664 : 1.83	23	1.04 (0.382)	1.00	0.509 : 2.20
AUC0-28	day*mg/L	4	2.53 (0.360)	2.49	2.14 : 3.00	14	8.71 (3.65)	8.42	3.27 : 17.7
Cmax	mg/L	12	0.115 (0.0442)	0.124	0 : 0.154	23	0.387 (0.135)	0.380	0.137 : 0.774
Cmax/Dose	mg/L/mg	12	0.0575 (0.0221)	0.0618	0 : 0.0771	23	0.0483 (0.0168)	0.0475	0.0171 : 0.0968
Clast	mg/L	11	0.104 (0.0314)	0.0961	0.0551 : 0.154	23	0.287 (0.136)	0.260	0.0649 : 0.599
Ctrough28	mg/L	12	0.0873 (0.0506)	0.0929	0 : 0.154	21	0.269 (0.149)	0.252	0 : 0.599
tmax	day	12	--	14.0	0 : 23.9	23	--	14.0	3.96 : 37.1
tlast	day	11	--	27.0	21.0 : 30.1	23	--	27.9	20.9 : 43.0

Abbreviations: PK=Pharmacokinetic; N,n=Number of patients; SD=Standard deviation; DME=Diabetic macular edema; 2q8=2 mg intravitreal aflibercept every 8 weeks following 5 initial monthly doses; HDq12=High-dose (8 mg) intravitreal aflibercept every 12 weeks following 3 initial monthly doses; HDq16=High-dose (8 mg) intravitreal aflibercept every 16 weeks following 3 initial monthly doses Note: Adjusted bound aflibercept = 0.717*bound aflibercept. HDq12+HDq16 = combined data from treatment groups HDq12 and HDq16. Patients in the dense PK substudy only received aflibercept injections unilaterally. Data presented were collected during the dense PK substudy (from pre-dose day 0 through day 28).

Expanded Population PK Analysis (referred to as the Population PK model, or PopPK).

[000514]With availability of the free and adjusted bound aflibercept concentration data from the CANDELA, PULSAR, and PHOTON along PK data from the other studies listed herein, a comprehensive PopPK model was developed, In this latter PopPK model, the PK of free and adjusted bound aflibercept following IV, SC, or IVT administration was adequately described by a 3-compartment PopPK model with the binding of free aflibercept from the central compartment to VEGF described by Michaelis-Menten kinetics. An additional tissue compartment that could represent platelets (Sobolewska *et al.*, Human Platelets Take up Anti-VEGF Agents. J Ophthalmol 2021; 2021:8811672) was added where the rate of elimination from the central compartment of free aflibercept to the platelet compartment was dependent on the number of platelets that were able to uptake anti-VEGF agents such as ranibizumab, bevacizumab, and aflibercept (Figure 31).

[000515]Although PK parameters for free and adjusted bound aflibercept in plasma were determined by noncompartmental analysis (NCA) and reported at the level of the individual study reports, the PK parameters determined by population PK analysis are considered to be the more accurate estimate and therefore the definitive PK parameters are those assessed by the population PK model.

[000516]Across all 3 studies (CANDELA, PULSAR, and PHOTON), the pharmacokinetic analysis set (PKAS) includes all treated participants who received any amount of study drug (aflibercept or HD aflibercept) and had at least 1 non-missing aflibercept or adjusted bound aflibercept measurement following the first dose of study drug. The PKAS is based on the actual treatment received (as treated), rather than as randomized. The PKAS-dense (PK-dense) analysis set is a subset of the PKAS and includes participants who had dense blood sample collection for systemic drug concentrations.

[000517]CANDELA, PULSAR, and PHOTON each included a PK substudy where drug concentration data were collected using dense blood sample collection schedules during the first dosing interval and sparse PK sampling thereafter in up to approximately 30 participants. Drug concentration data were also collected in each study for all participants using a sparse sampling schedule throughout the 44 weeks (CANDELA) or 48 weeks (PHOTON, PULSAR) of treatment.

[000518]Pharmacokinetic parameters for individual studies were calculated by non-compartmental analysis for free and adjusted bound aflibercept concentration data collected from participants with dense sampling schedules in these 3 studies.

[000519]Additionally, all concentration data from these 3 studies were incorporated into the Population PK data set.

[000520]The concentration time profiles of free and adjusted bound aflibercept in plasma after the initial dose of HD aflibercept by IVT administration were consistent between all studies in participants with nAMD or DME. The consistency of the concentration-time profiles for free and adjusted bound aflibercept in plasma between the nAMD and DME populations is further supported by population PK analysis (Figure 33 and Figure 34).

[000521]Population PK estimated post-hoc concentration-time profiles and PK parameters for combined nAMD and DME populations following single IVT administration of 2 mg aflibercept or HD aflibercept are provided in Figure 33 and Figure 34 and in Table 1-68 and Table 1-71.

[000522]Following single IVT administration of aflibercept 2 mg or HD aflibercept, the concentration-time profiles of free and adjusted bound aflibercept in plasma in participants who underwent dense sample collection for systemic drug concentrations (dense PK substudy) after the initial dosing of aflibercept 2 mg or HD aflibercept, respectively, were consistent between the 3 studies in participants with nAMD or DME (Figure 32). Notably, there was one excluded participant in the PULSAR dense-sampling PK substudy that had free aflibercept concentrations over time that were approximately 10-fold higher than the mean concentration-time profiles in that study.

[000523]The consistency of the concentration-time profiles for free and adjusted bound aflibercept between the nAMD and DME populations is further supported by Population PK analysis (Figure 33). Population PK estimated post-hoc concentration-time profiles and PK parameters for combined nAMD and DME populations following single IVT administration of 2 mg aflibercept or HD aflibercept are provided below in Figure 33 and in Table 1-69 and Table 1-70.

[000524]The corresponding observed and Population PK estimated post-hoc concentration-time profiles and PK parameters for participants with nAMD and DME are provided in Figure 36, Figure 37, and Figure 38 and Table 1-71, Table 1-72.

[000525]Following single IVT administration of 2 mg aflibercept or HD aflibercept, the concentration-time profiles of free aflibercept are characterized by an initial phase of increasing concentrations, as the drug moved from the ocular space into systemic circulation, followed by a mono-exponential elimination phase. The concentration time profiles of adjusted bound aflibercept in plasma are characterized by a slower attainment of Cmax compared to free aflibercept. Following attainment of C_{max}, a sustained plateau of the concentration-time profiles

of adjusted bound aflibercept in plasma was observed until approximately the end of the first dosing interval (Figure 32, Figure 33).

[000526]For participants who underwent dense blood sample collection for systemic drug concentrations across the CANDELA, PULSAR, and PHOTON studies, after the initial dosing of 2 mg IVT aflibercept (n = 34), observed concentrations of free aflibercept were detectable in 15 (44.1%) participants by week 1 and in 3 (8.8%) participants by week 2.

[000527]For participants who underwent dense blood sample collection for systemic drug concentrations after the initial dosing of 8 mg IVT aflibercept (n = 54), observed concentrations of free aflibercept were detectable in 46 (85.2%) participants by week 1 and in 44 (77.8%) participants by week 2. The observed and Population PK simulated free and adjusted bound aflibercept concentrations in plasma for up to 48 weeks are presented for the combined nAMD and DME population (Figure 34), and the nAMD (Figure 39) and DME (Figure 40) populations. Based on the Population PK analysis, the median time for free aflibercept concentrations to reach LLOQ in plasma following HDq12 or HDq16 was more than double (3.50 weeks versus 1.5 weeks) the median time needed to reach LLOQ following aflibercept 2q8 (Table 1-73).

[000528]The longer duration of systemic exposure to free aflibercept following HDq12 and HDq16 compared to the 2 mg aflibercept is attributed to not only a higher administered dose and nonlinear systemic target-mediated elimination, but also to a 34% slower ocular clearance of free aflibercept. The slower ocular clearance of free aflibercept for HD aflibercept is attributed to a HD drug product effect which was identified as a statistically significant covariate in the Population PK model.

[000529]Population PK analysis confirmed no relevant differences in PK between the nAMD and DME populations, and therefore all subsequent analyses are presented for the combined nAMD and DME population.

[000530]The pharmacokinetic (PK) data set forth above summarize the observed systemic concentration-time profiles and associated PK parameters for free and adjusted bound aflibercept for each individual study. The analyses utilized to estimate the PK parameters in each individual study were performed by non-compartmental analysis. While the individual PHOTON study results describe the observed systemic concentration-time profiles and associated PK parameters of free and adjusted bound aflibercept in plasma, they do not specifically identify PK characteristics of the HD 8 mg aflibercept drug product contributing to the unexpected pharmacodynamic (PD) and efficacy results for HD aflibercept observed in the CANDELA (NCT04126317), PULSAR (NCT04423718), and PHOTON (European Clinical Trials Database (EudraCT): 2019-003851-12) studies.

[000531]An expanded PopPK analysis that utilized free and adjusted bound concentration in plasma data from the HD clinical studies, as well as 13 prior studies:

DME population

- VGFT-OD-0307: A double-blind, randomised, dose-escalating study evaluating safety, tolerability and bio-effect after intravenous (IV) administration of VEGF Trap in subjects with DME. Subjects were planned to receive 4 IV infusions of VEGF Trap, once every 2 weeks (day 1, day 15, day 29, and day 43), at dose levels of 0.3 mg/kg, 1 mg/kg, or 3 mg/kg, or placebo. However, dosing was stopped before the planned sequential dose escalation when dose-limiting toxicities (grade 2 proteinuria in a single subject and grade 4 treatment-related malignant hypertension in a single subject) were observed in another phase 1 dose-escalation study in subjects with AMD (VGFT-OD-0305). The dose limiting toxicities observed in study VGFT-OD-0305 occurred at the 3 mg/kg IV dose. Therefore, only the lowest dose (0.3 mg/kg) of study drug was investigated. Nine subjects were randomised and treated (3 placebo, 6 VEGF Trap 0.3 mg/kg). Concentrations of free and bound VEGF Trap were determined at selected time intervals following dose administration (screening, day 1[pre-dose], day 8, day 15, day 29, day 43, day 57, day 71, day 85, and day 133 [3 months post-last dose]);
- VGFT-OD-0512: An open-label, proof-of-concept study evaluating safety, tolerability and bio-effect of VEGF Trap IVT administration in subjects with DME. Five (5) subjects with DME were enrolled. Subjects received a single IVT injection of 4 mg VEGF Trap into the study eye. During the first 6 weeks after the injection, vital signs as well as ocular and systemic adverse events (AEs) were recorded. Blood samples for analysis of free and bound VEGF Trap concentrations in plasma were collected at screening, day 1 (pre-dose), day 3, day 8, day 15, day 29, day 43 and day 155 following the single IVT administration;
- VGFT-OD-0706.PK (PK sub-study of VGFT-OD- 0706): DME And VEGF Trap-Eye [Intravitreal Aflibercept Injection (IAI;EYLEA®;BAY86-5321)] INvestigation of Clinical Impact (DA VINCI)-Clinicaltrials.gov Identifier NCT00789477; and
- 91745: Intravitreal Aflibercept Injection in Vision Impairment Due to DME (VIVID-DME)-ClinicalTrials.gov Identifier NCT01331681;

AMD population

- VGFT-OD-0305: A double-masked, placebo controlled, sequential group, dose escalating, (0.3 mg/kg, 1 mg/kg, 3 mg/kg, 5 mg/kg, 7 mg/kg, and 10 mg/kg) study of safety and bioeffect. The study included subjects with a diagnosis of visual impairment associated with neovascular AMD. Subjects were required to have visual loss due to subfoveal choroidal neovascularization (CNV) secondary to AMD, be 50 years of age or older, with no history of

Type I or Type II diabetes, without significant cardiac, liver or kidney disease, or congestive heart failure (CHF); and without confounding ophthalmic issues. The study treatments were: 1. VEGF Trap 0.3 mg/kg. 2. VEGF Trap 1 mg/kg, and 3. VEGF Trap 3 mg/kg;

- VGFT-OD-0306: An open label, long term safety and tolerability extension study of intravenous VEGF Trap in subjects with neovascular AMD who had been included in Study VEGF-OD-0305. The study treatments were VEGF Trap at the same dose level the subjects had been treated with in Study VEGF-OD-0305: either 0.3 mg/kg or 1 mg/kg, by intravenous administration every 2 weeks. Placebo patients from Study VGFT-OD-0305 were assigned to VEGF Trap at the dose level at which they were enrolled in Study VGFT-OD-0305. The efficacy outcome measures were: Visual acuity (ETDRS), Retinal thickness (OCT), Funduscopic examination, Fundus photography, and FA. The safety outcome measures were: AEs, Clinical laboratory tests, and Ophthalmic exam. Treatment duration was for up to 106 days. There were seven subjects: four subjects treated with 0.3 mg/kg, 3 subjects treated with 1 mg/kg. There were five females, two males and the age range was 68 to 84 years. Six of the seven subjects had a slight reduction in ERT in the study eye and six of seven subjects had slight reductions in macular volume in the study eye;
- VGFT-OD-0502 Part A: Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD-ClinicalTrials.gov Identifier: NCT00320775;
- VGFT-OD-0502 Part C: ClinicalTrials.gov Identifier: NCT00320775;
- VGFT-OD-0603: Safety and Tolerability of Intravitreal VEGF Trap Formulations in Subjects With Neovacular AMD-ClinicalTrials.gov Identifier: NCT00383370;
- VGFT-OD-0702.PK (PK sub-study of VGFT-OD-0702): Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD-ClinicalTrials.gov Identifier: NCT00527423; and
- 311523 (VIEW2): A multicentre, double masked, randomised, active controlled, parallel group, non-inferiority efficacy and safety study. The study was almost identical in design to Study VGFT-OD-0605/14393 (VIEW 1). The submission contained the report of the first 52 weeks of the study. The study was conducted at 186 centres in 26 countries.

The inclusion criteria, exclusion criteria and study treatments were identical to Study VGFT-OD-0605/14393 (VIEW 1). The efficacy outcome measures were the same, except for the additional outcome measure: change in scores of the EQ-5D questionnaire from screening at Week 52;

Oncology population

- VGFT-ST-0103, (also known as TED6113): VEGF Trap in Treating Patients With Relapsed or Refractory Solid Tumors or Non-Hodgkin's Lymphoma-ClinicalTrials.gov Identifier: NCT00036946;

Healthy participant population

- PDY6655: A Phase I, single centre, randomised, single dose, crossover, pharmacokinetic (PK) study in healthy volunteers to compare the pharmacokinetics and pharmacodynamic (PD) of intravenous and subcutaneous administration of aflibercept. The study included 40 healthy male subjects aged 18 to 45 years. The study treatments were: aflibercept 2.0 mg/kg as an intravenous infusion over 1 hour, and as a subcutaneous injection. The aflibercept was presented as 4 mL of 25 mg/mL solution. The treatments were administered as single doses followed by 6 week observation period. The treatment periods were separated by 1 to 2 weeks. The PK outcome measures were: Cmax, AUC, apparent volume of distribution at steady state (Vss), clearance and half life ($t_{1/2}$). The PD outcome measures were: systolic blood pressure, diastolic blood pressure, heart rate, mean arterial pressure, plasma renin activity, angiotensin I, aldosterone, and free endogenous VEGF. The safety outcome measures were: AEs, clinical laboratory test, injection site reactions, and anti-aflibercept antibodies. AUC and Cmax were slightly higher for Period 2, indicating some carry over. For Period 1, for free aflibercept mean (co-variance (CV%)) AUC was 177 (33) µg•day/mL and peak plasma concentration (Cmax) was 44.4 (36) µg/mL for intravenous and AUC was 84.9 (30) µg•day/mL and Cmax was 7.76 (39) µg/mL for subcutaneous. For Period 1, for bound aflibercept mean (CV%) AUC was 57.7 (19) µg•day/mL and Cmax was 1.84 (22) µg/mL for intravenous and AUC was 47.3 (27) µg•day/mL and Cmax was 1.60 (27) µg/mL for subcutaneous. The mean (90% CI) ratio for AUC, subcutaneous/ intravenous, was 0.51 (0.46 to 0.56) [(range)], and
- PDY6656: A single centre, Phase I, randomised, double blind, placebo controlled, sequential ascending dose study of intravenous aflibercept. The study included healthy male subjects 18 to 45 years of age; non-smoker; 18≤ body mass index (BMI) ≤28 kg/m^2; with normal vital signs and no symptomatic hypotension. The study treatments were aflibercept 1 mg/kg, 2 mg/kg and 4 mg/kg, and placebo. There were three cohorts of 16 subjects: twelve treated with aflibercept and four treated with placebo. The treatments were administered as a single dose by intravenous infusion over 1 hour. The pharmacodynamic outcome measures were: systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), plasma active renin, aldosterone and angiotensin I; markers of endothelium dysfunction (plasma endothelin-1, E-selectin, cyclic guanosine 3'5' monophosphate (cGMP), and urine nitrites/nitrates); renal function; and VEGF. The safety outcome measures were: AEs and

laboratory tests. The study included 48 subjects: 12 treated with 1 mg/kg, 12 with 2 mg/kg, 12 with 4 mg/kg and 12 with placebo. The age range was 21 to 45 years. For free aflibercept mean (CV%) Cmax was 18.2 (18) µg/mL for the 1 mg/kg dose, 39.7 (27) µg/mL for the 2 mg/kg dose and 78.6 (15) µg/mL for the 4 mg/kg dose; and mean (CV%) AUC was 64.8 (20) µg.day/mL for the 1 mg/kg dose, 180 (20) for the 2 mg/kg dose and 419 (21) for the 4 mg/kg dose. Bound aflibercept concentrations were not dose dependent and the proportion of bound aflibercept decreased with increasing dose. However, Cmax and AUC for total aflibercept were dose proportional [(range)];(See Australian Public Assessment Report for Afibercept, AusPAR Eylea Aflibercept Bayer Australia Ltd; PM-2010-03802-3-5 Final 30 July 2012; and Assessment Report, Eylea, Committee for Medicinal Products for Human Use (CHMP) 26 June 2014 EMA/430291/2014; FDA, Center for Drug Evaluation and Research, Approval Package for: APPLICATION NUMBER: 125387Orig1s048, Eylea, March 25, 2015)

of aflibercept 2 mg in the DME and nAMD populations, healthy participants, and participants with oncology diseases after intravenous (IV), subcutaneous (SC), or intravitreal (IVT) administration was performed to: characterize the concentration-time profiles of free and adjusted bound aflibercept in plasma; estimate population and individual PK parameters of aflibercept in patients with nAMD and DME; investigate the effects of relevant covariates which may explain variability in aflibercept PK parameters; and derive *post-hoc* estimates of individual exposure metrics in the nAMD and DME patients from the final PopPK model that formed the basis for pharmacokinetic/pharmacodynamic (PK/PD) analyses.

[000532]A key finding from this expanded PopPK analysis is that clearance of free aflibercept from the ocular compartment (ocular clearance) is 34.3% slower for HD drug product than for 2 mg IVT aflibercept reference drug product, and is attributed to an “HD aflibercept drug product effect”. Ultimately, it is this HD drug product effect on slowing the ocular clearance that resulted in a longer than expected ocular residence time, and the greater than expected proportion of patients able to be maintained on the longer dosing intervals of q12 and q16.

[000533]The consequences of the slower ocular clearance for HD (8 mg) aflibercept, as identified in the PopPK analysis, were further evaluated via PopPK model-based simulations to predict the time-course of free aflibercept in the eye (ocular compartment) under different dosing scenarios, and via exposure-response analyses to assess whether PopPK estimates of ocular clearance are predictive of the time required for dose regimen modification (DRM).

[000534]Efficacy data from the phase 3 PULSAR study in the nAMD population confirmed that the HDq12 and HDq16 regimens provide durable efficacy over the 48-week treatment period, as both regimens met the primary endpoint for efficacy of non-inferior change from baseline in

BCVA at week 48 compared to 2q8. A majority of participants randomized to HDq12 or HDq16 maintained their 12-week (79%) and 16-week (77%) dosing intervals, without the need for DRM, through 48 weeks.

[000535]Results from the phase 2/3 PHOTON study also confirmed efficacy of the HDq12 and HDq16 regimens in participants with DME and DR as both met the primary endpoint for efficacy of noninferior change from baseline in BCVA at week 48 compared to 2q8, with a majority of participants maintaining their HDq12 (91%) and HDq16 (89%) regimens, without the need for DRM, through the end of the 48-week treatment period.

[000536]As the vast majority of participants enrolled in the PHOTON study had underlying DR, they were also assessed for efficacy endpoints associated with the improvement of their underlying retinopathy. The HDq12 regimen met the key secondary efficacy endpoint of noninferiority for the proportion of participants with a ≥2-step improvement in DRSS score compared to 2q8 at the prespecified margin of 15%. Additionally, noninferiority was demonstrated using the FDA recommended 10% margin. Non-inferiority was not established for HDq16 at the 15% margin. The HDq16 group had more participants with mild to moderate disease than both the HDq12 and the 2q8 group, which may have contributed to these findings.

[000537]Regarding safety, similar ocular and systemic safety profiles for HDq12 and HDq16 compared to 2q8 aflibercept were observed in all 3 studies, with no new safety signals identified for HD aflibercept.

[000538]Residual variability was modeled separately for free and adjusted bound aflibercept using an additive + proportional error model. Estimated bioavailability for free aflibercept was 71.9% following IVT administration (Table 1-68). Parameter estimates for the Population PK model are presented in Table 1-68.

Table 1-68. Population Pharmacokinetic Parameter Estimates for the Final Model for Aflibercept

Parameter	Estimate	C.I.95	RSE %	CV %
K20 (1/day) [run431 Estimate]	0.0807	0.0438 — 0.136	29.5	—
V2 V4 (L) [run431 Estimate]	4.99	4.71 — 5.25	2.79	—
V3 (L) [run431 Estimate]	1.08	0.816 — 1.58	17	—
QF1 (L/day) [run431 Estimate]	0.849	0.435 — 1.33	29.2	—
V8 (L) [run431 Estimate]	1.18	0.281 — 0.541	16.8	—
QF2 (L/day) [run431 Estimate]	0.0763	0.147 — 0.186	5.93	—
KM (mg/L) [run431 Estimate]	0.411	0.293 — 0.442	10.5	—
VMK24 (mg/day/L) [run431 Estimate]	0.167	0.482 — 0.593	—	—
K40 (1/day) [run463 Estimate]	0.035	—	—	—

F1 & F5	0.719	0.706 — 0.731	—	—
QE (L/day)	0.000624	0.000577 — 0.000674	3.97	—
K62 (1/day) [run431 Estimate]	0.368	0.0165 — 0.0632	35.3	—
F6 [run431 Estimate]	0.536	0.00584 — 0.149	99	—
VMK27 (mg/day/L) [run431 Estimate]	0.031	4.17 — 340	159	—
K70 (1/day) [run431 Estimate]	0.0265	0.632 — 2.84	39.8	—
KMK27 (mg) [run431 Estimate]	42.7	0.0481 — 0.12	23.7	—
TWGT V2+V4 [run431 Estimate]	0.872	0.55 — 1.22	19.3	—
TWGT V3 [run431 Estimate]	1.08	-0.00762 — 2.45	51.3	—
TWGT V8 [run431 Estimate]	1.16	-2.97 — 6.58	135	—
TWGT K20 [run431 Estimate]	-0.192	-1.28 — 0.819	234	—
TWGT K40 [run463 Estimate]	-0.153	—	—	—
HD QE	0.657	0.607 — 0.712	4.08	—
AGE QE	-1.53	-1.76 — -1.3	7.68	—
TALB K40 [run463 Estimate]	-0.767	—	—	—
IIV K20 [run431 Estimate]	0.207	-0.0147 — 0.508	54.1	48
IIV covariance(K20, V2 & V4) [run431 Estimate]	-0.0727	-0.136 — -0.0183	38.9	—
IIV V2 & V4 [run431 Estimate]	0.0618	0.0198 — 0.105	34.7	25.3
IIV VMK24 [run431 Estimate]	0.305	-0.083 — 0.67	65.4	59.8
IIV K40 [run463 Estimate]	0.0452	—	—	21.5
IIV QE	0.297	0.257 — 0.336	6.86	58.8
IIV K62 [run431 Estimate]	0.852	0.124 — 1.45	43	116
IIV F6 [run431 Estimate]	0.629	0.288 — 0.905	26.4	93.6
SD ADD LLOQ 0.0313 (Free,IV+SC) [run463 Estimate]	0.025	—	—	—
SD PROP LLOQ 0.0313 (Free,IV+SC) [run463 Estimate]	0.403	—	—	—
SD ADD LLOQ 0.0156 (Free)	0.00779	0.00624 — 0.00973	11.4	—
SD PROP LLOQ 0.0156 (Free)	0.433	0.418 — 0.448	1.72	—
SD ADD LLOQ 0.0315 (Adj.Bound)	0.0216	0.0177 — 0.0264	10.2	—
SD PROP LLOQ 0.0315 (Adj.Bound)	0.159	0.12 — 0.197	12.4	—
SD ADD LLOQ 0.0224 (Adj.Bound)	0.0291	0.0202 — 0.0419	18.8	—
SD PROP LLOQ 0.0224 (Adj.Bound)	0.214	0.194 — 0.234	4.83	

ADD = additive, age = baseline age, C.I.95 = 95% confidence intervals, CV = coefficient of variation, F1 and F5 = bioavailability of intravitreal injections in ocular compartments, F6 = bioavailability of subcutaneous injections, HD = high dose (8 mg IVT cohorts), IIV = inter-participant variability, IV = intravenous, K20 = elimination rate of free aflibercept, K40 = elimination rate constant for adjusted bound aflibercept, K62 = rate of absorption from subcutaneous injection dosing compartment, K70 = elimination rate from tissue (platelet) compartment, KM = concentration of free aflibercept at half of maximum binding capacity with VEGF; KMK27 = concentration of free aflibercept at half of maximum binding capacity to platelets, LLOQ = lower limit of quantification, PROP = proportional, QE = inter-compartmental clearance between ocular compartment and central compartment of free aflibercept, QF1 and QF2 = inter-compartmental clearances of free aflibercept, RSE% = percent relative standard error, SC = subcutaneous, TALB = time varying albumin, TWGT = time varying body weight, V2

= central volume of free aflibercept in plasma, V3 and V8 = peripheral volumes of free aflibercept in tissues, V4 = central volume of adjusted bound aflibercept in plasma, VMK24 = maximum binding rate of free aflibercept to VEGF, VMK27 = maximum binding rate of aflibercept to platelets Estimates of fixed-effect parameters are presented in the natural scale; IIV are reported as variances around the log of the parameters or the logit of F6. Residual errors of IV and SC data not presented in the table for LLOQ=0.0156 (σ additive=0.00786, σproportional= 0.357) and LLOQ=0.0315 (σadditive=0.0206, σproportional=0.167) were fixed in the final model to estimates from run463. C.I.95 and %RSE% for run431 were calculated from bootstrap. η-shrinkage: ηK20= 54.2%, ηV2,V4= 15.2%, ηVMK24= 42.2%, ηK40= 39.1%, ηQE= 31.6%, ηK62= 1e-10%, ηF6= 17.7%.

[000539]Concentrations of free and bound aflibercept in plasma were measured using validated enzyme-linked immunosorbent assay (ELISA) methods. The assay for bound aflibercept is calibrated using the VEGF:aflibercept standards, and the results are reported for bound aflibercept as weight per volume (*e.g.*, ng/mL or mg/L) of the VEGF:aflibercept complex. Therefore, to account for the difference in molecular weight and normalize the relative concentrations between free and bound aflibercept, the concentration of the bound aflibercept complex is adjusted by multiplying the bound aflibercept concentration by 0.717. This is to account for the presence of VEGF in the bound complex and report the complex in terms of mg/L (i.e., mass/volume) that are corrected for, and consistent with, the molar concentrations (referred to as adjusted bound aflibercept in this module). Herein, concentrations of aflibercept:VEGF complex are limited to the adjusted bound concentrations.

[000540]The concentration of bound aflibercept was normalized to determine the amount of aflibercept present in the bound aflibercept complex. The bound aflibercept complex consisted of 71.7% aflibercept and 28.3% human $VEGF_{165}$ based on the molecular weight of each component. Therefore, the concentration of the bound aflibercept complex was multiplied by 0.717 to yield the concentration of adjusted bound aflibercept (Equation 1). Total aflibercept was calculated by summing the plasma concentrations of free and adjusted bound aflibercept (Equation 2).

Equation 1: Adjusted bound aflibercept (mg/L) = Bound aflibercept (mg/L) x 0.717

Equation 2: Total aflibercept (mg/L) = Sum of adjusted bound aflibercept (mg/L) + free aflibercept (mg/L)

Time-varying body weight was a predictor of the central volumes for free and adjusted bound aflibercept (V2=V4), the peripheral volumes of free aflibercept in tissues (V3, and V8), and elimination rate of free aflibercept (K20) and adjusted bound aflibercept (K40). The effect of time-varying albumin was also a predictor of elimination rate of adjusted bound aflibercept (K40). Age and the effect of HD drug product versus aflibercept groups with doses ≤4 mg presented as the reference drug product were predictors of clearance from the ocular

compartment (QE). The clearance of free aflibercept from the ocular compartment slowed with age, with an estimated exponent in the relationship of -1.53, resulting in clearance from the ocular compartment being approximately 25% slower for an 86 year-old (95th percentile of age in the analysis population) participant than a 71 year-old (median age in analysis population) participant.

[000541]Following IVT administration, HD drug product was estimated to have 34.3% slower clearance from the ocular compartment compared to the reference IVT aflibercept drug product for doses ≤4 mg. This slower ocular clearance resulted in a longer duration of ocular exposure to free aflibercept in the ocular compartment for the HD drug product. Through PopPK covariate analysis, the 34% slower ocular clearance (QE) and longer duration of free aflibercept ocular exposure for HD drug product is statistically attributed to an "HD aflibercept drug product effect". The exact nature or attributes of the HD drug product responsible for the attenuated ocular clearance cannot be fully explained by increasing the dose alone.

[000542]Exposure-Response Analyses. An exposure-response analysis was conducted using the time to dose regimen modification (TTDRM). A KM (Kaplan-Meier) plot of TTDRM stratified by indication showed a statistically significant ($p < 0.00001$) difference in TTDRM between participants with AMD and participants with DME, per the logrank test. KM plots of TTDRM, stratified by quartiles of ocular clearance (QE) within indication, showed rank ordering of longer TTDRM by lower ocular clearance percentile. A Cox proportional hazard model that included indication, baseline CRT, and ocular clearance as predictors of DRM showed that the rate of DRM due to the HD drug product effect is 20.6% lower than would have been expected if the HD drug product had the same ocular clearance as the 2 mg aflibercept presented as the reference drug product.

[000543]The need for DRM is determined by the clinician objective measurements obtained during an office visit, at which time a participant's dosing regimen can be shortened due to suboptimal efficacy. Faster transit of aflibercept from the eye into the systemic circulation leads to earlier depletion of the drug from the ocular space and therefore a more rapid loss of efficacy. While there may be other factors affecting efficacy, such as disease progression, comorbidities, or variability in response, this analysis shows a statistically significant relationship between an independently determined PK parameter (ocular clearance) that describes the transit of aflibercept from the eye and a reduction in efficacy as indicated by an earlier retreatment (DRM) than anticipated based on clinical assessment via BCVA and CRT.

[000544]For those participants requiring a DRM, Cox proportional hazard modeling was performed to evaluate factors that may contribute to the need for a reduction in the dosing

interval. The results of these analyses estimate a 260% higher rate for DRMs for participants with nAMD compared to participants with DME and DR. After accounting for indication (nAMD or DME and DR), ocular clearance of free aflibercept and baseline CRT were identified as significant covariates contributing to the need for DRM. Within an indication (nAMD or DME and DR), for participants with the same ocular clearance of free aflibercept, a 52.8% higher rate of DRM is predicted for participants at the 75th percentile vs 25th percentile of baseline CRT. Similarly, for participants with the same baseline CRT, a 32.9% higher rate of DRM is predicted for participants at the 75th vs 25th percentile of ocular clearance of free aflibercept. The results of these analyses also estimate that the lower ocular clearance for HD drug product resulted in a 20.6% lower rate of DRM than would have been expected if the HD drug product had the same ocular clearance as 2 mg aflibercept.

[000545]Comparison of Pharmacokinetics Across Studies in Participants with Neovascular Age-Related Macular Degeneration or Diabetic Macular Edema. In the clinical development of HD aflibercept for treatment of AMD and DME, a dosage regimen of 8 mg IVT (3 initial monthly doses followed by q12w or q16w IVT dosing) was evaluated and compared to an aflibercept 2 mg IVT dosage regimen (3 or 5 initial monthly doses followed by q8w or q12w IVT dosing) in the clinical studies CANDELA, PULSAR, and PHOTON. This allowed for a direct comparison of the systemic exposures of free and adjusted bound aflibercept across the 3 studies. CANDELA and PULSAR studies included participants with nAMD while PHOTON study included participants with DME and DR.

[000546]Following single IVT administration of aflibercept 2 mg or HD aflibercept, the concentration-time profiles of free and adjusted bound aflibercept in plasma in participants who underwent dense sample collection for systemic drug concentrations (dense PK sub-study) after the initial dosing of aflibercept 2 mg or HD aflibercept presented as the HD drug product, respectively, were consistent between the 3 studies in participants with nAMD or DME (Figure 32).

[000547]The consistency of the concentration-time profiles for free and adjusted bound aflibercept between the nAMD and DME populations is further supported by Population PK analysis (Figure 33). Population PK estimated *post-hoc* concentration-time profiles and PK parameters for combined nAMD and DME populations following single IVT administration of 2 mg aflibercept or HD aflibercept are provided in Figure 33 and in Table 1-69 and Table 1-70.

Table 1-69. Summary of *Post-hoc* Simulated Pharmacokinetic Parameters for Free Aflibercept in Plasma after Single Dose IVT Administration in the Combined nAMD and DME Population Treated Only in the Study Eye and Without Study Eye Dosing Modifications in the Dense PK Sub-studies (DPKS)

		Aflibercept		HD Aflibercept	
		2 mg IVT (N = 31)		8 mg IVT (N = 50)	
PK Parameters	Unit	Mean (SD)	Median	Mean (SD)	Median
AUC_{0-28}	mg x day/L	0.282 (0.189)	0.238	2.55 (2.31)	2
C_{max}	mg/L	0.0394 (0.0391)	0.0251	0.304 (0.267)	0.222
$C_{trough,28}$	mg/L	< LLOQ (0)	< LLOQ	< LLOQ (0.00853)	< LLOQ
t_{max}	day	2.26 (0.783)	2.16	2.8 (1.08)	2.89

AUC = area under the concentration-time curve, C_{max} = maximum (peak) concentration for a 28-day interval following dosing, C_{trough} = trough concentration, DME = diabetic macular edema, DPKS = dense pharmacokinetic sub-studies, IVT = intravitreally, LLOQ = lower limit of quantitation, n = number of participants, nAMD = neovascular age-related macular degeneration, PK = pharmacokinetics, SD = Standard deviation, t_{max} = median time to peak concentration; Note: Participants who had fellow eye treatment before day 28 are excluded.

Table 1-70. Summary of *Post-hoc* Simulated Pharmacokinetic Parameters for Adjusted Bound Aflibercept in Plasma after Single Dose IVT administration in the Combined nAMD and DME Population Treated Only in the Study Eye and Without Study Eye Dosing Modifications in the Dense PK Sub-studies (DPKS)

		Aflibercept		HD Aflibercept	
		2 mg IVT (N = 31)		8 mg IVT (N = 50)	
PK Parameters	Unit	Mean (SD)	Median	Mean (SD)	Median
AUC_{0-28}	mg x day/L	3.07 (1.31)	3.05	10.8 (6.14)	9.03
C_{max}	mg/L	0.142 (0.0616)	0.139	0.507 (0.282)	0.434
$C_{trough,28}$	mg/L	0.105 (0.0393)	0.0994	0.386 (0.21)	0.338
t_{max}	day	14.8 (5.65)	13.7	15.5 (5.22)	15.8

AUC = area under the concentration-time curve, C_{max} = maximum (peak) concentration for a 28-day interval following dosing, C_{trough} = trough concentration, DME = diabetic macular edema, DPKS = dense pharmacokinetic sub-studies, IVT = intravitreally, nAMD = neovascular age-related macular degeneration, PK = pharmacokinetics , SD = standard deviation, t_{max} = median time to peak concentration; Note: Participants who had fellow eye treatment before day 28 are excluded.

[000548]The corresponding observed and Population PK estimated *post-hoc* concentration-time profiles and PK parameters for participants with nAMD or DME are provided in Figure 36, Figure 37, Figure 38, Table 1-71 and Table 1-72.

Table 1-71. Summary of Simulated Pharmacokinetic Parameters for Free Aflibercept in Plasma after Single Dose IVT Administration in Participants with nAMD or DME Treated

Only in the Study Eye and Without Study Eye Dosing Modifications in the Dense PK Sub-studies (DPKS)

		2 mg IVT			8 mg IVT		
PK Parameters	**Unit**	**N**	**Mean (SD)**	**Median**	**N**	**Mean (SD)**	**Median**
nAMD participants							
AUC_{0-28}	mg x day/L	21	0.302 (0.223)	0.258	29	2.77 (2.77)	1.95
C_{max}	mg/L		0.0419 (0.0439)	0.0258		0.306 (0.302)	0.172
$C_{trough,28}$	mg/L		< LLOQ (0)	< LLOQ		< LLOQ (0.0094)	< LLOQ
t_{max}	day		2.19 (0.606)	2.16		2.97 (1.08)	3.05
DME participants							
AUC_{0-28}	mg x day/L	10	0.238 (0.0732)	0.236	21	2.25 (1.45)	2.17
C_{max}	mg/L		0.0343 (0.0275)	0.0212		0.302 (0.216)	0.265
$C_{trough,28}$	mg/L		< LLOQ (0)	< LLOQ		< LLOQ (0.00732)	< LLOQ
t_{max}	day		2.41 (1.09)	2.23		2.56 (1.06)	2.36

AUC_{0-28} = area under the concentration-time curve, C_{max} = maximum (peak) concentration for a 28-day interval following dosing, $C_{trough,28}$ = trough concentration, DME = diabetic macular edema, DPKS = dense pharmacokinetic sub-studies, IVT = intravitreally, LLOQ = lower limit of quantitation, n = number of participants, nAMD = neovascular age-related macular degeneration, PK = pharmacokinetic, SD = Standard deviation, t_{max} = median time to peak concentration. Note: Participants who had fellow eye treatment before day 28 are excluded.

Table 1-72. Summary of Simulated Pharmacokinetic Parameters for Adjusted Bound Aflibercept in Plasma after Single Dose IVT administration in Participants with nAMD or DME Treated Only in the Study Eye and Without Study Eye Dosing Modifications in the Dense PK Sub-studies (DPKS)

		Adjusted Bound Aflibercept					
		2 mg IVT			8 mg IVT		
PK Parameters	**Unit**	**N**	**Mean (SD)**	**Median**	**N**	**Mean (SD)**	**Median**
nAMD participants							
AUC_{0-28}	mg x day/L	21	3.35 (1.44)	3.16	29	11.8 (7.17)	11
C_{max}	mg/L		0.155 (0.0686)	0.144		0.558 (0.329)	0.51
$C_{trough,28}$	mg/L		0.113 (0.0418)	0.113		0.439 (0.23)	0.415
t_{max}	day		14.4 (4.89)	13.1		16.9 (5.26)	17.2
DME participants							
AUC_{0-28}	mg x day/L	10	2.46 (0.726	2.43	21	9.33 (4.06)	8.39
C_{max}	mg/L		0.115 (0.0317)	0.117		0.438 (0.187)	0.4
$C_{trough,28}$	mg/L		0.088 (0.0281)	0.09		0.314 (0.156)	0.25
t_{max}	day		15.6 (7.21)	15.4		13.7 (4.65)	12.9

$AUC_{0\text{-}28}$ = area under the concentration-time curve, C_{max} = maximum (peak) concentration for a 28-day interval following dosing, $C_{trough,28}$ = trough concentration, DME = diabetic macular edema, DPKS = dense pharmacokinetic sub-studies, IVT = intravitreally, LLOQ = lower limit of quantitation, n = number of participants, nAMD = neovascular age-related macular degeneration, SD = standard deviation, t_{max} = median time to peak concentration; Note: Participants who had fellow eye treatment before day 28 are excluded.

[000549]Following single IVT administration of 2 mg aflibercept or HD aflibercept presented as HD drug product, the concentration-time profiles of free aflibercept are characterized by an initial phase of increasing concentrations, as the drug moved from the ocular space into systemic circulation, followed by a mono-exponential elimination phase. The concentration time profiles of adjusted bound aflibercept in plasma are characterized by a slower attainment of C_{max} compared to free aflibercept. Following attainment of C_{max}, a sustained plateau of the concentration-time profiles of adjusted bound aflibercept in plasma was observed until approximately the end of the first dosing interval (Figure 32, Figure 33).

[000550]For participants who underwent dense blood sample collection for systemic drug concentrations across the CANDELA, PULSAR, and PHOTON studies, after the initial dosing of 2 mg IVT aflibercept (n = 34), observed concentrations of free aflibercept were detectable in 15 (44.1%) participants by week 1 and in 3 (8.8%) participants by week 2. For participants who underwent dense blood sample collection for systemic drug concentrations after the initial dosing of 8 mg IVT aflibercept (n = 54), observed concentrations of free aflibercept were detectable in 46 (85.2%) participants by week 1 and in 44 (77.8%) participants by week 2.

[000551]The observed and Population PK simulated free and adjusted bound aflibercept concentrations in plasma for up to 48 weeks are presented for the combined nAMD and DME population (Figure 34), and the nAMD (Figure 39) and DME (Figure 40) populations. Based on the Population PK analysis, the median time for free aflibercept concentrations to reach LLOQ following HDq12 or HDq16 was 3.5 weeks, which is more than double the median time needed to reach LLOQ (1.5 weeks) following aflibercept 2q8 (Table 1-73).

Table 1-73. Summary of Model-Predicted Time to LLOQ of Free Aflibercept in Plasma Following IVT for Participants With nAMD and DME, Combined

Regimen	Mean (SD) Week	Median (90% PI) Week
2q8	1.58 (0.712)	1.5 (0.524, 2.82)
HDq12	3.81 (1.61)	3.51 (1.83, 6.81)
HDq16	3.79 (1.58)	3.50 (1.83, 6.73)

Model-predicted time = time after a single IVT dose of the 2q8, HDq12 or HDq16 regimens. 2q8 = aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals, DME = diabetic macular edema, HDq12 = aflibercept 8 mg administered every 12 weeks following 3

initial monthly injections, HDq16 = aflibercept 8 mg administered every 16 weeks following 3 initial monthly injections, IVT = intravitreally, LLOQ = lower limit of quantification, nAMD = neovascular age related macular degeneration, PI = prediction interval, SD = standard deviation

[000552]The longer duration of systemic exposure to free aflibercept following HDq12 and HDq16 compared to the 2 mg aflibercept is attributed to not only a higher administered dose and nonlinear systemic target-mediated elimination, but also to a 34% slower ocular clearance of free aflibercept. The 34% slower ocular clearance of free aflibercept for HD aflibercept is attributed to a HD drug product effect which was identified as a statistically significant covariate in the Population PK model.

[000553]Ocular Elimination. Based on the Population PK analysis, HD aflibercept, presented as the HD drug product, was estimated to have a 34% slower clearance from the ocular compartment compared to the lower IVT doses of aflibercept (≤ 4 mg doses) that was presented as the standard, or reference drug product. The median time for the amount of free aflibercept to reach the adjusted LLOQ [the adjusted LLOQ imputes the LLOQ of free aflibercept in from the assay in plasma (that is, 0.0156 mg/L) times the assumed volume of the study eye compartment in the PK model (that is, 4 mL)] in the ocular compartment was estimated using Population PK simulation analyses, after a single 2 mg or 8 mg IVT dose. In the combined nAMD and DME population, the median time for the amount of free aflibercept to reach the adjusted LLOQ in the ocular compartment increased from 8.71 weeks after a 2 mg IVT dose to 15 weeks after an 8 mg IVT dose (i.e., the duration of free aflibercept ocular exposure following HD drug product is extended by approximately 6 weeks relative to 2 mg drug product). The slower ocular clearance and longer duration of free aflibercept ocular exposure for HD aflibercept are attributed to an HD aflibercept drug product effect. Assuming no HD aflibercept drug product effect (*i.e.*, that the 8 mg IVT dose has the same ocular clearance as the 2 mg IVT dose), the Population PK simulated median time for the amount of free aflibercept to reach the adjusted LLOQ in the ocular compartment was only 10 weeks for 8 mg aflibercept, which is only 1.3 weeks longer than that for 2 mg aflibercept (Figure 35).

[000554]As the PULSAR and PHOTON studies were designed to assess non-inferiority of the HDq12 and HDq16 regimens versus the 2q8 regimen, it was of interest to estimate how long it takes for the amount of free aflibercept in the ocular compartment for the HDq12 and HDq16 regimens to reach the same amount of free aflibercept remaining in the ocular compartment for the 2q8 regimen at the end of an 8-week dosing interval (2q8 target). Using a modified approach, using Population PK simulation analyses in the combined nAMD and DME population, the median time for HDq12 and HDq16 regimens to reach the 2q8 target in the

ocular compartment after single IVT administration was 14 weeks, suggesting that the HD aflibercept regimens may provide a 6-week longer duration of efficacy than the 2q8 regimen. In contrast, if there were no HD aflibercept drug product effect, the Population PK simulated median time for the amount of free aflibercept to reach the 2q8 target in the ocular compartment would be only 9.21 weeks for an 8 mg dose, representing an extension of only 1.21 weeks relative to the 2q8 regimen, and is consistent with the prior example.

[000555]High-Dose Aflibercept Drug Product. The totality of the composition of the HD drug product used to deliver the 8 mg dose is different from that for the 2 mg aflibercept IVT dose. Based on Population PK analysis, the HD aflibercept drug product is a statistically significant predictor of ocular clearance of free aflibercept that results in a slower ocular clearance for the HD aflibercept versus 2 mg aflibercept when administered by the IVT route. (Table 1-74). The slower ocular clearance and higher molar dose for the HD aflibercept drug product results in a longer duration of ocular exposure to free aflibercept compared to the 2 mg IVT dose. The slower ocular clearance of the HD aflibercept drug product is predicted to provide a 6-week longer duration of efficacy compared to 2q8, as the time to achieve the free aflibercept amount in the ocular compartment for the 2q8 regimen at the end of an 8-week dosing interval occurs 6 weeks later for the HD aflibercept drug product. Consistent with these predictions, the HDq12 and HDq16 regimens demonstrated noninferiority to the 2q8 regimen in the PHOTON (for DME only) and PULSAR studies. Correspondingly, a slower ocular clearance for the HD aflibercept drug product contributes in part to a longer duration of systemic exposure to free aflibercept for HD aflibercept versus the 2 mg IVT dose. The slower ocular clearance for HD aflibercept is attributed to a difference in the HD aflibercept drug product, not just an increase in the IVT dose from 2 mg to 8 mg. These results were further confirmed by a sensitivity analysis conducted in the final model.

Table 1-74. Comparison of Clearance from the Ocular Compartment (QE) (Mean [95% CI]) of Aflibercept for HD Aflibercept and 2 mg Aflibercept

Dose Group	Clearance from the Ocular Compartment (QE) Mean (95% CI) (mL/day)	k = QE/0.004 Mean (95% CI (day^{-1})
2 mg Aflibercept	0.624 (0.577 - 0.674)	0.156 (0.144 - 0.169)
HD 8 mg Aflibercept	0.41 (0.367 - 0.458)	0.102 (0.0916 - 0.115)

QE = inter-compartmental clearance between ocular compartment and central compartment of free aflibercept, 95% CI of parameters are provided.

[000556]Pharmacokinetic Conclusions. The concentration time profiles of free and adjusted bound aflibercept in plasma after the initial dose of HD aflibercept by IVT administration were consistent between all studies in participants with nAMD or DME. Population PK analysis confirmed no relevant differences in PK between the nAMD and DME populations, and therefore all subsequent analyses are presented for the combined nAMD and DME population.
[000557]Following the initial monthly IVT dose, the observed concentration-time profile of free aflibercept in plasma is characterized by an initial phase of increasing concentrations as the drug is absorbed from the ocular space into the systemic circulation, followed by a mono-exponential elimination phase. The longer duration of systemic exposure to free aflibercept for HD aflibercept is attributed to not only a higher administered dose and non-linear systemic target mediated elimination but also to a 34% slower ocular clearance of free aflibercept, which is statistically attributed to the HD drug product as a covariate in the expanded PopPK model. This slower than expected ocular clearance of free aflibercept when presented as the HD aflibercept drug product is simulated to provide a 6-week longer duration of efficacy compared to 2q8, as the time to achieve the free aflibercept amount in the ocular compartment for the 2q8 regimen at the end of an 8-week dosing interval occurs 6 weeks later for the HD aflibercept drug product. Consistent with these simulations for the 8mg presented as the HD drug product, the HDq12 and HDq16 regimens demonstrated noninferiority (at a longer treatment interval) to the 2q8 regimen presented as the reference drug product in the predefined statistical analysis plan for both the PHOTON (for DME only) and PULSAR phase 3 studies.
[000558]Based on expanded population PK analysis, following single IVT doses of 2 mg aflibercept and HD aflibercept, systemic exposures of free aflibercept ($AUC_{0\text{-}28}$ and C_{max}) in the combined nAMD and DME population increase in a greater than dose-proportional manner (approximately 9.0-fold and 7.7-fold). These results demonstrate and are consistent with the known nonlinear PK for free aflibercept. Bioavailability of free aflibercept following IVT administration is estimated to be approximately 72%, and the total volume of distribution of free aflibercept after IV administration is estimated to be approximately 7 L.
[000559]Following 3 initial monthly HD aflibercept doses, the population PK simulated mean accumulation ratio of free and adjusted bound aflibercept in plasma based on AUC was 1.16 and 2.28 in the combined DME and nAMD population. After the 3 initial monthly doses of HD aflibercept (presented as the HD drug product), no further accumulation of either free or adjusted bound aflibercept in plasma occurs as the dosing interval is extended from every 4 weeks to every 12 weeks or 16 weeks resulting in a decline in systemic concentrations of both free and adjusted bound aflibercept.

[000560]Amongst the covariates evaluated in the Population PK analysis, body weight was the covariate with the greatest impact on systemic exposures to free and adjusted bound aflibercept. For participants in the lowest quintile of body weight (38.1 kg to 64.5 kg), the predicted impact on systemic exposures (C_{max} and AUC_{tau}) was modest, with 27% to 39% higher exposures to free aflibercept and 25% to 27% higher exposures to adjusted bound aflibercept when compared to the reference body weight range (73.5 to 83.5 kg). The effects of other covariates (age, albumin, disease population, and race, which included evaluation of Japanese race) on systemic exposures (C_{max}, AUC_{tau}) to free and adjusted bound aflibercept were small (<25% increase in exposure for covariate subgroups relative to the reference group), with several of these other covariate effects correlating with a consistent trend in body weight. All of these covariates were independent of the HD drug product effect on ocular clearance and did not confound the interpretation of the HD drug product effect on the ocular clearance. No dosage adjustments of HD aflibercept are warranted based on the assessed covariates.

[000561]Mild to severe renal impairment also had a small impact on free aflibercept systemic exposures, as the increase in free aflibercept C_{max} and AUC_{tau} in these participants was less than approximately 28% compared to participants with normal renal function. Adjusted bound aflibercept systemic exposures in participants with mild to severe renal impairment ranged from 13% to 39% higher compared to participants with normal renal function. Here too, the perceived impact of renal impairment is best explained by the associated decrease in body weight with increasing renal impairment. Mild hepatic impairment had no effect on systemic exposures to free and adjusted bound aflibercept. No dosage adjustments of aflibercept are warranted for these populations.

[000562]Model-Based Exposure-Response Analysis for Proportion of Participants Requiring Dose Regimen Modification Cox proportional hazard modeling was performed to evaluate factors that may contribute to the need for a reduction in the dosing interval. Within any one specific patient population, nAMD, DME (with and without DR), ocular clearance of free aflibercept and baseline CRT were identified as significant predictors of time to DRM. Within an indication (nAMD or DME (with and without DR)), for participants with the same ocular clearance of free aflibercept, a 52.8% higher rate of DRM is modeled for participants at the 75th vs 25th percentile of baseline CRT. Similarly, for participants with the same baseline CRT, a 32.9% higher rate of DRM is modeled for participants at the 75th vs 25th percentile of ocular clearance of free aflibercept, corresponding to those participants who are predicted to have the lowest aflibercept concentration in the eye. These results are shown in Table 1-75. The outcomes of these analyses also estimate that the slower ocular clearance for HD aflibercept,

attributable to a HD drug product effect, results in a 20.6% lower rate of DRM than would have been expected if the HD drug product had the same ocular clearance as 2 mg aflibercept presented as the reference drug product.

Table 1-75. Hazard Ratio Contrasts for Time to DRM Model

Effect	Hazard Ratio
Baseline CRT	1.53 (1.34 - 1.75)
Ocular Clearance (QE)	1.33 (1.18 - 1.49)
Indication AMD Participants: DME Participants	3.6 (2.56-5.06)

AMD = age-related macular degeneration, CRT = central retinal thickness, DME = diabetic macular edema, DRM = dose regimen modification, QE = ocular clearance

[000563]Dose-Response and Exposure-Response Conclusions. As the IVT dose increased from 2 mg of aflibercept to 8 mg of HD aflibercept, no further increase in PD effect (decrease in CRT) was observed 4 weeks after each initial q4w dose through 12 weeks, in either the nAMD or DME population. Despite 2 mg of aflibercept (as reference drug product) and 8 mg of HD aflibercept (as HD drug product) having similar PD effect during the initial 3 x q4w dosing period, the 8 mg HD drug product provided a longer duration of pharmacological effect in the maintenance phase compared to 2 mg aflibercept. In nAMD participants, the small fluctuations in CRT or CST during a maintenance dosing interval attenuated over time for all dosing regimens, with only minor numerical differences observed between treatment groups. For DME participants, a greater reduction in CRT was observed from weeks 16 to 20 for 2q8 compared to both HD aflibercept regimens (HDq12 and HDq16). This is attributable to a difference in the number of doses administered during this time period, with the 2q8 regimen receiving 2 additional initial q4w doses at weeks 12 and 16 compared to the HD aflibercept regimens which received their last initial q4w dose at week 8. These differences in CRT did not translate into any meaningful difference in mean BCVA response. The fluctuations in CRT response over the course of a maintenance dosing interval attenuated over time for all dosing regimens. For participants with nAMD or DME, the HDq12 and HDq16 regimens provided rapid and durable response in CRT and BCVA over 48 weeks of treatment, with the majority of participants maintaining their randomized HDq12 (79% nAMD; 91% DME) and HDq16 (77% nAMD; 89% DME) treatment regimens, without the need for DRM. Ocular clearance of free aflibercept and baseline CRT were identified as significant covariates contributing to the need for DRM. Higher ocular clearance of free aflibercept and higher baseline CRT (indicative of more severe disease)

were associated with an increased rate of DRM. The slower ocular clearance for HD aflibercept, attributable to a HD drug product effect, is estimated to result in a 20.6% lower rate of DRM compared to HD aflibercept if the same ocular clearance was observed as the 2 mg aflibercept when presented as the reference drug product.

[000564]Overall Clinical Pharmacology Conclusions. Consistent with the known target-mediated kinetic properties exhibited at low plasma concentrations of aflibercept, free aflibercept exhibited nonlinear systemic PK over the 2 mg to 8 mg IVT dose range. Following the initial IVT dose, the concentration-time profile for free aflibercept in plasma is characterized by an initial absorption phase as drug moves from the ocular space into the systemic circulation. This absorption phase is followed by a mono-exponential elimination phase. The concentration time profile of adjusted bound aflibercept in plasma following the initial IVT dose is characterized by a slower attainment of C_{max} (t_{max}) compared to free aflibercept, after which the concentrations are sustained or slightly decrease until the end of the dosing interval.

[000565]Analyses of observed PK by cross-study comparison and by Population PK analyses suggested similar systemic PK in the nAMD and DME populations. Following IVT administration, Population PK methods estimate the bioavailability of free aflibercept at 72%, a median t_{max} of 2.89 days, and mean C_{max} of 0.304 mg/L for the 8 mg dose of HD aflibercept. As the aflibercept IVT dose increased from 2 mg to 8 mg and the treatment changes from 2 mg aflibercept (presented as the reference drug product) to 8 mg HD aflibercept (presented as the HD drug product), consistent with the known target-mediated related nonlinear PK of free aflibercept mean $AUC_{0\text{-}28}$ and C_{max} for free aflibercept increased in a greater than dose-proportional manner. After IV administration, free aflibercept has a low total volume of distribution of 7 L, indicating distribution largely in the vascular compartment. Following 3 initial monthly HD aflibercept IVT doses, the mean accumulation ratio of free and adjusted bound aflibercept in plasma based on AUC is 1.16 and 2.28. After the 3 initial monthly doses of HD drug product, no further accumulation of either free or adjusted bound aflibercept in plasma occurred as the dosing interval is extended from every 4 weeks to every 12 weeks or 16 weeks resulting in an expected decline in systemic concentrations of both free and adjusted bound aflibercept.

[000566]The longer duration of systemic exposure to free aflibercept for HD aflibercept is attributed to not only a higher administered dose and nonlinear systemic target-mediated elimination, but also to a 34% slower ocular clearance of free aflibercept. This 34% slower ocular clearance of free aflibercept for HD aflibercept is attributed to a HD drug product effect, which was identified as a statistically significant covariate in the Population PK model. Based

on the extended PopPK model, the slower ocular clearance of the HD aflibercept drug product provides a 6-week longer duration of efficacy compared to 2q8 when presented as the reference drug product. Resulting from this unexpected and non-obvious slower ocular clearance, was a longer than expected ocular residence time, leading to a greater than expected proportion of patients able to be maintained on the longer dosing intervals of q12 and q16 with HD drug product. Consistent with these predictions, the HDq12 and HDq16 regimens demonstrated non-inferiority to the 2q8 regimen in the PHOTON and PULSAR studies.

[000567]Body weight was the covariate with the greatest impact on systemic exposures to free and adjusted bound aflibercept. For participants in the lowest quintile of body weight (38.1 to 64.5 kg), the predicted impact on free aflibercept C_{max} and AUC_{tau} was modest, with 27% to 39% higher exposures and 25% to 27% higher for adjusted bound aflibercept when compared the reference body weight range (73.5 to 83.5 kg). The effects of other covariates (age, albumin, disease population. and race, which included evaluation of Japanese race) on systemic exposures (C_{max}, AUC_{tau}) to free and adjusted bound aflibercept were small (<25% increase in exposure for covariate subgroups relative to the reference group). These other covariates did not confound the assessment of the effect of HD drug product on ocular clearance. No dosage adjustments of aflibercept are warranted based on the above findings.

[000568]No formal studies were conducted in special populations (*e.g.*, participants with renal or hepatic impairment) because like most therapeutic proteins, the large molecular weight of aflibercept (approximately 115 kDa) is expected to preclude elimination via the kidney, and its metabolism is expected to be limited to proteolytic catabolism to small peptides and individual amino acids. Mild to severe renal impairment had a small impact on free aflibercept systemic exposures, as the increase in free aflibercept C_{max} and AUC_{tau} in these participants was less than approximately 28% compared to participants with normal renal function. Adjusted bound aflibercept systemic exposures in participants with mild to severe renal impairment ranged from 13% to 39% higher compared to participants with normal renal function. The perceived impact of renal impairment is explained by the associated decrease in body weight with increasing renal impairment. Mild hepatic impairment had no effect on systemic exposures to free and adjusted bound aflibercept. No dosage adjustments of aflibercept are warranted in these populations.

[000569]Dose-response analyses of CRT performed in the CANDELA, PULSAR, and PHOTON studies indicated no further increase in PD effect for 2 mg aflibercept and HD aflibercept IVT 4 weeks after each initial q4W dose through 12 weeks. Despite the 2 mg aflibercept and HD aflibercept having similar PD effect during the initial q4w dosing period, the HD aflibercept drug

product provided a longer duration (up to 16 weeks) of pharmacological effect in the maintenance phase than the 2 mg dose presented as the reference drug product (up to 8 weeks).

[000570]For participants with nAMD or DME, the HDq12 and HDq16 regimens provided rapid and durable response in CRT and BCVA over 48 weeks of treatment, with the majority of participants maintaining their randomized HDq12 (79% nAMD; 91% DME) and HDq16 (77% nAMD; 89% DME) treatment regimens, without the need for DRM.

[000571]Ocular clearance of free aflibercept and baseline CRT were identified as significant covariates contributing to the need for DRM. Higher ocular clearance and higher baseline CRT (indicative of more severe disease) were associated with an increased rate of DRM. For HD aflibercept, the slower ocular clearance and longer duration of ocular exposure to free aflibercept, attributable to the HD drug product effect, have been identified in an exposure-response analysis to result in a reduction of DRM of 20.6%.

[000572]Immunogenicity of HD aflibercept administered IVT was low across all treatment groups for both nAMD and DME participants. During the 48-week treatment with aflibercept administered IVT, the incidence of ADA in the combined 8 mg HD aflibercept treatment group was 2.7% (25/937 participants with nAMD or DME). None of the TE ADA positive samples were found to be positive in the NAb assay. Based on the lack of impact of ADA on concentrations of aflibercept in plasma, no effect on efficacy is anticipated. Positive responses in the ADA assays were not associated with significant AEs.

[000573]Overall, the clinical pharmacology data support the proposed aflibercept dosing regimens of 8 mg every 8 to 16 weeks after 3 initial monthly doses for the treatment of adults with nAMD, DME (with and without DR).

Baseline Characteristics of Patients Treated With Aflibercept 8 mg Who Did or Did Not Maintain Their Randomized Dosing Intervals Through Week *48*

[000574]At baseline, best-corrected visual acuity (BCVA), central retinal thickness (CRT), and Diabetic Retinopathy Severity Scale (DRSS) scores were generally balanced across all 3 treatment groups in the overall population. Of patients completing the Week 48 visit, 273/300 (91.0%) in the HDq12 group and 139/156 (89.1%) in the HDq16 group maintained their randomized dosing intervals. In the HDq12 and HDq16 groups, 27/300 (9.0%) and 17/156 (10.9%) patients, respectively, met DRM criteria and had their dosing intervals shortened. Mean (SD) baseline BCVA in eyes with maintained vs shortened dosing intervals was 63.9 (10.1) vs 59.4 (10.0) letters in the HDq12 group and 62.7 (11.2) vs 53.7 (12.8) letters in the HDq16 group. Mean (SD) central retinal thickness (CRT) at baseline (maintained vs shortened

dosing intervals) was 444.9 (129.8) vs 511.4 (117.5) µm in the HDq12 group and 447.1 (112.5) vs 534.8 (134.3) µm in the HDq16 group. Baseline DRSS score (maintained vs shortened dosing intervals) was 47 or worse in 33.7% vs 40.7% of patients in the HDq12 group and 26.6% vs 41.2% of patients in the HDq16 group. No clinically meaningful differences were observed based on age, BMI, or HbA1c at baseline.

[000575]The vast majority of patients with DME who received aflibercept 8 mg maintained 12- or 16-week dosing. Patients who did not maintain their randomized dosing intervals appeared to have more severe disease at baseline than patients who maintained their randomized dosing intervals, and this trend was more pronounced in the HDq16 group.

Treatment intervals

[000576]For masking purposes, assessments for dose regimen modifications (DRMs) were performed in all participants at all visits (through the interactive web response system [IWRS]) beginning at week 16. Based on these assessments, participants in the HD groups might have had their treatment intervals shortened (year 1 and year 2) or extended (year 2). The minimum interval between injections was 8 weeks which was considered a rescue regimen for participants randomized to HD aflibercept and unable to tolerate a dosing interval greater than every 8 weeks. Participants in the aflibercept 2 mg group remained on fixed q8 dosing throughout the study (*i.e.*, did not have modifications of their treatment intervals regardless of the outcomes of the DRM assessments).

[000577]During the first year, beginning at week 16, participants in the HD groups had the dosing interval shortened (at the visits described below) if BOTH of the following criteria were met:

1. > 10 letter loss in BCVA from week 12 in association with persistent or worsening DME; AND
2. > 50 µm increase in CRT from week 12

(It should be noted that the change in CRT for these criteria was assessed at the site).

[000578]If a participant in the HDq12 group or the HDq16 group met both criteria at week 16 or week 20, the participant was dosed with 8 mg aflibercept at that visit and continued on a rescue regimen (aflibercept 8 mg, every 8 weeks). If a participant in the HDq16 group who had not met the criteria at week 16 or 20 met both criteria at week 24, the participant was dosed with 8 mg aflibercept at that visit and continued on q12 week dosing.

[000579]For participants whose interval was not shortened to q8 dosing at or before week 24, the interval was shortened if the DRM criteria were met at a subsequent dosing visit.

Participants in the HDq12 group who met the criteria received the planned dose at that visit and then continued on a rescue regimen (aflibercept 8 mg, every 8 weeks). Participants in the HDq16 group who met these criteria received the planned dose at that visit and were to be continued on an every 12 week regimen if they were on a 16-week interval, or switched to the rescue regimen (aflibercept 8 mg, every 8 weeks) if they were previously shortened to a 12-week interval. Therefore, a participant randomized to HDq16 whose injection interval had been shortened to q12 had their injection interval further shortened to q8 if these criteria were met at any subsequent dosing visit.

[000580]From week 52 through the end of study (year 2), all participants in the HD groups will continue to have the interval shortened in 4-week intervals by four weeks if the DRM criteria for shortening are met at dosing visits using the DRM criteria described above for year 1. As in year 1, the minimum dosing interval for participants in all treatment groups is every 8 weeks.

[000581]In addition to shortening of the interval, all participants in the HD groups (including participants whose interval was shortened during year 1) may be eligible for interval extension (by 4-week increments), if BOTH the following criteria are met at dosing visits in year 2:

1. <5 letter loss in BCVA from week 12; AND
2. CRT <300 µm on SD-OCT (or <320 µm on Spectralis SD-OCT).

For participants who do not meet the criteria for shortening or extension of the interval, the dosing interval will be maintained.

[000582]As in year 1, all participants in all treatment groups (including the 2q8 group) will be evaluated against both DRM criteria at all visits through the IWRS for masking purposes. However, changes to dosing schedule will only be implemented as described above for those participants randomized to HDq12 or HDq16 treatment groups. No changes to the dosing schedule will be made to the 2q8 treatment group at any time.

[000583]The optional extension phase will begin at week 96, after all procedures at the EOS visit (week 96) have been completed and will continue through week 156.

[000584]Table 1-76 presents the proportion of participants who maintained their assigned dosing intervals through week 48 and week 60, those whose intervals were shortened through week 48 and week 60, and those whose intervals were extended between week 48 and week 60 (exploratory endpoints) among those who completed the respective timepoints. The vast majority of participants in the pooled HD group (≥ 91%) were able to maintain their target interval of either 12 or 16 weeks through week 60 (Table 1-76).

Table 1-76. Summary of Treatment Exposure in the Study Eye (Safety Analysis Set Completing Week 48 and Week 60, respectively)

		HD		
Through Week 48	**2q8 (N=157)**	**HDq12 (N=300)**	**HDq16 (N=156)**	**All HD (N=456)**
Patients maintained with q12 or longer dosing interval, n (%)	-	273 (91.0%)	150 (96.2%)	423 (92.8%)
Patients maintained with q16 dosing interval,- n (%)	-	-	139 (89.1%)	-
Patients with q12 or longer dosing interval as the last [a] intended dosing interval, n (%)	-	262 (87.3%)	146 (93.6%)	408 (89.5%)
Patients with q16 dosing interval as the last [a] intended dosing interval, n (%)	-	-	136 (87.2%)	-
Patients shortened to q8 dosing interval at week 16, n (%)	-	3 (1.0%)	1 (0.6%)	4 (0.9%)
Patients shortened to q8 dosing interval at week 20, n (%)	-	12 (4.0%)	3 (1.9%)	15 (3.3%)
Patients with a shortened dosing interval anytime, n (%)	-	27 (9.0%)	17 (10.9%)	44 (9.6%)
Patients with a shortened dosing interval to q8 anytime, n (%)	-	27 (9.0%)	6 (3.8%)	33 (7.2%)
Patients with a shortened dosing interval to q12 anytime,- n (%)b	-	-	13 (8.3%)	-

Through Week 60	**2q8 (N=155)**	**HDq12 (N=289)**	**HDq16 (N=152)**	**All HD (N=441)**
Patients maintained with q12 or longer dosing interval, n (%)	-	261 (90.3%)	142 (93.4%)	403 (91.4%)
Patients maintained with q16 or longer dosing interval,- n (%)	-	-	130 (85.5%)	-
Patients with q12 or longer dosing interval as the last [c] intended dosing interval, n (%)	-	248 (85.8%)	136 (89.5%)	384 (87.1%)
Patients with q16 or longer dosing interval as the last [c] intended dosing interval, n (%)	-	123 (42.6%)	124 (81.6%)	247 (56.0%)
Patients with q20 dosing interval as the last [c] intended dosing interval,- n (%)	-	0	52 (34.2%)	52 (11.8%)
Patients shortened to q8 dosing interval at week 16, n (%)	-	3 (1.0%)	1 (0.7%)	4 (0.9%)
Patients shortened to q8 dosing interval at week 20, n (%)	-	12 (4.2%)	3 (2.0%)	15 (3.4%)
Patients with a shortened dosing interval anytime, n (%)	-	28 (9.7%)	22 (14.5%)	50 (11.3%)
Patients with a shortened dosing interval to q8 anytime, n (%)	-	28 (9.7%)	10 (6.6%)	38 (8.6%)
Patients with a shortened dosing interval to q12 anytime,- n (%) b	-	-	20 (13.2%)	20 (4.5%)
Patients never extended dosing interval, n (%)	155 (100 %)	156 (54.0%)	93 (61.2%)	249 (56.5%)

Patients extended dosing interval anytime, n (%)	0	133 (46.0%)	59 (38.8%)	192 (43.5%)

Abbreviations: 2q8= Aflibercept 2 mg administered every 8 weeks after 5 initial injections at 4-week intervals; HDq12= High dose aflibercept 8 mg administered every 12 weeks after 3 initial injections at 4-week intervals; HDq16= High dose aflibercept 8 mg administered every 16 weeks after 3 initial injections at 4-week intervals; All HD= Pooled HDq12 and HDq16 groups; n = number; q8= every 8 weeks; q12= every 12 weeks; q16= every 16 weeks.
Hyphen indicates categories that do not apply.
a. Refers to the patient's assigned interval at week 48.
b. Includes participants who were only shortened to q12 as well as participants who were shortened to q12 and further shortened to q8.
c. Refers to the patient's assigned interval at week 60.
Study drugs given at week 48 or beyond were not included in this table.
Study drugs given at week 60 or beyond were not included in this table.

Summary

[000585]This is an ongoing Phase 2/3, multi-center, randomized, double-masked study in participants with DME involving the center of the macula that is investigating the efficacy and safety of intravitreal (IVT) HD aflibercept injection (8 mg). The primary objective of this study was to determine if treatment with HD aflibercept at intervals of 12 or 16 weeks (HDq12 or HDq16) provided non inferior BCVA compared to 2 mg aflibercept dosed every 8 weeks (2q8).
[000586]A total of 660 participants were randomized into 3 treatment groups, of whom 658 participants received at least 1 dose of study treatment. All treated participants were included in the safety analysis set (SAF). The analysis of efficacy was based on the full analysis set (FAS) (n=658, which was identical to the SAF), and the per protocol set (PPS) (n=649), which included approximately 98% of subjects randomized to each treatment group. The analysis of general PK assessments was based on the data in the pharmacokinetic analysis set (PKAS) (n=648), and the analysis in the dense PK study on the data of the dense pharmacokinetic analysis set (DPKS) (n=35).
[000587]The FAS (and SAF) had 401 (60.9%) male and 257 (39.1%) female participants aged from 24 to 90 years (median: 63 years). Most participants were White (71.6%) or Asian (15.3%). The mean (SD) visual acuity score BCVA at baseline was 62.5 (10.86) letters. Participants were stratified by screening CRT category and a majority had a CRT ≥ 400 microns (58.1%); the mean CRT was well balanced across groups and ranged from 449.1 to 457.2 microns. The treatment groups were generally well balanced with respect to demographics. At baseline, the mean BCVA, IOP, CRT, prior DME treatment, and DRSS score were comparable across groups.

[000588]The primary endpoint was the change from baseline in BCVA (as measured by ETDRS letter score) at week 48. The primary endpoint was met: the HDq12 and HDq16 groups demonstrated non-inferiority to 2q8 using the margin of 4 letters with least square (LS) mean change from baseline in BCVA of 8.10 letters (HDq12) and 7.23 letters (HDq16), respectively versus 8.67 letters in the 2q8 group. The LS_{mean} differences compared to 2q8 (95% CI) were 0.57 (-2.26, 1.13) and -1.44 (-3.27, 0.39) for HDq12 and HDq16, respectively. The robustness of these results for the primary endpoint were supported by the sensitivity analyses and the PPS analysis for the primary efficacy endpoint as the supplementary analysis.

[000589]The non-inferiority in mean change in BCVA was achieved in the context of participants in the HD groups being treated at extended dosing intervals compared to the 2q8 group. The vast majority of participants were treated only according to their randomized dosing interval, 90% and 85% in the HDq12 and HDq16 groups, respectively, through week 60 without the need for dose regimen modification.

[000590]The key secondary efficacy endpoint, the proportion of participants with a ≥ 2 step improvement in DRSS score, was met for HDq12 at week 48 (non-inferiority to 2q8). The non-inferiority margin was pre-specified at 15%, however HDq12 also met a 10% NI margin. In Cochran-Mantel-Haenszel (CMH)-weighted estimates, the adjusted difference (95% CI) was 1.98% (-6.61, 10.57) for HDq12 and 7.52% (-16.88, 1.84) for HDq16, respectively versus 2q8. Non-inferiority was not met for this key secondary endpoint in the HDq16 group, and therefore the hierarchical testing strategy was stopped at this point. The HDq16 group had more participants with moderate to mild (level 43 or better as opposed to level 47 or worse) retinopathy at baseline. Thus, fewer participants in this group would have been expected to achieve ≥ 2-step improvement in DRSS. This was apparent at week 12, a timepoint at which all groups had received the same number of doses; at this visit, the HDq16 group had a numerically lower proportion of participants with ≥ 2-step improvements in DRSS compared to the other treatment groups.

[000591]Overall, no relevant differences in the primary and key secondary endpoints were identified on a descriptive level across the various levels of the subgroups prespecified for analysis, which were categorized based on demographic and disease characteristics, including sex, age group, race, ethnicity, baseline BCVA, geographic region, baseline CRT category, and prior DME treatment.

[000592]The descriptive analyses of the additional secondary and exploratory endpoints (including proportion of participants without retinal fluid at the foveal center, mean change in CRT, and mean change in leakage on fluorescein angiography) evaluated at week 48 and week

60 suggested similar outcomes for HD aflibercept dosed q12 or q16 compared to 2q8, providing further evidence for the benefit of HD compared to 2q8. Robust reductions from baseline in CRT were observed in both HD groups beginning at week 4 through week 60. Some fluctuation in mean CRT was seen in all treatment groups with attenuation in magnitude over the course of 60 weeks. Despite these fluctuations, similar functional and anatomic outcomes were observed at week 60 across treatment groups.

[000593]The safety profile of HD was similar to that of 2 mg aflibercept. The overall rates of ocular and non-ocular TEAEs and SAEs reported up to week 60 were similar across the treatment groups. Most of the reported TEAEs were evaluated as mild and resolved within the observation period with no need to permanently discontinue the study drug. Ocular TEAEs in the study eye that resulted in discontinuation of the study drug affected few participants; 2 (0.6%) participants in the HDq12 group and no participants in the 2q8 and HDq16 groups. Similarly, non-ocular TEAEs resulted in discontinuation of the study drug in few participants; 3 (1.8%) participants in the 2q8 group and 9 (1.8%) participants in the Pooled HD groups.

[000594]A total of 18 deaths were reported during this study. None of the deaths were considered related to study drug or study procedure. All cases of death were consistent with concurrent medical conditions and the complications of these conditions associated with an older population.

[000595]No dose-relationship in the incidence or the types of TEAEs was apparent between participants in the HD groups and the 2q8 group. The results of the subgroup analyses of the TEAEs were comparable to those in the entire study population and did not suggest clinically relevant differences between the treatment groups in any of the subgroups examined.

[000596]The analyses of laboratory data, vital signs, and ECG data (including QT interval) did not show any clinically meaningful changes over time within the HD groups and the 2q8 group or differences between the groups.

[000597]There were no clinically meaningful trends in mean or median changes from baseline to pre-dose intraocular pressure (IOP) in the study eye in any treatment group through week 4860, and the proportion of participants meeting the pre-defined IOP criteria was comparable across treatment groups.

[000598]After the initial aflibercept dose of 2 mg (2q8) or 8 mg (HDq12+HDq16), the concentration-time profiles of free aflibercept were characterized by an initial phase of increasing concentrations as the drug moved from the ocular space into systemic circulation with a median time to peak concentration (t_{max}) of 0.268 to 0.965 days followed by a mono-exponential elimination phase. The concentration time profiles of adjusted bound aflibercept

were characterized by a slower attainment of peak concentration (C_{max}) compared to free aflibercept with a median t_{max} of 14 days. Following attainment of C_{max}, a sustained plateau of the concentration-time profile was observed until approximately the end of the dosing interval.

[000599]As the intravitreal (IVT) dose of aflibercept increased from 2 mg to 8 mg (a 4-fold increase in dose), the mean C_{max} and AUC_{last} for free aflibercept increased in a greater than dose-proportional manner (approximately 12 to 14-fold). Conversely, mean C_{max} and AUC_{last} for adjusted bound aflibercept increased in a slightly less than dose proportional manner (approximately 3 to 4-fold). These findings are consistent with historical data and the known nonlinear target-mediated kinetics of aflibercept.

[000600]Following the third initial monthly IVT dose of aflibercept, based on the ratio of aflibercept concentration at week 12 to week 4 (C_{week12}/C_{week4}), the accumulation of free aflibercept ranged from 1.8 to 2.0 for the 8 mg treatments. The accumulation of free aflibercept could not be determined for the 2 mg treatment since all week 12 aflibercept concentrations were below the limit of quantitation (BLQ). The accumulation of adjusted bound aflibercept ranged from 1.5 to 1.7 for the 2 mg and 8 mg treatments.

[000601]The pharmacokinetics of free and adjusted bound aflibercept were similar between Japanese and non-Japanese participants enrolled in the dense PK sub-study.

[000602]Immunogenicity was low across all treatment groups. Out of the 541 participants included in the anti-drug antibody analysis set (AAS), the incidence of TE anti-drug antibody (ADA) in the 2q8, HDq12, and HDq16 treatment groups during the 48-week period of treatment with intravitreally administered aflibercept was 0/137 (0%), 3/263 (1.1%), and 2/141 (1.4%), respectively; all of these responses were of low maximum titer. None of the ADA positive samples were found to be positive in the neutralizing antibody (Nab) assay.

Example 2: Randomized, Double-Masked, Active-Controlled, Phase 3 Study of the Efficacy and Safety of High Dose Aflibercept in Patients with Neovascular Age-Related Macular Degeneration (PULSAR) (clinicaltrials.gov ID. NCT04423718)

[000603]Data in these trials was previously presented in WO2023/177691. Additional data from PULSAR to week 96 or 100 is presented herein.

[000604]This phase 3, multi-center, randomized, double-masked, active-controlled study investigates the efficacy, safety, and tolerability of IVT administration of aflibercept 8 mg (HD) versus aflibercept 2 mg in participants with treatment-naïve nAMD.

[000605]The study consists of a screening/baseline period, a treatment period with duration of 92 weeks, and an end of study visit at Week 96. No study intervention will be administered at the end of study visit at Week 96.

[000606]Approximately 960 eligible participants with nAMD are randomly assigned to receive IVT injections of HD or 2 mg in a 1:1:1 ratio to 3 parallel treatment groups:

- **2q8**: aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
- **HDq12**: aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals.
- **HDq16**: aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals.

See Figure 41, Figure 43 and Figure 45.

[000607]Participants are stratified based on baseline BCVA and geographical region, to ensure balanced distribution of the treatment groups within each stratum. Only one eye can be treated within the study. Sham procedures are done on visits when an active injection is not planned. No sham procedures will be done at the non-treatment visit at Week 12. At all subsequent visits, all participants will receive either active study treatment injection or sham procedure (for masking purposes), depending on their assigned treatment schedule and eligibility for dose regimen modification.

[000608]Safety will be assessed by ophthalmic examinations, vital signs (including heart rate, blood pressure and temperature), electrocardiogram (ECG), AEs, and laboratory assessments. All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®).

[000609]In all participants, blood samples for measurement of drug concentrations (for PK) will be obtained prior to the first treatment and at pre-specified time points throughout the course of the study. In addition, a deoxyribonucleic acid (DNA) blood sample will be collected from those who sign the informed consent form (ICF) for the optional genomic sub-study.

[000610]The study also includes a PK sub-study, with dense PK blood sampling for systemic drug concentrations and PK assessments for approximately 12 Japanese participants from Japan sites and 12 non-Asian participants from Europe or US sites (distributed across all 3 treatment groups). All participants in the PK sub-study will participate in the main study for 96 weeks but will have extra visits. Blood pressure and heart rate measurements will also be taken in these participants at the same timepoints as for the PK sampling.

Dosing Schedule (Figure 43)
The dosing schedule is set forth below in Table 2-1.

Table 2-1. Dosing Schedule

					*								**
	Day1	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48
2q8	X	X	X		X	o	X	o	X	o	X	o	X
HDq12	X	X	X		o (a)	X (a)	o	o	X (c)	o	o	X (c)	o
HDq16	X	X	X		o (b)	o (b)	X (b)	o	o	o	X (c)	o	o
			*										
	Wk52	W56	Wk60	Wk64	Wk68	Wk72	Wk76	Wk80	Wk84	Wk88	Wk92	Wk96	
2q8	o	X	o	X	o	X	o	X	o	X	o		
HDq12	o	X (d)	o	o	X (d)	o	o	X (d)	o	o	X (d)		
HDq16	o	X (d)	o	o	o	X (d)	o	o	o	X (d)	o		

* Key 2° Endpoint at week 16 and 60
** 1° Endpoint at week 48
For masking purposes, DRM assessments will be performed in all participants at all visits (through the IXRS) starting from Week 16.
a HDq12 group: If DRM criteria are met, participants will continue on q8 rescue regimen.
b HDq16 group: If DRM criteria are met at Week 16 or 20, participant will continue on q8 rescue regimen. If DRM criteria are met at Week 24, participant will continue on q12 regimen.
c For participants remaining on a dosing interval of q12 or q16 weeks after Week 24, if DRM criteria are met at an active injection visit, the next dosing interval will be reduced by 4 weeks (to a minimum of q8).
d From Week 52, all participants in HD groups will be eligible for dose interval shortening (to a minimum of q8) or extension (by 4-week increments) according to pre-specified DRM criteria. If DRM criteria are met at an active injection visit, the next dosing interval will be changed by 4 weeks.
This table does not reflect all available dosing options, once a participant's dose regimen is shortened or extended.
X=active injection, o=sham procedure 2q8=aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals, HDq12=high dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals, HDq16=high dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals, 1º=primary, 2º=secondary, DRM=dose regimen modification, HD=high dose, q8=every 8 weeks, q12=every 12 weeks, q16=every 16 weeks, Wk=Week

Primary Endpoints

[000611]The primary endpoint is:

- Change from baseline in BCVA measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at Week 48

Secondary Endpoints

[000612]The key secondary efficacy endpoints are:

- Change from baseline in BCVA measured by the ETDRS letter score at Week 60

- Proportion of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in central subfield at Week 16

[000613]The additional secondary efficacy endpoints are:

- Proportion of participants gaining at least 15 letters in BCVA from baseline at Week 48
- Proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 48
- Change in choroidal neovascularization (CNV) size from baseline to Week 48
- Change in total lesion area from baseline to Week 48
- Proportion of participants with no IRF and no SRF in the center subfield at Week 48
- Change from baseline in central subfield retinal thickness (CST) at Week 48
- Change from baseline in National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) total score at Week 48

Exploratory Endpoints

[000614]The exploratory endpoints are:

- Change from baseline in BCVA measured by the ETDRS letter score at Week 96
- Change from baseline in BCVA averaged over the period from Week 36 to Week 48 and from Week 48 to Week 60
- Proportion of participants gaining at least 15 letters in BCVA from baseline at Week 60 and Week 96
- Proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 60 and Week 96
- Proportions of participants gaining and losing at least 5 or at least 10 letters in BCVA from baseline at Week 48, Week 60, and Week 96
- Proportion of participants losing at least 15 letters in BCVA from baseline at Week 48, Week 60, and Week 96
- Change in CNV size from baseline to Week 60 and Week 96
- Change in total lesion area from baseline to Week 60 and Week 96
- Change from baseline in CST at Week 60 and Week 96
- Proportion of participants with no IRF and no SRF in the center subfield at Week 96
- Proportion of participants without retinal fluid (total fluid, IRF, and/or SRF) and subretinal pigment epithelium fluid in center subfield at Week 48, Week 60, and Week 96

- Time to fluid-free retina over 48 weeks, 60 weeks, and 96 weeks (total fluid, IRF, and/or SRF in the center subfield)
- Proportion of participants with sustained fluid-free retina over 48 weeks, 60 weeks, and 96 weeks (total fluid, IRF, and/or SRF in the center subfield)
- Change from baseline in BCVA at each visit in relation to fluid outcomes
- Change from baseline in NEI-VFQ-25 total score at Week 60 and Week 96

Number of Patients Planned

[000615]The study will enroll approximately 960 eligible participants with nAMD that will be randomly assigned to receive IVT injections of 8 mg or 2 mg in a 1:1:1 ratio in three parallel treatment groups.

Study Population

[000616]The study population consists of treatment-naïve patients with nAMD.

Inclusion Criteria (Figure 42)

[000617]Participants are eligible to be included in the study only if all of the following criteria apply at both screening and baseline:

1. At least 50 years of age at the time of signing the informed consent.
2. Active subfoveal CNV secondary to nAMD, including juxtafoveal lesions that affect the fovea as assessed in the study eye.
3. Total area of CNV (including both classic and occult components) must comprise greater than 50% of the total lesion area in the study eye.
4. BCVA ETDRS letter score of 78 to 24 (corresponding to a Snellen equivalent of approximately 20/32 to 20/320) in the study eye.
5. Decrease in BCVA determined to be primarily the result of nAMD in the study eye.
6. Presence of IRF and/or SRF affecting the central subfield of the study eye on OCT. The central subfield is defined as a circle with diameter 1 mm, centered on the fovea.
7. Male or female.
8. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male participants: Men who are sexually active with partners of childbearing potential must agree to use highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 3 months after the last administration of study intervention.

b. Female participants: Women of childbearing potential (WOCBP) must practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 3 months after the last administration of study intervention. Pregnancy testing and contraception are not required for women not considered WOCBP.
9. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Exclusion Criteria (Figure 42)
[000618]Participants are excluded from the study if any of the following criteria apply at either screening or baseline:
Medical Conditions – Per Eye
1. Causes of CNV other than nAMD in the study eye.
2. Prior or concomitant conditions in the study eye:
a. Subretinal hemorrhage that is at least 50% of the total lesion area, or if the blood under the fovea is 1 or more disc areas in size in the study eye.
b. Scar or fibrosis making up more than 50% of the total lesion in the study eye.
c. Scar, fibrosis, or atrophy involving the central subfield in the study eye.
d. Presence of retinal pigment epithelial tears or rips involving the central subfield in the study eye.
e. Total lesion size >12 disc areas (30.5 mm^2, including blood, scars, and neovascularization) as assessed by FA in the study eye.
f. Uncontrolled glaucoma (defined as IOP >25 mmHg despite treatment with anti-glaucoma medication) in the study eye.
g. History of idiopathic or autoimmune uveitis in the study eye.
h. Vitreomacular traction or epiretinal membrane in the study eye evident on biomicroscopy or OCT that is thought to affect central vision.
i. Any history of macular hole of stage 2 and above in the study eye.
j. Structural damage to the center of the macula in the study eye that is likely to preclude improvement in BCVA following the resolution of retinal fluid including but not limited to, atrophy of the retinal pigment epithelium, subretinal fibrosis or scar or significant macular ischemia.
k. History of, or likely future need of, filtration or tube shunt surgery on the study eye.
l. Aphakia, or pseudophakia with absence of posterior capsule (unless it occurred as a result of a yttrium-aluminum-garnet [YAG] posterior capsulotomy performed more than 4 weeks (28 days) before screening), in the study eye.

m. Myopia of a spherical equivalent of at least 8 diopters in the study eye prior to any refractive or cataract surgery.
n. Significant media opacities, including cataract, that interfere with BCVA assessment, fundus photography or OCT imaging in the study eye.
o. History of corneal transplant or corneal dystrophy in the study eye.
p. History of irregular astigmatism or amblyopia with chronic limitation of BCVA in the study eye.
Medical Conditions – Per Participant
3. Prior or concomitant conditions:
a. History or clinical evidence of diabetic retinopathy, diabetic macular edema, or any retinal vascular disease other than nAMD in either eye.
b. Evidence of extraocular or periocular infection or inflammation (including infectious blepharitis, keratitis, scleritis, or conjunctivitis) in either eye at the time of screening/randomization.
c. Any intraocular inflammation/infection in either eye within 12 weeks (84 days) of the screening visit.
d. Only 1 functional eye, even if that eye was otherwise eligible for the study (*e.g.*, BCVA of counting fingers or less in the eye with worse vision).
e. Ocular conditions with poorer prognosis in the fellow eye.
4. Uncontrolled blood pressure (defined as systolic >160 mmHg or diastolic >95 mmHg). Participants may be treated with up to 3 agents known to have anti-hypertensive effects for arterial hypertension to achieve adequate blood pressure control. This limit applies to drugs that could be used to treat hypertension even if their primary indication in the participant was not for blood pressure control. Any recent changes in medications known to affect blood pressure need to be stable for 12 weeks prior to screening.
5. History of cerebrovascular accident or myocardial infarction within 24 weeks (168 days) before the screening visit.
6. Renal failure requiring dialysis, or renal transplant at screening or potentially during the study.
7. Allergy or hypersensitivity to any of the compounds/excipients in the study interventions formulations.
8. Presence of any contraindications indicated in the locally approved label for aflibercept.
9. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, might affect interpretation of the results of the study, or renders the participant at high risk for treatment complications.

10. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor.
11. Pregnant or breastfeeding women.

Prior Therapy

12. Any prior or concomitant ocular (in the study eye) or systemic treatment (with an investigational or approved, anti-VEGF or other agent) or surgery for nAMD, except dietary supplements or vitamins.
13. Prior treatment of the study eye with any of the following drugs (any route of ophthalmic administration) or procedures before baseline visit (Day 1):
a. Anti-angiogenic drugs at any time including investigational therapy (*e.g.*, with anti-angiopoietin/anti-VEGF bispecific monoclonal antibodies).
b. Long-acting steroids, within 16 weeks (112 days) before the screening visit, or any treatment with IVT implant, gene therapy, or cell therapy at any time.
c. Ocriplasmin (Jetrea®) at any time.
d. Vitreoretinal surgery and/or including scleral buckling at any time.
e. Any other intraocular surgery within 90 days before the screening visit.
f. Panretinal laser photocoagulation or macular laser photocoagulation within 90 days before the screening visit.
g. YAG capsulotomy in the study eye within 30 days before the screening visit.
14. Prior treatment of the fellow eye with any of the following:
a. Investigational therapy (*e.g.*, with anti-angiopoietin/anti-VEGF bispecific monoclonal antibodies) within 180 days before the screening visit.
b. IVT implant, gene therapy, or cell therapy at any time.
Prior treatment in the fellow eye with approved anti-VEGF therapy is allowed. Prior treatment in the fellow eye with bevacizumab (although not approved but a component of standard of care in some countries) is also allowed.
15. Participation in other clinical trials requiring administration of investigational treatments (other than vitamins and minerals) at the time of screening, or within 30 days or 5 half-lives of administration of the previous study intervention, whichever is longer.

Additional Exclusion Criteria for the Dense PK Sub-study

[000619]Participants who meet any of the following criteria will be not be eligible for the Dense PK Sub-study:
1. Prior treatment with IVT aflibercept in the fellow eye within 12 weeks (84 days) before the screening visit.

2. Active CNV in the fellow eye requiring anti-VEGF treatment at the time of screening visit.
3. Other IVT anti-VEGF treatment (ranibizumab, bevacizumab, brolucizumab, conbercept, pegaptanib sodium) in the fellow eye within 4 weeks (28 days) before the screening visit.
4. Systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg.
5. Known cardiac arrhythmia, based on medical history and/or outcome of ECG at screening.
6. Variation by more than 10% in the 3 pre-randomization blood pressure measures recorded at the screening visits and at randomization
7. Participants who, in the opinion of the investigator, are unlikely to have stable blood pressure over the course of the study (*e.g.*, due to known or suspected non-compliance with medication).

Investigational and Reference Treatments

[000620]The HD will be provided as a liquid formulation in a vial. The target concentration of aflibercept is 114.3 mg/mL. The dose will be delivered in an injection volume of 70 µl. The IAI will be provided as a liquid formulation in a vial. The target concentration of aflibercept is 40 mg/mL. The dose will be delivered in an injection volume of 50 µl.

Study Assessments and Procedures

[000621]Study procedures and their timing are summarized in the following tables.

Table 2-2. Schedule of Activities – Year 1

Visit	1 Screening	2 Baseline	3	4	5	6	7	8	9	10	11	12	13	14	15
Week			4	8		12	16	20	24	28	32	36	40	44	48
Day	-21 to -1	1	29	57	60-64	85	113	141	169	197	225	253	281	309	337
Window (day)[1]			±5	±5	[b]	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Administrative:															
Informed Consent (ICF)	X														
Dense PK Substudy ICF[c]	X														
Genomic Substudy ICF[d]	X														
FBR ICF[e]	X														
Inclusion/Exclusion Eligibility	X	X[f]													
Medical History	X														
Demographics	X														
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X													
Study Intervention[g]:															
Study Intervention (active or sham)		X	X	X			X	X	X	X	X	X	X	X	X
DRM Assessment[h]							X	X	X	X	X	X	X	X	X
Ocular Efficacy and Safety (bilateral unless indicated):															
NEI-VFQ-25[i]		X							X						X
BCVA (ETDRS) and Refraction	X	X	X	X		X	X	X	X	X	X	X	X	X	X
IOP[j]	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Slit Lamp Examination[k]	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Indirect Ophthalmoscopy[l]	X	X	X	X		X	X	X	X	X	X	X	X	X	X
FA, FP[m]	X					X			X			X			X
SD-OCT[n]	X	X	X	X		X	X	X	X	X	X	X	X	X	X
ICGA[o]	X														X
OCT-A[p]	X					X			X			X			X

Visit	1 Screening	2 Baseline	3	4	5	6	7	8	9	10	11	12	13	14	15
Week			4	8		12	16	20	24	28	32	36	40	44	48
Day	-21 to -1	1	29	57	60-64	85	113	141	169	197	225	253	281	309	337
Window (day)[a]			±5	±5	[b]	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Nonocular Safety:															
Physical Examination	X														
Vital Signs[c]	X	X	X	X	X[c]	X	X	X	X	X	X	X	X	X	X
ECG	X														X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[d]:															
Hematology	X														X
Blood Chemistry	X														X
Pregnancy Test (WOCBP)[e]	X Serum	X Urine	X Urine	X Urine		X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine
Urinalysis, UPCR	X														X
Pharmacokinetics and Other Sampling:															
PK Samples (Sparse)[f]		X	X		X	X				X					X
PK Samples (Dense)[f]		See Table 1-3													
Anti-drug Antibody Serum Sample[g,i]		X													X
Genomic DNA Sample (optional)[g]		X													

BCVA=best corrected visual acuity, DNA=deoxyribonucleic acid, DRM = dose regimen modification, ECG=electrocardiogram, ETDRS=Early Treatment Diabetic Retinopathy Study, FA=fluorescein angiography, FBR=future biomedical research, FP=fundus photography, ICF=informed consent form, ICGA=indocyanine green angiography, IOP=Intraocular pressure, NEI-VFQ-25=National Eye Institute Visual Functioning Questionnaire-25, OCT-A=optical coherence tomography angiography, PK=pharmacokinetics, SD-OCT=spectral domain optical coherence tomography, UPCR=urine protein:creatinine ratio, WOCBP=women of childbearing potential

Table 2-3. Schedule of Activities – Year 2

Visit	16	17	18	19	20	21	22	23	24	25	26	27 EOS or ED
Week	52	56	60	64	68	72	76	80	84	88	92	96
Day	365	393	421	449	477	505	533	561	589	617	645	673
Window (day)[a]	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5
Administrative:												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Study Intervention[e]:												
Study Intervention (active or sham)	X	X	X	X	X	X	X	X	X	X	X	
DRM Assessment[h]	X	X	X	X	X	X	X	X	X	X	X	
Ocular Efficacy and Safety (bilateral unless indicated):												
NEI-VFQ-25[i]			X									X
BCVA (ETDRS) and refraction	X	X	X	X	X	X	X	X	X	X	X	X
IOP[j]	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp examination[k]	X	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy[l]	X	X	X	X	X	X	X	X	X	X	X	X
FA, FP[m]			X									X
SD-OCT[n]	X	X	X	X	X	X	X	X	X	X	X	X
ICGA[o]												X
OCT-A[o]			X									X
Nonocular Safety:												
Physical examination												X
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X
ECG												X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[d]:												
Hematology												X
Blood Chemistry												X
Pregnancy Test (women of childbearing potential)[e]	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine	X Urine
Urinalysis, UPCR												X
Anti-drug Antibody Serum Sample[g,i]												X

BCVA=best corrected visual acuity, DNA=deoxyribonucleic acid, DRM=dose regimen modification, ECG=electrocardiogram, ED=Early Discontinuation, EOS=End of Study, ETDRS=Early Treatment Diabetic Retinopathy Study, FA=fluorescein angiography, FP=fundus photography, ICF=informed consent form, ICGA=indocyanine green angiography, IOP=Intraocular pressure, NEI-VFQ-25=National Eye Institute Visual Functioning

Questionnaire-25, OCT-A=optical coherence tomography angiography, PK=pharmacokinetics, SD-OCT=spectral domain optical coherence tomography, UPCR=urine protein:creatinine ratio, WOCBP=women of childbearing potential

Footnotes for the Schedule of Activities Tables
a Visit schedules may deviate by up to ±5 days. Set schedule visits (except Visit 5) use baseline for the calculation. The procedures required at each visit have to be complete within 3 days, *i.e.*, split visits are allowed. Additionally, all procedures have to be complete within the 5-day window. Slit lamp (anterior segment), IOP measurement, and indirect ophthalmoscopy are recommended to take place on the same day as the IVT injection.
b Visit 5 must be within 3 to 7 days after the Week 8 injection. This visit uses the date of Visit 4 for calculation.
c Dense PK sampling will be performed in a subgroup including participants at Japanese and non-Asian sites. The Dense PK Sub-study ICF should be presented and signed at the screening visit. Refer to Table 1–3. Participants in the Dense PK Sub-study have extra visits but otherwise participate in the main study with a 96 week duration.
d The optional genomic sub-study ICF should be presented to participants at the screening visit and may be signed at any subsequent visit at which the participant chooses to participate after screening. The genomic DNA blood sample should be collected on Day 1/baseline (pre-injection) or at any time during the study, only from participants who consent to participate in the genomic sub-study. Participants from China will not be enrolled in this optional sub-study.
e The optional FBR ICF should be presented to participants and signed at the screening visit. No additional blood sample is required – remaining blood samples (from *e.g.*, PK or anti-drug antibody [ADA] sampling) may be used.
f Inclusion/exclusion criteria will be evaluated at screening and baseline to confirm subject's eligibility. The investigator is responsible for confirming that any changes between screening and baseline do not affect the participant's eligibility.
g Following study intervention injection or sham procedure, participants will be observed for at least 30 minutes.
h For masking purposes, assessments for dose regimen modification (DRM) or potential shortening to the rescue regimen (8 mg q8) will be performed in all participants at all visits starting from Week 16. Actual DRMs will be implemented. (See Figure 43, Figure 44 and Figure 65)
i NEI-VFQ-25 to be administered in a quiet room by a masked study-related person trained to administer this type of questionnaire, preferably before other visit procedures are performed.
j IOP will be measured at all study visits (bilateral). On days when study intervention is administered, IOP should be measured pre-injection (bilaterally) and approximately 30 minutes after administration of study intervention (study eye only). IOP will be measured using Goldman applanation tonometry, rebound tonometry Icare, or Tonopen and the same method of measurement must be used in each participant throughout the study.
k Slit lamp examination will be performed bilaterally.
l Indirect ophthalmoscopy will be performed bilaterally at all visits. On days when study intervention is administered, it should also be performed immediately after administration of study intervention (study eye only).
m The same SD-OCT/FA/FP imaging system used at screening and Day 1 must be used at all follow-up visits in each participant. Images will be taken in both eyes before dosing (active or sham injection).
n Optional at all sites that have the relevant equipment. ICGA will be used to diagnose and characterize the polypoidal choroidal vascularization (PCV) subtype of nAMD. If ICGA cannot be performed at screening visit, it may be done at baseline visit.

o OCT-A is optional at all sites that have the relevant equipment. If OCT-A cannot be performed at screening visit, it may be done at baseline visit.
p Vital signs (temperature, blood pressure, heart rate) should be measured per the procedure outlined in the study manual. At Visit 5, only blood pressure and heart rate are required. Vital signs should be measured prior to injection and any blood sampling. When possible, timing of all blood pressure assessments should be within 2 hours of clock time of dosing on Day 1. Measurements will be taken pre-dose (active or sham injection).
q All samples collected for laboratory assessments should be obtained prior to administration of fluorescein and/or indocyanine green, and prior to administration of study intervention.
r For women of childbearing potential, a negative serum pregnancy test at screening is required for eligibility. A negative urine pregnancy test is required before any treatment (including rescue regimen) is administered at subsequent visits.
s Sparse PK sampling will be performed in all participants (optional for participants in China). Any PK sampling will be done prior to dosing if scheduled at the sampling time point.
t Anti-drug antibody sample collection is optional for participants in China.

Table 2-4. Schedule of Activities – Dense PK Sub-Study

Visit	Dose	Assessment Day	Assessment Time (h)	PK Sample	Heart Rate and Blood Pressure[a]
Screening 2[b]		-21 to -1	±2h		X
Visit 2 (Baseline)	X	1	Pre-dose[c]	X (pre-injection)	X
			4[c]	X	
			8[c]	X	
		2	±2h[c]	X	X
		3	±2h[c]	X	X
		5	±2h[c]	X	X
		8	±2h[c]	X	X
		15	±2h[c]	X	X
		22	±2h[c]	X	X

PK=pharmacokinetics
Participants enrolled in the Dense PK Sub-study will also have blood pressure and heart rate assessed at each visit within the sub-study.
Participants enrolled in the Dense PK Sub-study will also have blood pressure and heart rate assessed at each visit within the sub-study.
a Timing of all blood pressure assessments must be within ±2 hours of the clock time of dosing on Day 1. Blood pressure assessments for participants in the Dense PK Sub-study will be taken prior to blood sample collection using automated office blood pressure (AOBP) measurement with the Omron Model HEM 907XL (or comparable). Measures will be recorded in the electronic case report form (eCRF). Detailed instructions can be found in the study manual.
b Additional blood pressure assessment between screening and baseline, to confirm eligibility for participants in the Dense PK Sub-study. Screening 2 may occur on the same day as the screening visit.
c On Day 1, the 4 hour and 8 hour PK sampling is to be within ±30 minutes and ±2 hours, respectively, of the scheduled time. For subsequent days, PK sampling is to be performed within ±2 hours of the clock time of dosing on Day 1.

Ophthalmic and General Examinations
[000622]All ophthalmic examinations are described, irrespective of whether they are used for efficacy or safety assessments. All ophthalmic examinations are to be conducted pre-injection in both eyes and post-injection in the study eye only, unless indicated otherwise. At any visit, ophthalmic examinations not stipulated by this protocol may take place outside of this protocol at the discretion of the investigator.

[000623] *Best Corrected Visual Acuity (BCVA)* - Visual function will be assessed using the ETDRS protocol (2) starting at 4 meters. Refraction is to be done at each visit. Visual acuity examiners must be certified to ensure consistent measurement of BCVA. Any certified and trained study personnel may perform this assessment (including but not limited to ophthalmologist, optometrist, or technician) and must remain masked to treatment assignment. For each participant, the same examiner must perform all assessments whenever possible. BCVA should be done before any other ocular procedures are performed.

[000624] *Intraocular Pressure (IOP)* - IOP will be measured using Goldman applanation tonometry, rebound tonometry Icare, or Tonopen and the same method of measurement must be used in each participant throughout the study. At all visits, IOP should be measured bilaterally by the masked investigator (or designee). On days when study intervention is administered, IOP should also be measured approximately 30 minutes after administration of study intervention (study eye only) by the unmasked investigator (or designee). If multiple post-injection measurements are performed, the final measurement before the participant leaves should be documented in the eCRF. Any injection-related increase in IOP (and treatment) should be documented in a masked fashion.

[000625] *Slit Lamp Examination* - The slit lamp examination will be performed according to local medical practice and applicable medical standards at the site. Participants' anterior eye structure and ocular adnexa will be examined bilaterally (pre-dose on visits with active injection) at each study visit using a slit lamp.

[000626] *Indirect Ophthalmoscopy* - Indirect ophthalmoscopy will be performed according to local medical practice and applicable medical standards at the site. Participants' posterior pole and peripheral retina will be examined by indirect ophthalmoscopy at each study visit pre-dose (bilateral) by the masked investigator and post-dose (study eye). Post-dose evaluation must be performed immediately after injection.

[000627] *Fundus Photography (FP) and Fluorescein Angiography (FA)* -The anatomical state of the retinal vasculature of the study eye will be evaluated by FP and FA. The treating investigator may perform additional FA/FP at other times during the study based on his/her medical judgment and standard of care. Photographers must be masked to treatment assignment and must be certified by the reading center to ensure consistency and quality in image acquisition. FP and FA images will be read by the investigator for individual treatment decisions and sent to an independent reading center where images will be read by masked readers. The participants' eligibility to participate in the study in terms of FA will be confirmed by the central reading center before randomization. The same FA/FP imaging system used at screening and Day 1 must be

used at all subsequent visits in each participant. Images will be taken in both eyes before dosing (active or sham injection).

[000628] *Spectral Domain Optical Coherence Tomography (SD-OCT)* -Retinal and lesion characteristics will be evaluated using SD-OCT. For all visits where the SD-OCT procedure is scheduled, images will be captured and read by the technician and investigator for individual treatment decisions and sent to an independent reading center. The participants' eligibility to take part in the study in terms of SD-OCT will be confirmed by the central reading center before randomization. The same SD-OCT imaging system used at screening and Day 1 must be used at all follow-up visits in each participant. Images will be taken in both eyes before dosing (active or sham injection).

[000629] *Indocyanine Green Angiography (ICGA)* - ICGA will be optional, performed at sites with the appropriate equipment. ICGA will be used to diagnose and characterize the PCV subtype of nAMD. The same imaging modality used at screening must be used at all follow-up visits in each participant. Images will be taken in both eyes before dosing (active or sham injection).

[000630] *Optical Coherence Tomography Angiography (OCT-A)* - Optical coherence tomography angiography (OCT-A) will be optional, performed at sites with the relevant equipment. The same imaging modality used at screening must be used at all follow-up visits in each participant. Images will be taken in both eyes before dosing (active or sham injection).

[000631] *National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25)* - Vision-related quality of life (QoL) will be assessed using the NEI-VFQ-25 questionnaire (3) in the interviewer-administered format. It is a reliable and valid 25-item version of the 51-item NEI-VFQ.

[000632] *Dose Regimen Modification (DRM)*-For masking purposes, assessments for dose regimen modifications (DRM) will be performed in all participants at all visits starting from Week 16. Based on these assessments, participants in the HD groups may have their treatment intervals shortened or extended. The minimum interval between injections will be 8 weeks, which is considered a rescue regimen for participants randomized to HD aflibercept who are unable to tolerate a dosing interval greater than every 8 weeks. Participants in the aflibercept 2 mg group will remain on fixed q8 dosing throughout the study (i.e., will not have modifications of their treatment intervals regardless of the outcomes of the DRM assessments).

Baseline to Week 48 - Beginning at Week 16, participants in the HD groups will have the dosing interval shortened (at the visits described below) if BOTH the following DRM criteria are met:

1. BCVA loss >5 letters from Week 12, AND
2. >25 µm increase in central retinal thickness (CRT) from Week 12 OR new foveal hemorrhage OR new foveal neovascularization If a participant in the HDq12 group or the HDq16 group meets both criteria at Week 16 or Week 20, the participant will be dosed with 8 mg aflibercept at that visit and will continue on rescue regimen (aflibercept 8 mg, every 8 weeks).

[000633]If a participant in the HDq16 group who has not met the criteria at Week 16 or Week 20 meets both criteria at Week 24, the participant will be dosed with 8 mg aflibercept at that visit and will continue on q12 dosing.

[000634]For participants whose interval was not shortened to q8 dosing at or before Week 24, the interval will be shortened if the DRM criteria are met at subsequent visits with active injection. Participants in the HDq12 group who meet the criteria will receive the planned dose at that visit and will then continue on rescue regimen (aflibercept 8 mg, every 8 weeks). Participants in the HDq16 group who meet these criteria will receive the planned dose at that visit and will then continue to be dosed every 12 weeks if they were on a 16-week interval, or switch to the rescue regimen (aflibercept 8 mg, every 8 weeks) if they were on a 12-week interval. Therefore, a participant randomized to HDq16 whose injection interval has been shortened to q12 will have their injection interval further shortened to q8 if these criteria are met at any subsequent assessment.

[000635]Week 52 to Week 96 (End of Study) - From Week 52 through the end of study (Year 2), all participants in the HD groups will continue to have the interval shortened in 4-week intervals (to a minimum of q8) if the DRM criteria for shortening are met at visits with active injection, using the criteria described above for Year 1.

[000636]In addition to shortening of the interval, all participants in the HD groups (including HD group participants whose interval was shortened during Year 1) may be eligible for interval extension (by 4-week increments) (if the following DRM criteria are met at visits with active injection in Year 2:

1. BCVA loss <5 letters from Week 12, AND
2. No fluid at the central subfield on OCT, AND
3. No new onset foveal hemorrhage or foveal neovascularization

[000637]For participants who do not meet the criteria for shortening or extension of the interval, the dosing interval will be maintained.

[000638]As in Year 1, all participants in all treatment groups (including the 2q8 group) will be evaluated against both DRM criteria at all visits. However, changes to dosing schedule will only be implemented as described above. No changes to the dosing schedule will be made to the

2q8 treatment group at any time. All anatomic criteria will be based on the site evaluations/OCT assessments, not on the reading center assessments.

[000639]Intervention After the End of the Study Intervention will not be supplied after the end of the study. Participants will not be restricted with regard to pursuing available approved treatments for nAMD.

Treatment group descriptions

2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals.

HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals.

HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals.

All HD: Pooled high dose aflibercept 8 mg administered every 12 weeks or every 16 weeks, after 3 initial injections at 4-week intervals.

Results at Week 48

[000640] *Visual Outcomes.* The primary analysis of the change from baseline in BCVA resulted in LS_{mean} changes from baseline to Week 48 (*i.e.*, estimated, adjusted mean changes) of 7.03, 6.06 and 5.89 letters for the 2q8, HDq12 and HDq16 groups, respectively (Table 2-5).

[000641]The estimated difference in LS_{means} changes from baseline to Week 48 in BCVA (with corresponding 95% CI) of HDq12 vs. 2q8 was -0.97 (-2.87, 0.92) letters and of HDq16 vs. 2q8 was -1.14 (-2.97, 0.69) letters (Table 2-5). The p-values for the non-inferiority test at a margin of 4 letters were 0.0009 for HDq12 vs. 2q8, and 0.0011 for HDq16 vs. 2q8; p-values for a superiority test were 0.8437 for HDq12 vs. 2q8 and of 0.8884 for HDq16 vs. 2q8.

[000642]The arithmetic mean (SD) changes from baseline in BCVA to Week 48 (*i.e.*, observed, unadjusted mean changes) were 7.6 (12.2), 6.7 (12.6), and 6.2 (11.7) letters for the 285, 299, and 289 participants with Week 48 data, *i.e.*, excluding data after an ICE as handled by the hypothetical strategy, in the 2q8, HDq12, and HDq16 groups, respectively (Table 2-5).

Table 2-5. Change From Baseline in BCVA Measured by the ETDRS Letter Score at Week 48 and Week 60 in the Study Eye, MMRM (Full Analysis Set)

	2q8 N = 336	HDq12 N = 335	HDq16 N = 338
Week 48 (primary endpoint)			
Baseline mean (a)	58.9	59.9	60.0
Number of subjects with Week 48 data	285	299	289
Arithmetic mean (SD) change from baseline (a)	7.6 (12.2)	6.7 (12.6)	6.2 (11.7)
LS mean (SE) change from baseline	7.03 (0.74)	6.06 (0.77)	5.89 (0.72)
DF	/	622.1	647.7
Contrast (b)	/	HDq12 - 2q8	HDq16 - 2q8
t-value	/	3.14	3.07
p-value of one-sided test for non-inferiority at a margin of 4 letters	/	0.0009	0.0011
Estimate for Contrast and two-sided 95% CI (c)	/	-0.97 (-2.87,0.92)	-1.14 (-2.97,0.69)
Week 60 (key secondary endpoint)			
Baseline mean (a)	58.9	59.9	60.0
Number of subjects with Week 60 data	268	283	282
Arithmetic mean (SD) change from baseline (a)	7.8 (12.6)	6.6 (13.6)	6.6 (11.7)
LS mean (SE) change from baseline	7.23 (0.68)	6.37 (0.74)	6.31 (0.66)
DF	/	896.3	928.7
Contrast (b)	/	HDq12 - 2q8	HDq16 - 2q8
t-value	/	3.61	3.81
p-value of one-sided test for non-inferiority at a margin of 4 letters	/	0.0002	<0.0001
Estimate for Contrast and two-sided 95% CI (c)	/	-0.86 (-2.57,0.84)	-0.92 (-2.51,0.66)

BCVA = best corrected visual acuity, CI = Confidence interval, DF = Degrees of freedom, ETDRS = Early Treatment Diabetic Retinopathy Study, LS = Least Square, SAP = statistical analysis plan, SD = Standard deviation, SE = Standard error

[000643]A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit.

[000644]A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured (for Week 48) and Toeplitz with heterogeneity (for Week 60).

[000645]Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints.

(a): Based on observed assessments.

(b): The contrast also includes the interaction term for treatment x visit

(c): Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively, with two-sided 95% CIs.

[000646]The proportions of participants gaining at least 15 letters in BCVA from baseline at Week 48, using LOCF (last observation carried forward) in the FAS (full analysis set), were similar across the 3 treatment groups; the small numerical differences across the treatment groups were not clinically meaningful (Table 2-6). The proportions and between-treatment differences obtained for the corresponding analysis based on OC (observed case) prior to ICE (intercurrent event) were consistent with the results using LOCF.

Table 2-6. Proportion of Participants who Gained at Least 15 Letters in BCVA from Baseline at Week 48, LOCF (Full Analysis Set)

	2q8 N=336	HDq12 N=335	HDq16 N=338
Week 48 (additional secondary efficacy variable)			
Subjects who gained ≥ 15 letters, Num/Den (%)	74/335 (22.1%)	69/334 (20.7%)	73/337 (21.7%)
Contrast	/	HDq12 - 2q8	HDq16 - 2q8
Difference (a) % (two-sided 95% CI)	/	-1.748 (-7.784, 4.287)	-0.939 (-6.997, 5.119)
CMH test (b) p-value	/	0.5704	0.7611

[000647] *BCVA ≥69.* The proportions of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 48 using LOCF in the FAS were similar across the 3 treatment groups; the small numerical differences between the treatment groups were not clinically meaningful. The proportions and between-treatment differences obtained for the corresponding analysis based on OC prior to ICE were consistent with the results using LOCF.

Table 2-7. Proportion of Participants who Achieved an ETDRS Letter Score of at Least 69 at Week 48, LOCF (Full Analysis Set)

	2q8 N = 336	HDq12 N = 335	HDq16 N = 338
Subjects who achieved ≥ 69 letters, Num/Den (%)	194/335 (57.9%)	190/334 (56.9%)	183/337 (54.3%)
Contrast	/	HDq12 - 2q8	HDq16 - 2q8
Difference (a) % (two-sided 95% CI)	/	-0.182 (-6.565, 6.200)	-2.221 (-8.435, 3.994)
CMH test (b) p-value	/	0.9554	0.4834

BCVA = best corrected visual acuity, CI = Confidence interval, ETDRS = Early Treatment Of Diabetic Retinopathy Study, LOCF = Last observation carried forward, Num/Den = numerator/denominator, SAP = statistical analysis plan; LOCF method for the last available observed value prior to ICE was carried forward to impute missing data; Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints. (a) Difference is HD groups minus 2q8 and CI was calculated using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60) and is displayed with two-sided 95% CIs. (b) Nominal p-value for the two-sided Cochran-Mantel-Haenszel (CMH) test.

[000648] *Gaining at least 15 Letters.* The proportions of participants gaining at least 15 letters in BCVA from baseline at Week 48, using LOCF in the FAS, were similar across the 3 treatment groups; the small numerical differences between the treatment groups were not clinically meaningful (see Table 2-15 below). The proportions and between-treatment differences

obtained for the corresponding analysis based on OC prior to ICE were consistent with the results using LOCF.

[000649] *Compliance with Study Treatment.* 79% of patients in the HDq12 group and 77% of patients in the HDq16 group and 83% of combined patients in the HDq12 and HDq16 groups (≥ 12 weeks) were maintained in these groups through week 48 of the study. Treatment compliance in the safety analysis set is summarized in Table 2-8; see also Table 2-51.

Table 2-8. Compliance with Study Treatment: Through Week 48 (Safety Analysis Set)

	2q8 N = 336 (100%)	**HDq12** N = 335 (100%)	**HDq16** N = 338 (100%)	**All HD** N = 673 (100%)
Number of subjects receiving 100% planned injections within 48-week period	275 (81.8%)	287 (85.7%)	284 (84.0%)	571 (84.8%)
Treatment compliance (%)				
n	336	335	337	672
Mean (SD)	97.69 (5.80)	98.03 (5.48)	98.02 (5.16)	98.03 (5.32)
Median	100.00	100.00	100.00	100.00
Min, Max	63.6,100	63.6,100	63.6,100	63.6,100
Compliance categories, n (%)				
> 90 to ≤ 100%	321 (95.5%)	317 (94.6%)	321 (95.0%)	638 (94.8%)
> 80 to ≤ 90%	7 (2.1%)	12 (3.6%)	12 (3.6%)	24 (3.6%)
≤ 80%	8 (2.4%)	6 (1.8%)	4 (1.2%)	10 (1.5%)

SD = standard deviation
Compliance = (Number of actual study interventions received during period before Week 48 or up to premature discontinuation)/
(Number of planned study interventions during period before Week 48 or up to premature discontinuation) x 100

[000650] *Retinal Fluid.* The proportion of participants with no retinal fluid (no IRF and no SRF) in the center subfield at Week 48 was numerically higher in the HDq12 and HDq16 groups (71.1% and 66.8%, respectively) compared to the 2q8 treatment group 59.4%, based on LOCF in the FAS. The pair-wise differences (95% CI) for the 2-sided tests, using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60), of 11.725% points (4.527%, 18.923%) for HDq12 vs. 2q8 and 7.451% points (0.142%, 14.760%) for HDq16 vs. 2q8 were both in favor of HD treatment.

[000651] Even larger differences in favor of HD treatment were obtained using OC prior to ICE for the pair-wise comparisons in the FAS, providing differences of 15.417% points (7.664%, 23.170%) for HDq12 vs. 2q8 and 11.397% points (3.452%, 19.343%) for HDq12 vs. 2q8. See Table 2-9.

Table 2-9. Proportion of Participants with No IRF and No SRF in the Central Subfield at Week 48, LOCF (Full Analysis Set)

	2q8 N = 336	HDq12 N = 335	HDq16 N = 338
Subjects who had no IRF and no SRF, Num/Den (%)	199/335 (59.4%)	236/332 (71.1%)	223/334 (66.8%)
Contrast	/	HDq12 - 2q8	HDq16 - 2q8
Difference (a) % (two-sided 95% CI)	/	11.725 (4.527, 18.923)	7.451 (0.142, 14.760)
CMH test (b) p-value	/	0.0015	0.0458

BCVA = best corrected visual acuity, CI = Confidence interval, CMH = Cochran-Mantel-Haenszel, IRF = Intraretinal fluid, LOCF = Last observation carried forward, Num/Den = numerator/denominator, SAP = statistical analysis plan, SRF = Subretinal fluid
LOCF method for the last available observed value prior to ICE were carried forward to impute missing data.
Intercurrent events (ICE) were handled according to primary estimand strategy for binary endpoints.
(a) Difference is HD groups minus 2q8 and CI was calculated using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60) and is displayed with two-sided 95% CIs.
(b) Nominal p-value for the two-sided Cochran-Mantel-Haenszel (CMH) test.

[000652]*Retinal Thickness.* The mean values of CST at baseline were similar, ranging from 367.1 to 370.7 µm across the 3 treatment groups. Mean decreases from baseline were observed in all treatment groups at Week 48, which were higher in the HD groups than in the 2q8 group. The estimated contrasts (95% CIs) for the 2-sided tests, using the MMRM in the FAS, of -11.12 (-21.06,-1.18) µm for HDq12 vs. 2q8 and of -10.51 (-20.12,-0.90) µm for HDq16 vs. 2q8 were both numerically in favor of HD treatment (Table 2-10).

[000653]The corresponding analysis using an ANCOVA with LOCF in the FAS provided mean changes from baseline to Week 48 and estimated contrasts (95% CIs) for the 2-sided tests between the HD groups and the 2q8 group that were numerically also in favor of HD treatment and thus consistent with the results from the analysis using MMRM.

Table 2-10. Change from Baseline in CST (µm) at Week 48, MMRM (full analysis set)

	2q8 N = 336	HDq12 N = 335	HDq16 N = 338
LS mean (SE) change from baseline	-136.25 (4.24)	-147.37 (4.01)	-146.76 (3.76)
Arithmetic mean (SD) change from baseline (a)	-126.3 (124.3)	-141.9 (120.1)	-147.1 (131.2)
Baseline mean (a)	367.1	370.3	370.7
Number of subjects with Week 48 data	273	289	282
DF	/	626.1	608.6
Contrast (b)	/	HDq12-2q8	HDq16-2q8
t-value	/	-2.20	-2.15
P-value(c)	/	0.0283	0.0321
Estimate for Contrast and two-sided 95% CI (d)	/	-11.12 (-21.06,-1.18)	-10.51 (-20.12,-0.90)

BCVA = best corrected visual acuity, CI = confidence interval, CST = central subfield retinal thickness, DF = degrees of freedom, LS = least square, SAP = statistical analysis plan, SD = standard deviation, SE = standard error

[000654]A mixed model for repeated measurements (MMRM) was used with baseline CST as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline CST and visit and the interaction between treatment and visit.

[000655]A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured.

Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints.

(a) Based on observed assessments.

(b) The contrast also includes the interaction term for treatment x visit.

(c) P-value for the two-sided test.

(d) Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

[000656]*Patient Reported Outcomes.* The mean values of the NEI-VFQ-25 total score at baseline were similar across the 3 treatment groups, ranging from 76.4 to 77.8. Mean increases from baseline were observed in all groups at Week 48, which were numerically lower in the HD groups than in the 2q8 group. The estimated contrasts (95% CIs) for the 2-sided tests using the

MMRM in the FAS were small and not clinically meaningful for both comparisons, HDq12 vs. 2q8 and HDq16 vs. 2q8 (Table 2-11).

[000657]The corresponding analysis using an ANCOVA with LOCF in the FAS provided mean changes from baseline to Week 48 and estimated contrasts (95% CIs) for the 2-sided tests between the HD groups and the 2q8 group that were similar to those based on MMRM and thus also not clinically meaningful.

Table 2-11. Change from Baseline in NEI-VFQ-25 Total Score at Week 48, MMRM (Full Analysis Set)

	2q8 N = 336	**HDq12** N = 335	**HDq16** N = 338
Baseline mean (a)	77.8	76.4	77.7
Number of subjects with Week 48 data	266	285	266
Arithmetic mean (SD) change from baseline (a)	4.6 (11.0)	4.1 (10.4)	3.4 (10.8)
LS mean (SE) change from baseline	4.22 (0.70)	3.50 (0.70)	3.35 (0.72)
DF	/	571.7	540.3
Contrast (b)	/	HDq12-2q8	HDq16-2q8
t-value	/	-0.88	-1.02
P-value (c)	/	0.3817	0.3070
Estimate for Contrast and two-sided 95% CI (d)	/	-0.72 (-2.35,0.90)	-0.87 (-2.55,0.80)

CI = Confidence interval, DF = Degrees of freedom, LS = Least Square, NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25, SAP = statistical analysis plan, SD = Standard deviation, SE = Standard error

[000658]A mixed model for repeated measurements (MMRM) was used with baseline total lesion area as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline NEI-VFQ-25 total score and visit and the interaction between treatment and visit.

[000659]A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured.

[000660]Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints.

(a) Based on observed assessments.

(b) The contrast also includes the interaction term for treatment x visit.

(c) Nominal p-value for the two-sided test.

(d) Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

[000661]*CNV Size.* The mean CNV size at baseline was similar ranging from 6.0 to 6.5 mm^2 across the 3 treatment groups. Mean changes from baseline at Week 48 showed mean decreases in the HD groups and the 2q8 group. The estimated contrasts (95% CI) for the 2-sided test, using the MMRM in the FAS, of -1.22 (-1.94, -0.51) mm^2 for HDq12 vs. 2q8 and of -0.48 (-1.22, 0.27) mm^2 for HDq16 vs. 2q8 were both numerically in favor of HD treatment (Table 2-12).

[000662]The corresponding analysis using an ANCOVA with LOCF in the FAS provided mean changes from baseline to Week 48 and estimated contrasts (95% CIs) for the 2-sided tests between the HD groups and the 2q8 group that were numerically also in favor of HD treatment and thus consistent with the results from the analysis using MMRM.

Table 2-12. Change from baseline in CNV size (mm^2) at Week 48, MMRM (Full Analysis Set)

	2q8 N = 336	HDq12 N = 335	HDq16 N = 338
LS mean (SE) change from baseline	-2.43 (0.31)	-3.65 (0.28)	-2.91 (0.29)
Arithmetic mean (SD) change from baseline (a)	-2.4 (5.3)	-3.5 (5.0)	-2.9 (5.3)
Baseline mean (a)	6.4	6.0	6.5
Number of subjects with Week 48 data	276	285	274
DF	/	614.0	609.2
Contrast (b)	/	HDq12-2q8	HDq16-2q8
t-value	/	-3.35	-1.26
P-value(c)	/	0.0009	0.2076
Estimate for Contrast and two-sided 95% CI (d)	/	-1.22 (-1.94,-0.51)	-0.48 (-1.22,0.27)

BCVA = best corrected visual acuity, CI = Confidence interval, CNV = Choroidal neovascularization, DF = Degrees of freedom, LS = Least Square, SAP = statistical analysis plan, SD = Standard deviation, SE = Standard error

[000663]A mixed model for repeated measurements (MMRM) was used with baseline CNV measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline CNV and visit and the interaction between treatment and visit.

[000664]A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured.

[000665]Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints.

(a) Based on observed assessments.

(b) The contrast also includes the interaction term for treatment x visit.

(c) p-value for the two-sided test.

(d) Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

[000666] *Total Lesion Area.* The mean total lesion area at baseline was similar across the 3 treatment groups, ranging from 6.4 to 6.9 mm^2. Mean changes from baseline at Week 48 showed mean decreases in the HD groups but a mean increase in the 2q8 group. The estimated contrasts (95% CI) for the 2-sided test, using the MMRM in the FAS, of -0.55 (-1.04, -0.06) mm^2 for HDq12 vs. 2q8 and and of -0.44 (-0.94,0.06) mm^2 for HDq16 vs. 2q8 were numerically in favor of HD treatment (Table 2-13).

[000667] The corresponding analysis using an ANCOVA with LOCF in the FAS provided mean changes from baseline to Week 48 and estimated contrasts (95% CIs) for the 2-sided tests between the HD groups and the 2q8 group that were numerically also in favor of HD treatment and thus consistent with the results from the analysis using MMRM.

Table 2-13. Change in total lesion area (mm^2) from baseline to Week 48, MMRM (full analysis set)

	2q8 N = 336	**HDq12** N = 335	**HDq16** N = 338
Baseline mean (a)	6.9	6.4	6.9
Number of subjects with Week 48 data	277	285	273
Arithmetic mean (SD) change from baseline (a)	0.1 (3.6)	-0.4 (2.9)	-0.2 (3.1)
LS mean (SE) change from baseline	0.09 (0.22)	-0.46 (0.19)	-0.35 (0.20)
DF	/	631.4	640.4
Contrast (b)	/	HDq12-2q8	HDq16-2q8
t-value	/	-2.19	-1.71
P-value (c)	/	0.0287	0.0870
Estimate for Contrast and two-sided 95% CI (d)	/	-0.55 (-1.04,-0.06)	-0.44 (-0.94,0.06)

BCVA = best corrected visual acuity, CI = Confidence interval, DF = Degrees of freedom, LS = Least Square, SAP = statistical analysis plan, SD = Standard deviation, SE = Standard error

[000668] A mixed model for repeated measurements (MMRM) was used with baseline total lesion area as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline total lesion area and visit and the interaction between treatment and visit.

[000669] A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured.

[000670] Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints

(a) Based on observed assessments.
(b) The contrast also includes the interaction term for treatment x visit
(c) Nominal p-value for the two-sided test.
(d) Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.

[000671]*Safety.* Ocular and non-ocular safety for patients receiving the 8 mg doses of aflibercept was similar to that of patients receiving aflibercept intravitreally dosed at 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months.
[000672]*Summary.* At 48 weeks, PULSAR met the primary endpoints of non-inferiority of aflibercept 8 mg to EYLEA, with BCVA improvements from baseline demonstrated across dosing groups (all p=≤0.003). The EYLEA outcomes in wet AMD were consistent with previous clinical trial experience. In the every 16-week dosing regimen groups, 77% of wet AMD patients in PULSAR maintained this dosing interval with an average of 5 injections in the first year. In the every 12-week dosing regimen groups, 79% of wet AMD patients in PULSAR maintained this dosing interval with an average of 6 injections in the first year. In a pooled analysis of aflibercept 8 mg dosing groups, 83% of wet AMD patients in PULSAR maintained 12-week dosing or longer. These data demonstrated that a remarkably high percentage of patients can be maintained on 12- and 16-week dosing intervals.
[000673]Key efficacy findings at 48 weeks are set forth in Table 2-14.

Table 2-14. Key Week 48 Efficacy Findings

	High-dose aflibercept 12-week regimen	**High-dose aflibercept 16-week regimen**	**EYLEA 8-week regimen**
PULSAR (wet AMD)	**n=335**	**n=338**	**n=336**
Mean BCVA improvement, primary endpoint	6.7 letters	6.2 letters	7.6 letters
Non-inferiority p-value	0.0009	0.0011	N/A
Absolute BCVA	66.9 letters	66.3 letters	66.5 letters
Patients maintained on dosing interval	79%	77%	N/A

Patients with no fluid in the central subfield at 16 weeks, key secondary endpoint	63% (one-sided superiority p=0.0002)	52%

DRSS: diabetic retinopathy severity scale; N/A: not applicable

[000674]Mean changes from BL in BCVA at Week 48 were numerically larger in patients with lower BL BCVA (≤54 letters), and smaller in those with higher BL BCVA (≥74 letters). Within the BL subgroups, mean changes and absolute BCVA letter scores at Week 48 were similar in the HDq12, HDq16 and 2q8 treatment groups. Mean increases from BL in BCVA with HDq12, HDq16 and 2q8 were also similar, with overlapping CIs, in patients with BL central subfield retinal thickness (CRT) <400 µm and ≥400 µm, again resulting in similar absolute BCVA letter scores at Week 48 irrespective of treatment group. The same trends were also observed in the subgroup of patients with minimally classic, occult, and predominantly classic disease. Data will also be presented for additional patient subgroups, including by race. In patients with nAMD, BCVA gains from baseline at Week 48 were seen in all subgroups based on baseline BCVA, CRT, and lesion type, with comparable BCVA letter scores at Week 48 achieved with aflibercept 8 mg and 2 mg. See Table 2-15.

Table 2-15. Week 48 Mean Change in BCVA Letter Scores According to BL BCVA, CRT or Lesion Type.

	N	Mean±SD absolute BL BCVA	Mean (95% CI) W48 change from BL	Mean±SD absolute W48 BCVA
Baseline BCVA ≤58				
8q12	97	42.6±9.3	+10.2 (7.2, 13.2)	52.8±16.5
8q16	89	44.3±8.1	+7.1 (3.9, 10.3)	51.4±16.5
2q8	106	41.4±9.2	+11.1 (8.2, 14.0)	52.4±16.9
Baseline BCVA 59–73				
8q12	196	65.0±5.7	+5.1 (3.4, 6.9)	70.1±13.0
8q16	191	64.3±5.3	+6.1 (4.7, 7.5)	70.4±10.4
2q8	181	64.7±5.1	+6.9 (5.3, 8.4)	71.6±11.5
Baseline BCVA ≥74				
8q12	42	75.6±1.5	+1.5 (−1.8, 3.7)	77.4±10.4
8q16	48	75.6±1.5	+2.9 (0.8, 4.9)	78.5±7.6
2q8	49	75.6±1.5	+2.3 (0.2, 4.4)	77.9±7.9
Baseline CRT <400 µm				
8q12	228	60.4±11.6	+4.6 (3.1, 6.2)	68.1±15.5
8q16	225	63.4±10.9	+6.3 (4.9, 7.6)	69.7±12.9
2q8	231	62.9±11.6	+6.2 (4.8, 7.7)	69.2±15.1
Baseline CRT ≥400 µm				
8q12	197	52.2±12.7	+9.4 (6.4, 12.3)	61.6±17.3
8q16	110	55.0±10.4	+5.2 (2.5, 8.0)	58.1±17.9
2q8	104	49.9±14.7	+10.3 (7.7, 12.9)	60.2±16.7
Minimally classic CNV				
8q12	56	57.8±12.9	+2.6 (−2.2, 7.4)	60.5±20.3
8q16	69	58.3±11.7	+5.9 (2.5, 9.4)	62.2±15.9
2q8	61	54.4±13.7	+6.4 (2.6, 10.2)	60.8±17.0
Occult only CNV				
8q12	197	61.9±12.5	+5.3 (3.8, 6.9)	68.5±15.2
8q16	186	63.7±11.5	+5.1 (3.7, 6.5)	68.8±14.1
2q8	192	63.6±11.8	+7.2 (5.7, 8.6)	70.8±13.7
Predominantly classic CNV				
8q12	73	53.5±12.8	+10.4 (7.2, 13.6)	63.9±15.8
8q16	67	53.8±12.5	+6.6 (3.1, 10.1)	60.2±18.4
2q8	73	50.9±15.0	+9.2 (5.9, 12.5)	60.1±17.9

BCVA, best corrected visual acuity; BL, baseline; CNV, choroidal neovascularization; CRT, central subfield retinal thickness; Wk, week.

[000675]The safety of high-dose (HD) aflibercept was similar to EYLEA and consistent with the safety profile of EYLEA. There were no new safety signals for high-dose aflibercept and EYLEA, and no cases of retinal vasculitis, occlusive retinitis or endophthalmitis. Comparing pooled data for the 12- and 16-week high-dose aflibercept groups to the EYLEA groups, the following rates were observed:

- Serious ocular adverse events (AE): 1.6% versus 0.6% in PULSAR
- Intraocular inflammation: 0.7% versus 0.6% in PULSAR
- Patients meeting intraocular pressure criteria: 1.3% versus 2.1% in PULSAR
- Serious non-ocular AEs: 9.8% versus 13.7% in PULSAR

Results at Week 60

[000676]There were 1395 enrolled participants at 251 sites in 27 countries countries/regions (Europe, North America, Latin America, Australia, and Asia Pacific), of whom 383 participants did not complete screening; one participant was randomized in error although he/she did not complete screening and had withdrawn consent. Therefore, this participant was not considered

as randomized in the Week 48 datasets and thus 1011 participants at 223 sites were randomized.

[000677] *Disposition of Subjects.* With the exception of 2 participants who did not receive any study treatment, all other randomized participants were included in the FAS and the SAF (N=1009). Of these, 937 participants completed study treatment phase through Week 48 and 925 participants through Week 60. At the time of the last participant last Week 48 and last Week 60 visits, 66 and 80 participants, respectively, did not complete study treatment, with no notable differences between the treatment groups with regard to the reasons for premature discontinuation. For 6 and 4 participants it was unknown as to whether they had completed study treatment through Week 48 and Week 60, respectively. See Table 2-16.

Table 2-16. Disposition in overall study: Week 48 and Week 60 (all enrolled participants)

Number of subjects	2q8	HDq12	HDq16	All HD	Total
Week **48**					
Enrolled, n					1395
Randomized, n (%)	337 (100%)	336 (100%)	338 (100%)	674 (100%)	1011 (100%)
Treated, n (%)	336 (99.7%)	335 (99.7%)	338 (100%)	673 (99.9%)	1009 (99.8%)
Completed study until Week 48, n (%)	309 (91.7%)	316 (94.0%)	312 (92.3%)	628 (93.2%)	937 (92.7%)
Unknown if completed study until Week 48[a], n (%)	3 (0.9%)	2 (0.6%)	1 (0.3%)	3 (0.4%)	6 (0.6%)
Did not complete study until Week 48, n (%)	25 (7.4%)	18 (5.4%)	25 (7.4%)	43 (6.4%)	68 (6.7%)
Primary reason[b]					
Adverse event	5 (1.5%)	1 (0.3%)	5 (1.5%)	6 (0.9%)	11 (1.1%)
Physician decision	1 (0.3%)	3 (0.9%)	2 (0.6%)	5 (0.7%)	6 (0.6%)
Non-compliance with study treatment	0	0	0	0	0
Pregnancy	0	0	0	0	0
Protocol deviation	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.2%)
Lost to follow-up	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Study terminated by sponsor	0	0	0	0	0
Lack of efficacy	2 (0.6%)	0	0	0	2 (0.2%)
Technical problems	0	0	0	0	0
Logistical problems	0	0	0	0	0
Withdrawal by subject	5 (1.5%)	5 (1.5%)	12 (3.6%)	17 (2.5%)	22 (2.2%)
Wish for pregnancy	0	0	0	0	0
Death	5 (1.5%)	3 (0.9%)	1 (0.3%)	4 (0.6%)	9 (0.9%)
Other	4 (1.2%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	8 (0.8%)
COVID-19 pandemic	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	6 (0.6%)
Subject decision: COVID-19 pandemic related	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	6 (0.6%)
Physician decision: COVID-19 pandemic related	0	0	0	0	0
Logistical reason: COVID-19 pandemic related	0	0	0	0	0
Other: COVID-19 pandemic related	0	0	0	0	0
Week **60**					
Enrolled, n					1395
Randomized, n (%)	337 (100%)	336 (100%)	338 (100%)	674 (100%)	1011 (100%)
Treated, n (%)	336 (99.7%)	335 (99.7%)	338 (100%)	673 (99.9%)	1009 (99.8%)
Completed study until Week 60, n (%)	305 (90.5%)	310 (92.3%)	308 (91.1%)	618 (91.7%)	923 (91.3%)
Unknown if completed study until Week 60[c], n (%)	3 (0.9%)	3 (0.9%)	1 (0.3%)	4 (0.6%)	7 (0.7%)
Did not complete study until Week 60, n (%)	29 (8.6%)	23 (6.8%)	29 (8.6%)	52 (7.7%)	81 (8.0%)
Primary reason[d]					

Adverse event	6 (1.8%)	2 (0.6%)	5 (1.5%)	7 (1.0%)	13 (1.3%)
Physician decision	1 (0.3%)	4 (1.2%)	1 (0.3%)	5 (0.7%)	6 (0.6%)
Non-compliance with study treatment	0	0	0	0	0
Pregnancy	0	0	0	0	0
Protocol deviation	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.2%)
Lost to follow-up	1 (0.3%)	1 (0.3%)	2 (0.6%)	3 (0.4%)	4 (0.4%)
Study terminated by sponsor	0	0	0	0	0
Lack of efficacy	2 (0.6%)	0	0	0	2 (0.2%)
Technical problems	0	0	0	0	0
Logistical problems	0	0	0	0	0
Withdrawal by subject	6 (1.8%)	8 (2.4%)	14 (4.1%)	22 (3.3%)	28 (2.8%)
Wish for pregnancy	0	0	0	0	0
Death	5 (1.5%)	3 (0.9%)	2 (0.6%)	5 (0.7%)	10 (1.0%)
Other	6 (1.8%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	10 (1.0%)
COVID-19 pandemic	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	6 (0.6%)
Subject decision: COVID-19 pandemic related	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (0.6%)	6 (0.6%)
Physician decision: COVID-19 pandemic related	0	0	0	0	0
Number of subjects	**2q8**	**HDq12**	**HDq16**	**All HD**	**Total**
Logistical reason: COVID-19 pandemic related	0	0	0	0	0
Other: COVID-19 pandemic related	0	0	0	0	0

COVID-19 = Coronavirus Disease 2019.
a 6 participants who had missing Week 48 information (*i.e.* they neither discontinued during Week 48 time frame, nor had Week 48 visit performed or marked as not done) were summarized as Unknown if completed study until Week 48.
b For some participants the reason for premature discontinuation of study was inconsistently reported.
c 7 participants who had missing Week 60 information (*i.e.*, they neither discontinued during Week 60 time frame, nor had Week 60 visit performed or marked as not done) were summarized as Unknown if completed study until Week 60.
d For some participants the reason for premature discontinuation of study was inconsistently reported.
Definition of completed study until Week 60 = did not answer NO to the question “Did the subject complete the study?” on the “End of study” form prior to Week 60 visit.
Number of subjects enrolled is the number of subjects who signed informed consent.

[000678]*Protocol Deviations.* The frequency of participants with important protocol deviations through Week 60 was similar across the treatment groups (Table 2-17).

[000679]Overall, 355 (35.1%) participants reported important protocol deviations. The most frequent (≥ 5%) important protocol deviations were related to the categories “procedure deviations”, “treatment deviations”, “time schedule deviations” and “informed consent”.

[000680]Among the total of 59 participants with important protocol deviations related to informed consent, there were 57 screen failure participants who did not provide sufficient authorization for use of their data but were included in the database. These deviations and those regarding the 4 randomized and treated participants with similar deviations who were excluded from the database as well as the preventive and corrective actions taken because of that are described in more detail in a Note to File.

[000681]The most frequent important deviation of the category "inclusion/exclusion criteria not met but subject entered treatment" was related to Exclusion criterion 4 (participant had uncontrolled blood pressure [defined as systolic > 160 mmHg or diastolic > 95 mmHg]), which was reported for 20 (2.0%) participants. All other important protocol deviations for this category were reported for 1 or 2 participants.

[000682]Of note, 3 additional protocol deviations in 3 participants who met exclusion criteria were reported late and were thus not part of the Week 48 database and not included in the analyses for Week 48. Two of these additional protocol deviations were judged as being important, and one of them should have resulted in exclusion of the participant from the PPS for the Week 48 analysis. This participant met the exclusion criterion "Subject has subretinal hemorrhage that is at least 50% of the total lesion area, or if the blood under the fovea is 1 or more disc areas in size in the study eye" and was excluded from the Week 60 PPS analysis. Therefore, the PPS in the Week 48 database, which was used for supplemental analyses of the primary and key secondary efficacy endpoints (Change from baseline in BCVA at Week 48 and Proportion of subjects with no IRF and no SRF in central subfield at Week 16, respectively) included a total of 970 (95.9%) participants, whereas the PPS in the Week 60 database, which was used for a supplemental analysis of the key secondary endpoint at Week 60 (Change from baseline in BCVA at Week 60) included a total of 969 (95.8%) participants. The other deviation considered to be important but not included in the Week 48 database was deleted as it was entered by mistake. The third protocol deviation, judged not important, was still not included in the Week 60 database and analyses. This third participant was included in the Week 48 and Week 60 PPS; the deviation, judged non- important, would not have affected inclusion in the PPS.

[000683]In addition, there were 5 protocol deviations related to "time schedule deviations" for missing Visit 15, which were not included in the Week 48 database. Four of these protocol deviations were resolved or included in the Week 60 database and analyses, whereas the remaining 1 protocol deviation was still queried at the site and thus not included in the Week 60 database.

Table 2-17. Number of participants with important protocol deviations through Week 60 (all randomized participants)

Protocol Deviation category	2q8 N = 337 (100%)	HDq12 N = 336 (100%)	HDq16 N = 338 (100%)	All HD N = 674 (100%)	Total N = 1011 (100%)
Excluded concomitant medication treatment	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)	3 (0.3%)
Subject received any standard or investigational agents for treatment of their nAMD in the study eye other than IVT	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)	3 (0.3%)

aflibercept as specified in this protocol					
Inclusion/exclusion criteria not met but subject entered treatment [a]	8 (2.4%)	9 (2.7%)	11 (3.3%)	20 (3.0%)	28 (2.8%)
Exclusion Criteria: Subject has subretinal hemorrhage that is at least 50% of the total lesion area. or if the blood under the fovea is 1 or more disc areas in size in the study eye [b]	0	1 (0.3%)	0	1 (0.1%)	1 (0.1%)
Exclusion Criteria: Subject has a history or clinical evidence of diabetic retinopathy. diabetic macular edema. or any retinal vascular disease other than nAMD in either eye.	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Exclusion Criteria: Subject has known cardiac arrhythmia. based on medical history and/or outcome of ECG at screening. (Dense PK Substudy)	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)
Exclusion Criteria: Subject has uncontrolled blood pressure (defined as systolic >160 mmHg or diastolic >95 mmHg).	5 (1.5%)	6 (1.8%)	9 (2.7%)	15 (2.2%)	20 (2.0%)
Inclusion Criteria: Subject does not have BCVA ETDRS letter score of 78 to 24 at Baseline (corresponding to a Snellen equivalent of approximately 20/32 to 20/320) in the study eye (Left Eye).	1 (0.3%)	0	0	0	1 (0.1%)
Inclusion Criteria: Subject does not have BCVA ETDRS letter score of 78 to 24 at Baseline (corresponding to a Snellen equivalent of approximately 20/32 to 20/320) in the study eye (Right Eye).	0	0	1 (0.3%)	1 (0.1%)	1 (0.1%)
Inclusion Criteria: The patient does not have evidence of IRF and/or SRF affecting the central subfield of the study eye on OCT	0	0	1 (0.3%)	1 (0.1%)	1 (0.1%)
Informed consent	22 (6.5%)	20 (6.0%)	17 (5.0%)	37 (5.5%)	59 (5.8%)
Informed consent process not followed properly	0	0	1 (0.3%)	1 (0.1%)	1 (0.1%)
The Informed Consent is incomplete. The subject's signature/sign date are missing or partially signed or incorrect etc.	21 (6.2%)	20 (6.0%)	16 (4.7%)	36 (5.3%)	57 (5.6%)
The subject signed the ICF after starting his/her participation on the study (The ICF date is after the assessment date).	1 (0.3%)	0	0	0	1 (0.1%)
Other protocol deviations [c]	13 (3.9%)	14 (4.2%)	11 (3.3%)	25 (3.7%)	38 (3.8%)
Procedure deviations [c]	38 (11.3%)	55 (16.4%)	48 (14.2%)	103 (15.3%)	141 (13.9%)
Time schedule deviations [c, d]	23 (6.8%)	20 (6.0%)	29 (8.6%)	49 (7.3%)	72 (7.1%)
Treatment deviations	44 (13.1%)	20 (6.0%)	25 (7.4%)	45 (6.7%)	89 (8.8%)
Expired study drug administered to patient	8 (2.4%)	0	0	0	8 (0.8%)
Incorrect study drug kit administered to patient	0	1 (0.3%)	4 (1.2%)	5 (0.7%)	5 (0.5%)
Patient was randomized to the wrong stratum	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	2 (0.2%)

Protocol deviation category	**2q8** N = 337 (100%)	**HDq12** N = 336 (100%)	**HDq16** N = 338 (100%)	**All HD** N = 674 (100%)	**Total** N = 1011 (100%)
Study drug not administrated for reason other than documented medical issue.	16 (4.7%)	6 (1.8%)	3 (0.9%)	9 (1.3%)	25 (2.5%)
Received wrong dose treatment (high dose (5.6%)	19	12 (3.6%)	13 (3.8%)	25 (3.7%)	44 (4.4%)

instead of low dose or vice versa; sham injection instead of active injection or vice versa)					
Regional Crisis Study drug not administered	2 (0.6%)	0	6 (1.8%)	6 (0.9%)	8 (0.8%)
Subject was given incorrect study treatment	0	1 (0.3%)	2 (0.6%)	3 (0.4%)	3 (0.3%)

BCVA = best corrected visual acuity, ECG = electrocardiogram, ETDRS = Early Treatment Diabetic Retinopathy Study, ICF = informed consent form, IRF = intraretinal fluid, nAMD = neovascular (wet) age-related macular degeneration, IVT = intravitreal, OCT = optical coherence tomography, PK = pharmacokinetics, PPS = per protocol set, SRF = subretinal fluid
Subjects could have more than one protocol deviation but are only counted once within each deviation category.
a A protocol deviation for 1 participant who was randomized and completed Day 1 assessments but did not receive study drug and was later found to meet Exclusion criterion 13 was not included in the Week 60 database.
b This protocol deviation, which was not included in the Week 48 analysis but was included in the Week 60 analysis, resulted in exclusion of the participant from the PPS.
c Subcategories are provided in source table.
d There was 1 protocol deviation related to "time schedule deviations" for missing Visit 15 related to the COVID-19 pandemic, which was not included in the analyses for Week 60

[000684]Mean treatment compliance through Week 60 was > 97% in each of the 3 treatment groups (Table 2-18).

Table 2-18. Compliance with study treatment: through Week 60 (safety analysis set)

	2q8 N = 336 (100%)	**HDq12** N = 335 (100%)	**HDq16** N = 338 (100%)	**All HD** N = 673 (100%)
Number of subjects receiving 100% planned injections within 60-week period				
Treatment compliance (%)				
n	336	335	337	672
Mean (SD)	97.24 (5.99)	97.60 (5.80)	97.93 (4.89)	97.77 (5.36)
Median	100.00	100.00	100.00	100.00
Min, Max	64.3,100	57.1,100	66.7,100	57.1,100
Compliance categories, n (%)				
> 90 to ≤ 100%	306 (91.1%)	308 (91.9%)	314 (92.9%)	622 (92.4%)
> 80 to ≤ 90%	15 (4.5%)	16 (4.8%)	15 (4.4%)	31 (4.6%)
≤ 80%	15 (4.5%)	11 (3.3%)	8 (2.4%)	19 (2.8%)

Max = maximum, Min = minimum, SD = standard deviation
Compliance = (Number of actual study interventions received during period before Week 60 or up to premature discontinuation)/ (Number of planned study interventions during period before Week 60 or up to premature discontinuation) x 100
See Figure 70

[000685] *Visual Outcomes.* The primary analysis of the change from baseline in BCVA resulted in LS_{mean} changes from baseline to Week 48 (*i.e.*, estimated, adjusted mean changes) of 7.03, 6.06 and 5.89 letters for the 2q8, HDq12 and HDq16 groups, respectively (Table 2-19).

[000686]The estimated difference in LS_{means} changes from baseline to Week 48 in BCVA (with corresponding 95% CI) of HDq12 vs. 2q8 was -0.97 (-2.87, 0.92) letters and of HDq16 vs. 2q8 was -1.14 (-2.97, 0.69) letters (Table 2-19). The p-values for the non-inferiority test at a margin

of 4 letters were 0.0009 for HDq12 vs. 2q8, and 0.0011 for HDq16 vs. 2q8; p-values for a superiority test were 0.8437 for HDq12 vs. 2q8 and of 0.8884 for HDq16 vs. 2q8.

[000687] The arithmetic mean (SD) changes from baseline in BCVA to Week 48 (*i.e.*, observed, unadjusted mean changes) were 7.6 (12.2), 6.7 (12.6), and 6.2 (11.7) letters for the 285, 299, and 289 participants with Week 48 data, *i.e.*, excluding data after an ICE as handled by the hypothetical strategy, in the 2q8, HDq12, and HDq16 groups, respectively (Table 2-19).

[000688] The analysis of the key secondary efficacy variable (Change from baseline in BCVA measured by the ETDRS letter score at Week 60) resulted in LS_{mean} changes from baseline to Week 60 (*i.e.*, estimated, adjusted mean changes) of 7.23, 6.37 and 6.31 letters for the 2q8, HDq12 and HDq16 groups, respectively (Table 2-19).

[000689] The estimated difference in LS_{means} changes from baseline to Week 60 in BCVA (with corresponding 95% CI) of HDq12 vs. 2q8 was -0.86 (-2.57, 0.84) letters and of HDq16 vs. 2q8 was -0.92 (-2.51, 0.66) letters (Table 2-19). The p-values for the non-inferiority test at a margin of 4 letters were 0.0002 for HDq12 vs. 2q8, and < 0.0001 for HDq16 vs. 2q8; p-values for a superiority test were 0.8393 for HDq12 vs. 2q8 and of 0.8731 for HDq16 vs. 2q8.

[000690] The arithmetic mean (SD) changes from baseline in BCVA to Week 60 (*i.e.*, observed, unadjusted mean changes) were 7.8 (12.6), 6.6 (13.6), and 6.6 (11.7) letters for the 268, 283, and 282 participants with Week 60 data, *i.e.*, excluding data after an ICE as handled by the hypothetical strategy, in the 2q8, HDq12, and HDq16 groups, respectively (Table 2-19).

Table 2-19. Change from baseline in BCVA measured by the ETDRS letter score at Week 48 and Week 60 in the study eye, MMRM (full analysis set) (see Table 2-5)

	2q8 N = 336	**HDq12** N = 335	**HDq16** N = 338
Week **48 (primary endpoint)**			
Baseline mean (a)	58.9	59.9	60.0
Number of subjects with Week 48 data	285	299	289
Arithmetic mean (SD) change from baseline (a)	7.6 (12.2)	6.7 (12.6)	6.2 (11.7)
LS mean (SE) change from baseline	7.03 (0.74)	6.06 (0.77)	5.89 (0.72)
DF	/	622.1	647.7
Contrast (b)	/	HDq12 - 2q8	HDq16 - 2q8
t-value	/	3.14	3.07
p-value of one-sided test for non-inferiority at a margin of 4 letters	/	0.0009	0.0011
Estimate for Contrast and two-sided 95% CI (c)	/	-0.97 (-2.87,0.92)	-1.14 (-2.97,0.69)
Week **60 (key secondary endpoint, according to EP-SAP)**			
Baseline mean (a)	58.9	59.9	60.0
Number of subjects with Week 60 data	268	283	282
Arithmetic mean (SD) change from baseline (a)	7.8 (12.6)	6.6 (13.6)	6.6 (11.7)
LS mean (SE) change from baseline	7.23 (0.68)	6.37 (0.74)	6.31 (0.66)
DF	/	896.3	928.7
Contrast (b)	/	HDq12 - 2q8	HDq16 - 2q8
t-value	/	3.61	3.81
p-value of one-sided test for non-inferiority at a	/	0.0002	<0.0001

margin of 4 letters			
Estimate for Contrast and two-sided 95% CI (c)	/	-0.86 (-2.57,0.84)	-0.92 (-2.51,0.66)

BCVA = best corrected visual acuity, CI = confidence interval, DF = degrees of freedom, ETDRS = Early Treatment Diabetic Retinopathy Study, LS = least squares, SAP = statistical analysis plan, SD = standard deviation, SE = standard error

[000691]A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification variables (geographic region [Japan vs. Rest of World]; baseline BCVA [< 60 vs. ≥ 60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit.

[000692]A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: unstructured (for Week 48) and Toeplitz with heterogeneity (for Week 60).

[000693]Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints.

(a) : Based on observed assessments.

(b) : The contrast also includes the interaction term for treatment x visit (at Week 48 or Week 60).

(c) : Estimate based on the MMRM model, was computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively, with two-sided 95% CIs.

[000694]Mean (SD) values in BCVA were similar among treatment groups in the FAS at baseline across all treatment groups. The observed mean (SD) changes from baseline in BCVA averaged over the period from Week 36 to Week 48 and from Week 48 to Week 60 were similar to those for the primary endpoint (Table 2-20). Similar mean changes from baseline averaged over the period from Week 36 to Week 48 and from Week 48 to Week 60 were also observed using LOCF in the FAS.

Table 2-20. Summary Statistics for Averaged BCVA from Week 36 to 48 and Week 48 to 60 in ETDRS Letter Score, OC Prior to ICE (Full Analysis Set)

		Averaged value for period				Change from baseline			
Treatment	Visit / Period	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
2q8 (N = 336)	Baseline	336	58.94 (14.02)	62.00	24.00, 78.00	/	/	/	/
	Average BCVA over the period from Week 36 to Week 48	299	66.88 (15.59)	72.25	10.50, 92.00	299	7.78 (11.42)	8.25	-44.75, 47.50
	Average BCVA over the period from Week 48 to Week 60	300	66.93 (15.60)	72.25	10.50, 92.00	300	7.88 (11.53)	8.25	-44.75, 47.50

HDq12 (N = 335)	Baseline	335	59.85 (13.37)	62.00	24.00, 78.00	/	/	/	/
	Average BCVA over the period from Week 36 to Week 48	313	66.87 (15.02)	71.50	13.25, 91.00	313	6.85 (11.58)	6.25	-58.75, 46.25
	Average BCVA over the period from Week 48 to Week 60	313	66.87 (15.02)	71.50	13.25, 91.00	313	6.85 (11.58)	6.25	-58.75, 46.25
HDq16 (N = 338)	Baseline	338	60.04 (12.38)	61.00	24.00, 78.00	/	/	/	/
	Average BCVA over the period from Week 36 to Week 48	308	66.21 (14.85)	69.75	6.75, 94.00	308	6.21 (11.14)	6.75	-43.25, 39.50
	Average BCVA over the period from Week 48 to Week 60	308	66.20 (14.85)	69.75	6.75, 94.00	308	6.20 (11.15)	6.75	-43.25, 39.50

BCVA = best corrected visual acuity, ETDRS = Early Treatment Diabetic Retinopathy Study, Max = maximum, Min = minimum, SAP = statistical analysis plan, SD = standard deviation
OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded.
Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints.

[000695]Overall, the proportions of participants gaining or losing at least 5 or 10 letters in BCVA from baseline at Week 48 were similar across the treatment groups, with minor numerical differences in favor of the 2q8 group, as can be seen from Table 2-21. This is consistent with the primary endpoint data, which showed that the overall changes in BCVA through Week 48 and Week 60 in the HDq12 and HDq16 groups were non-inferior to that in the 2q8 group.

[000696]The proportion of participants gaining at least 10 letters or at least 5 letters in BCVA from baseline at Week 48 were numerically higher in the 2q8 group than in the HDq12 and HDq16 treatment groups, based on LOCF in the FAS. In contrast, the proportion of participants who showed any gain (> 0 letters) in BCVA from baseline was similar in the HDq16 and 2q8 groups and lower in the HDq12 group. Similar results for the proportions of participants gaining at least 10 letters, at least 5 letters, or any gain (> 0 letters) in BCVA from baseline were observed at Week 60.

[000697]The numerical differences in the proportion of participants who lost at least 5 or 10 letters across the treatment groups were generally small, with the lowest proportions observed in the 2q8 group at Week 48 as well as at Week 60.

[000698]The results of the analysis for the same endpoint using OC prior to ICE at Week 48 and at Week 60 were in line with those based on LOCF in the FAS.

Table 2-21. Proportion of Participants who Gained or Lost at Least 5, 10 or 15 Letters in BCVA from Baseline at Week 48 and Week 60, LOCF (Full Analysis Set)

		Subjects with response category, Num/Den (%)	
Response category	Treatment	Week **48**	Week **60**
Gained ≥ 15 letters	2q8 (N = 336)	74/335 (22.1%)	78/335 (23.3%)
	HDq12 (N = 335)	69/334 (20.7%)	79/334 (23.7%)
	HDq16 (N = 338)	73/337 (21.7%)	78/337 (23.1%)

Gained ≥ 10 letters	2q8 (N = 336)	142/335 (42.4%)	143/335 (42.7%)
	HDq12 (N = 335)	130/334 (38.9%)	137/334 (41.0%)
	HDq16 (N = 338)	130/337 (38.6%)	126/337 (37.4%)
Gained ≥ 5 letters	2q8 (N = 336)	213/335 (63.6%)	216/335 (64.5%)
	HDq12 (N = 335)	186/334 (55.7%)	191/334 (57.2%)
	HDq16 (N = 338)	196/337 (58.2%)	204/337 (60.5%)
Gained > 0 letters (any gain)	2q8 (N = 336)	255/335 (76.1%)	266/335 (79.4%)
	HDq12 (N = 335)	240/334 (71.9%)	233/334 (69.8%)
	HDq16 (N = 338)	258/337 (76.6%)	253/337 (75.1%)
Lost ≥ 5 letters	2q8 (N = 336)	37/335 (11.0%)	35/335 (10.4%)
	HDq12 (N = 335)	44/334 (13.2%)	45/334 (13.5%)
	HDq16 (N = 338)	48/337 (14.2%)	50/337 (14.8%)
Lost ≥ 10 letters	2q8 (N = 336)	21/335 (6.3%)	26/335 (7.8%)
	HDq12 (N = 335)	27/334 (8.1%)	30/334 (9.0%)
	HDq16 (N = 338)	31/337 (9.2%)	30/337 (8.9%)
Lost ≥ 15 letters	2q8 (N = 336)	14/335 (4.2%)	14/335 (4.2%)
	HDq12 (N = 335)	18/334 (5.4%)	22/334 (6.6%)
	HDq16 (N = 338)	18/337 (5.3%)	17/337 (5.0%)

BCVA = best corrected visual acuity, Num/Den = numerator/denominator, SAP = statistical analysis plan; LOCF (last observation carried forward): last available observed value prior to ICE was used to impute missing data. Intercurrent events (ICE) were handled according to sensitivity estimand strategy for continuous endpoints.

[000699]The proportion of participants who lost at least 15 letters in BCVA from baseline was < 6.0% at Week 48 and < 7.0% at Week 60 in all 3 treatment groups, based on LOCF in the FAS, with only small numerical differences across the treatment groups.

[000700]The analysis of the same endpoint using OC prior to ICE in the FAS provided proportions of participants who lost at least 15 letters in BCVA from baseline at Week 48 of 4.2%, 4.3% and 4.8% in the 2q8, HDq12, and HDq16 group, respectively. Similar proportions of 4.1%, 6.0% and 4.3% in the 2q8, HDq12, and HDq16 group, respectively, were observed at Week 60. This was largely in line with the results based on LOCF in the FAS.

[000701]See Figure 71.

[000702]*BCVA≥69 ETDRS Letter Score.* The proportions of participants achieving an ETDRS letter score of at least 69 increased from values of 29.5% (2q8), 34.0% (HDq12), and 28.4% (HDq16) at baseline to values > 50% at Week 8 (2q8), Week 12 (HDq12), or Week 16 (HDq16) and remained > 50% with similar values in all 3 treatment groups at Week 48 (54.3% to 57.9%) and at Week 60 (54.6% to 58.2%).

[000703]*Retinal Fluid.* This key secondary efficacy endpoint, proportion of participants with no IRF and no SRF in central subfield at Week 16, describes the proportion of all participants with no IRF and no SRF in central subfield at Week 16 as assessed by the reading center.

[000704]As both HD groups and the 2 mg group were all treated identically with 3 initial monthly doses prior to Week 16, the pooled HDq12 and HDq16 were compared to the 2q8 group for this

endpoint. At Week 16, 63.3% of participants in the pooled HD groups had no retinal fluid (no IRF and no SRF) compared to 51.6% in the 2q8 treatment group. The difference (95% CI) between pooled HD groups vs. 2q8 treatment was 11.733% points (5.263%, 18.204%) superiority. The p-value of the 1-sided Cochran-Mantel-Haenszel test for superiority was 0.0002. See Table 2-22.

[000705]Of note, the observation that 3.6% of the participants in the 2q8 and the pooled HD groups, respectively, in the FAS had no IRF and no SRF in central subfield at screening with similar proportions at baseline, although Inclusion criterion 6 required the presence of IRF and/or SRF, can be explained by the fact that the eligibility criteria were assessed by the investigators at screening based on preliminary data, whereas the above observations of no retinal fluid (no IRF and no SRF) in some participants were based on updated reading center data. The reading center provided eligibility assessment for all participants based on imaging exams performed at screening, while the investigator confirmed eligibility based on imaging exams performed at randomization. The imaging exams performed at screening, baseline and every other visit subsequently underwent detailed grading by the reading center, independently from the eligibility check. Based on this detailed grading, a very small number of discrepancies were noted in the assessment of fluid in screening OCTs. These do not represent a protocol deviation since the initial eligibility check was positive in all cases.

[000706]This observation did not appear to have a major impact on the results: The analysis of this key secondary endpoint was repeated on the PPS as supplementary analysis, in which participants with no IRF and no SRF in central subfield at baseline were excluded, and the results were consistent with those obtained in the FAS.

[000707]At Week 16, 62.5% of participants in the pooled HD groups had no retinal fluid (no IRF and no SRF) compared to 50.3% in the 2q8 treatment group. The difference (95% CI) between the pooled HD groups and the 2q8 group, using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60), was 12.327% points (5.726%, 18.929%).

Table 2-22. Proportion of Participants with no IRF and no SRF in Central Subfield at Week 16, LOCF (Full Analysis Set)

	2q8 N = 336	**HDq12** N = 335	**HDq16** N = 338	**All HD** N = 673
Subjects who had no IRF and no SRF, Num/Den (%)	173/335 (51.6%)	205/333 (61.6%)	217/334 (65.0%)	422/667 (63.3%)
Contrast	/	/	/	All HD - 2q8
Difference (a) % (two-sided 95% CI)	/	/	/	11.733 (5.263, 18.204)
CMH test (b) p-value	/	/	/	0.0002

[000708]Summary statistics for the proportion of participants with no IRF and no SRF in central subfield at baseline, Week 16, Week 48, and Week 60, using LOCF for the FAS, are presented in Table 2-23. As can be seen from this table, the proportions of participants with no retinal fluid were > 50% at both Week 16 and Week 48 and numerically higher at Week 48 than at Week 16 in all 3 treatment groups and the pooled HD groups. At Week 60, the proportions of participants with no retinal fluid were > 70% and similar in all 3 treatment groups and the pooled HD groups.

Table 2-23. Summary Statistics for Proportion of Participants with No IRF and No SRF in Central Subfield by Visit through Week 60, LOCF (Full Analysis Set)

		2q8	HDq12	HDq16	All HD
		N = 336	N = 335	N = 338	N = 673
Visit	Fluid status	Num/Den(%)	Num/Den(%)	Num/Den(%)	Num/Den(%)
Baseline	Dry [a]	13/336 (3.9%)	8/335 (2.4%)	9/336 (2.7%)	17/671 (2.5%)
	Not dry [b]	323/336 (96.1%)	327/335 (97.6%)	327/336 (97.3%)	654/671 (97.5%)
	Missing or undetermined	0	0	2	2
Week 16	Dry [a]	173/335 (51.6%)	205/333 (61.6%)	217/334 (65.0%)	422/667 (63.3%)
	Not dry [b]	162/335 (48.4%)	128/333 (38.4%)	117/334 (35.0%)	245/667 (36.7%)
	Missing or undetermined	1	2	4	6
Week 48	Dry [a]	199/335 (59.4%)	236/332 (71.1%)	223/334 (66.8%)	459/666 (68.9%)
	Not dry [b]	136/335 (40.6%)	96/332 (28.9%)	111/334 (33.2%)	207/666 (31.1%)
	Missing or undetermined	1	3	4	7
Week 60	Dry [a]	249/334 (74.6%)	247/331 (74.6%)	242/335 (72.2%)	489/666 (73.4%)
	Not dry [b]	85/334 (25.4%)	84/331 (25.4%)	93/335 (27.8%)	177/666 (26.6%)
	Missing or undetermined	2	4	3	7

ICE = intercurrent events, IRF = intraretinal fluid, LOCF = last observation carried forward, Num/Den = numerator/denominator, SAP = statistical analysis plan, SRF = subretinal fluid
LOCF method for the last available observed value prior to ICE was carried forward to impute missing data.
Intercurrent events (ICE) were handled according to primary estimand strategy for binary endpoints
a Dry = defined as no IRF nor SRF detected
b Not dry = defined as IRF and/or SRF detected
See Figure 72

[000709]There were no clinically meaningful pairwise differences between the HD treatment groups and the 2q8 group in the median time to fluid-free retina (no IRF and no SRF), median time to IRF-free retina, or median time to SRF-free retina over 48 weeks in the FAS.
[000710]There were also no clinically meaningful pairwise differences between the HD treatment groups and the 2q8 group in the median time to fluid-free retina (no IRF and no SRF), median time to IRF-free retina, or median time to SRF-free retina over 60 weeks in the FAS.
[000711]There were no clinically meaningful pairwise differences between the HD treatment groups and the 2q8 group in the median time to sustained fluid-free retina (no IRF and no SRF), median time to IRF-free retina, or median time to SRF-free retina over 48 weeks in the FAS

[000712] There were also no clinically meaningful pairwise differences between the HD treatment groups and the 2q8 group in the median time to sustained fluid-free retina (no IRF and no SRF), median time to IRF-free retina, or median time to SRF-free retina over 60 weeks in the FAS.

[000713]The proportion of participants without subRPE fluid in central subfield at Week 48 using LOCF in the FAS increased to values > 90% in both HD treatment groups and 86.2% in the 2q8 group. At Week 60, the proportion of participants without subRPE fluid in central subfield increased to values > 90% in all treatment groups (Table 2-24).

[000714]The proportion of participants with both no subRPE fluid and no retinal fluid (no IRF and no SRF) in central subfield increased from approximately 2% in each treatment group at baseline to proportions > 60% in both HD treatment groups and of 54.6% in the 2q8 group at Week 48. At Week 60, the proportion of participants with both no subRPE fluid and no retinal fluid in central subfield increased further to values of approximately 69% to 71% in all treatment groups (Table 2-24).

Table 2-24. Proportion of Participants without Retinal Fluid and Subretinal Pigment Epithelium Fluid in Central Subfield by Visit, LOCF (Full Analysis Set)

		2q8 N = 336	HDq12 N = 335	HDq16 N = 338
Visit	Fluid status	Num/Den(%)	Num/Den(%)	Num/Den(%)
Baseline	No SubRPE fluid	237/335 (70.7%)	225/334 (67.4%)	236/336 (70.2%)
	Dry	7/335 (2.1%)	5/334 (1.5%)	6/336 (1.8%)
	Not dry (IRF and/or SRF)	230/335 (68.7%)	220/334 (65.9%)	230/336 (68.5%)
	Both IRF and SRF missing or undetermined	0/335	0/334	0/336
	SubRPE fluid present	98/335 (29.3%)	109/334 (32.6%)	100/336 (29.8%)
	Dry	6/335 (1.8%)	3/334 (0.9%)	3/336 (0.9%)
	Not dry (IRF and/or SRF)	92/335 (27.5%)	106/334 (31.7%)	97/336 (28.9%)
	Both IRF and SRF missing or undetermined	0/335	0/334	0/336
	SubRPE missing or undetermined	1	1	2
Week 48	No SubRPE fluid	281/326 (86.2%)	298/325 (91.7%)	308/330 (93.3%)
	Dry	178/326 (54.6%)	216/325 (66.5%)	207/330 (62.7%)
	Not dry (IRF and/or SRF)	103/326 (31.6%)	82/325 (25.2%)	100/330 (30.3%)
	Both IRF and SRF missing or undetermined	0/326	0/325	0/330
	SubRPE fluid present	45/326 (13.8%)	27/325 (8.3%)	22/330 (6.7%)
	Dry	17/326 (5.2%)	16/325 (4.9%)	14/330 (4.2%)
	Not dry (IRF and/or SRF)	28/326 (8.6%)	11/325 (3.4%)	8/330 (2.4%)
	Both IRF and SRF missing or undetermined	0/326	0/325	0/330
	SubRPE missing or undetermined	10	10	8
Week 60	No SubRPE fluid	296/326 (90.8%)	305/328 (93.0%)	309/331 (93.4%)
	Dry	226/326 (69.3%)	232/328 (70.7%)	228/331 (68.9%)
	Not dry (IRF and/or SRF)	70/326 (21.5%)	72/328 (22.0%)	81/331 (24.5%)
	Both IRF and SRF missing or undetermined	0/326	0/328	0/331
	SubRPE fluid present	30/326 (9.2%)	23/328 (7.0%)	22/331 (6.6%)
	Dry	18/326 (5.5%)	12/328 (3.7%)	13/331 (3.9%)

Not dry (IRF and/or SRF)	12/326 (3.7%)	11/328 (3.4%)	9/331 (2.7%)
Both IRF and SRF missing or undetermined	0/326	0/328	0/331
SubRPE missing or undetermined	10	7	7

IRF = Intraretinal fluid, LOCF = Last observation carried forward, Num/Den = numerator/denominator, SAP = statistical analysis plan, SRF = Subretinal fluid, subRPE = subretinal pigment epithelium fluid; LOCF: last available observed value prior to ICE was used to impute missing data. Intercurrent events (ICE) were handled according to primary estimand strategy for binary endpoints. Dry = defined as no IRF nor SRF in central subfield detected; Not dry = defined as IRF and/or SRF in central subfield detected.

[000715]Fluid Leakage. The proportion of participants without leakage on FA increased in all groups over time reaching values of > 40% in the HDq16 and the 2q8 groups and > 60% in the HDq12 group at Week 48. At Week 60, the proportion of participants without leakage on FA increased further, reaching values of > 50% in the HDq16 and the 2q8 groups and > 60% in the HDq12 group. The number of participants with an undetermined leakage status was generally small and similar across the treatment groups over time (Table 2-25).

[000716]The analysis for the same endpoint based on OC in the FAS provided results that were consistent with the results using LOCF.

Table 2-25. Proportion of Participants without Leakage on FA by Visit, LOCF (Full Analysis Set)

Visit	Leakage status	2q8 N = 336 Num/Den(%)	HDq12 N = 335 Num/Den(%)	HDq16 N = 338 Num/Den(%)
Baseline	No leakage	0/336	0/335	1/337 (0.3%)
	Any leakage	336/336 (100%)	335/335 (100%)	336/337 (99.7%)
	Undetermined	0	0	1
Week 12	No leakage	61/308 (19.8%)	70/305 (23.0%)	67/307 (21.8%)
	Any leakage	247/308 (80.2%)	235/305 (77.0%)	240/307 (78.2%)
	Undetermined	9	8	7
Week 48	No leakage	136/322 (42.2%)	193/319 (60.5%)	140/319 (43.9%)
	Any leakage	186/322 (57.8%)	126/319 (39.5%)	179/319 (56.1%)
	Undetermined	8	9	8
Week 60	No leakage	178/320 (55.6%)	195/318 (61.3%)	169/316 (53.5%)
	Any leakage	142/320 (44.4%)	123/318 (38.7%)	147/316 (46.5%)
	Undetermined	10	10	10

ICE = Intercurrent events, FA = fluorescein angiography, LOCF = Last observation carried forward, Num/Den = numerator/denominator, SAP = statistical analysis plan
LOCF: last available observed value prior to ICE was used to impute missing data.
ICE were handled according to primary estimand strategy for binary endpoints

[000717]*Choroidal Neovascularization.* Summary statistics for the CNV size at baseline, Week 12, Week 48, and Week 60 based on OC prior to ICE in the FAS, are presented in Table 2-26.

[000718]The mean (SD) CNV size at baseline ranged from 5.9768 (4.8306) mm^2 to 6.5459 (5.5315) mm^2 across the 3 treatment groups. Numerical mean and median decreases from baseline were observed in all 3 treatment groups at Week 12, Week 48, and Week 60. At Week

60, the mean (SD) decreases in CNV size from baseline were of similar extent in all 3 treatment groups ranging from -3.6610 (5.6624) mm² to -3.8795 (5.4295) mm².

Table 2-26. Summary Statistics for Choroidal Neovascularization Size (mm²) by Visit, OC prior to ICE (Full Analysis Set)

		Value at Visit				Change from Baseline			
Treatment	Visit	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
2q8 (N = 336)	Baseline	336	6.3593 (5.0394)	4.9970	0.148, 24.129	/	/	/	/
	Week 12	314	5.2107 (5.4069)	3.7455	0.000, 29.362	314	-1.1702 (3.4604)	-0.4930	-22.149, 11.671
	Week 48	280	4.1366 (5.5680)	1.6195	0.000, 27.675	280	-2.3934 (5.2421)	-1.3125	-24.129, 16.636
	Week 60	250	2.7613 (4.5855)	0.0000	0.000, 24.233	250	-3.8795 (5.4295)	-2.5440	-24.129, 12.664
HDq12 (N = 335)	Baseline	335	5.9768 (4.8306)	4.8990	0.115, 30.023	/	/	/	/
	Week 12	312	4.3936 (4.6561)	3.0690	0.000, 30.212	312	-1.4886 (3.6500)	-0.5530	-21.998, 11.890
	Week 48	287	2.4733 (4.6964)	0.0000	0.000, 27.034	287	-3.5530 (5.0074)	-2.5760	-21.998, 15.501
	Week 60	249	2.1483 (4.2820)	0.0000	0.000, 26.051	249	-3.8080 (4.9944)	-2.7740	-21.998, 12.783
HDq16 (N = 338)	Baseline	337	6.5459 (5.5315)	4.6980	0.000, 28.650	/	/	/	/
	Week 12	313	4.8923 (5.1756)	3.3660	0.000, 27.081	313	-1.5729 (4.2200)	-0.4950	-25.133, 16.628
	Week 48	279	3.5367 (5.1716)	0.7110	0.000, 28.936	279	-2.9790 (5.3189)	-1.4060	-25.354, 15.869
	Week 60	258	2.6576 (4.7255)	0.0000	0.000, 30.991	258	-3.6610 (5.6624)	-2.1700	-26.231, 16.769

Max = maximum, Min = minimum, SAP = statistical analysis plan, SD = standard deviation
OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded. Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints.

[000719] *Total Lesion Area.* Summary statistics for the total lesion area at baseline, Week 12, Week 48, and Week 60 based on OC prior to ICE in the FAS, are presented in Table 2-27. The mean (SD) total lesion area at baseline ranged from 6.3820 (5.0664) mm² to 6.8814 (5.6514) mm² across the 3 treatment groups.

[000720]Numerical mean and median decreases in total lesion area from baseline were observed in all 3 treatment groups from Week 12 to Week 60, except for a numerical mean increase in the 2q8 group at Week 48. At Week 60, the mean (SD) decreases in total lesion area from baseline were of similar extent in all 3 treatment groups ranging from -0.3095 (3.1708) mm² to -0.5199 (2.8399) mm².

Table 2-27. Summary Statistics for Total Lesion Area (mm^2) by Visit, OC prior to ICE (Full Analysis Set)

		Value at Visit				Change from Baseline			
Treatment	Visit	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
2q8 (N = 336)	Baseline	336	6.8647 (5.4145)	5.4120	0.148, 27.409	/	/	/	/
	Week 12	314	6.6722 (5.4651)	4.8480	0.271, 29.362	314	-0.2130 (2.4653)	-0.1510	-11.233, 13.520
	Week 48	281	7.2282 (6.1106)	5.5800	0.271, 35.332	281	0.1110 (3.5498)	-0.2690	-11.242, 24.641
	Week 60	250	6.8963 (5.7963)	5.1360	0.379, 30.953	250	-0.3095 (3.1708)	-0.3715	-11.494, 15.885
HDq12 (N = 335)	Baseline	335	6.3820 (5.0664)	5.0260	0.185, 30.023	/	/	/	/
	Week 12	312	5.8133 (4.7055)	4.9645	0.154, 30.212	312	-0.4475 (2.2635)	-0.2345	-8.654, 10.872
	Week 48	287	6.0700 (5.2298)	4.9800	0.110, 30.259	287	-0.3628 (2.8917)	-0.2550	-8.719, 13.190
	Week 60	249	5.8150 (5.2904)	4.4550	0.138, 31.583	249	-0.5199 (2.8399)	-0.3180	-11.011, 14.006
HDq16 (N = 338)	Baseline	336	6.8814 (5.6514)	5.0685	0.180, 28.650	/	/	/	/
	Week 12	312	6.3994 (5.2627)	5.0060	0.180, 27.081	312	-0.3923 (2.6320)	-0.1355	-11.856, 16.628
	Week 48	278	6.5391 (5.5705)	4.9190	0.137, 28.936	278	-0.2856 (3.1628)	-0.0460	-13.105, 15.869
	Week 60	257	6.2872 (5.6288)	4.5190	0.134, 34.294	257	-0.3530 (3.2158)	-0.1350	-12.755, 16.769

Max = maximum, Min = minimum, SAP = statistical analysis plan, SD = standard deviation
OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded.
Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints

[000721] *Central Retinal Thickness.* The mean and LS_{mean} decreases from baseline in CST over time, based on OC prior to ICE, were similar across all groups through Week 48 with generally minor numerical differences between the treatment groups that were not considered clinically meaningful. The mean (SD) decreases from baseline were maintained through Week 60 where they reached values between -143.0 (120.9) µm in the 2q8 group and -153.4 (134.1) µm in the HDq16 group.

[000722] Mean changes from baseline in CST (µm) by visit through Week 60, based on OC prior to ICE in the FAS, are graphically displayed in post-hoc Figure 69(B); the LS_{mean} (95% CIs) changes from baseline in CST (µm) by visit through Week 48, based on MMRM in the FAS, are graphically displayed in post-hoc Figure 69(C).

[000723] *Patient-Reported Outcomes.* The mean NEI-VFQ-25 total score at baseline was similar across the 3 treatment groups, ranging from 76.36 to 77.81. The mean changes from baseline in NEI-VFQ-25 total score over time, based on OC prior to ICE, were all mean increases, which were numerically lower in the HD groups than in the 2q8 group at Week 24,

Week 48, and Week 60. The mean (SD) increases from baseline at Week 60, which ranged from 3.65 (12.08) in the HDq12 group to 5.10 (11.38) in the 2q8 group, were similar to those at Week 48 and the minor differences across the treatment groups were not clinically meaningful.

Results at week 96

[000724]Two-year PULSAR trial results for aflibercept 8 mg demonstrated durable vision gains at extended dosing intervals in wet age-related macular degeneration (See Tables below). The results demonstrate long term efficacy of aflibercept 8 mg with extended dosing intervals reaching up to 24 weeks and vision improvements comparable to Eylea (aflibercept 2 mg) at fixed 8-weekly dosing over two years. See Tables below for patient disposition at week 96. Patient and study eye baseline demographics/characteristics are summarized in Tables below. Through one and two years of treatment, aflibercept 8 mg has demonstrated durability in maintaining clinically meaningful outcomes for patients with retinal disease with extended dosing regimens, thus imposing less treatment burden on patients (See Tables below). Patients randomized at baseline to aflibercept 8 mg 16-week dosing regimen received a mean of 8.2 injections (4.6 fewer than Eylea (aflibercept 2 mg)) over two years (See Tables below). Specifically, 88% were on a ≥12-week dosing interval at the end of two years (See Tables below); 78% maintained ≥12-week dosing intervals throughout the two-year study period, compared to 83% throughout the one-year of study (48 weeks) (See Tables below); of those assigned to ≥16-week dosing regimen at baseline, 70% maintained ≥16-week dosing intervals throughout the two-year study period (See Tables below); at the end of two years, 78% were eligible for ≥16 week dosing, with 53% eligible for ≥20-dosing week intervals; and 71% met the extension criteria for even longer dosing intervals, including 47% for ≥20-week intervals and 28% for 24-week intervals (See Tables below).

[000725]In PULSAR, the safety of aflibercept 8 mg also continued to be similar to EYLEA through two years and remained consistent with the known safety profile of EYLEA from previous clinical trials for DME (See Tables below). There were no cases of retinal vasculitis, occlusive retinitis or endophthalmitis (See Tables below). The rate of intraocular inflammation was 1.3% for the aflibercept 8 mg group and 2.1% for the EYLEA group (See Tables below). Anti-platelet trialists' collaboration-defined arterial thromboembolic treatment-emergent adverse

events occurred in 1.8% of patients treated with aflibercept 8 mg and 3.3% of patients treated with EYLEA (See Tables below).

[000726]The retinal fluid status of patients in the trial cohorts is summarized in Tables below.

Table 2-28. Summary of Visual Gains through One and Two Years.

	Through 48 weeks (one year)				Through 96 weeks (two years)		
	EYLEA 8-week regimen	**aflibercept 8 mg 12-week regimen**	**aflibercept 8 mg 16-week regimen**		**EYLEA 8-week regimen**	**aflibercept 8 mg 12-week regimen**	**aflibercept 8 mg 16-week regimen**
Mean number of injections^	6.9	6.1	5.2		12.8	9.7	8.2
LS_{mean} (SE) change from baseline, letters	7.0 (0.74)	6.1 (0.77)	5.9 (0.72)		6.6 (0.73)	5.6 (0.77)	5.5 (0.75)
Difference in LS_{mean} (95% CI), letters		-0.97* (-2.87, 0.92)	-1.14† (-2.97, 0.69)			-1.01‡ (-2.82, 0.80)	-1.08§ (-2.87, 0.71)

LS: least squares; SE: standard error
^Based on patients completing week 48 or 96 in the trial
*Non-inferiority p-value: p=0.0009
†Non-inferiority p-value: p=0.0011
‡Nominal non-inferiority p-value: p=0.0006
§Nominal non-inferiority p-value: p=0.0007

Table 2-29. Baseline Demographics

	2q8	**HDq12**	**HDq16**	**Total**
N (FAS/SAF)	336	335	338	1009
Age (years (SD))	74.2 (8.8)	74.7 (7.9)	74.5 (8.5)	74.5 (8.4)
Women # (%)	188 (56.0%)	182 (54.3%)	180 (53.3%)	550 (54.5%)
Race # (%)				
Asian	83 (24.7%)	74 (22.1%)	77 (22.8%)	234 (23.2%)

Black or African American	2 (0.6%)	2 (0.6%)	0	4 (0.4%)
White	249 (74.1%)	256 (76.4%)	260 (76.9%)	765 (75.8%)
Not reported	2 (0.6%)	2 (0.6%)	1 (0.3%)	5 (0.5%)
Multiple	0	1 (0.3%)	0	1 (0.1%)
Hispanic or Latino	12 (3.6%)	7 (2.1%)	9 (2.7%)	28 (2.8%)

Table 2-30. Baseline Characteristics of the Study Eye

	2q8	**HDq12**	**HDq16**	**Total**
N (FAS/SAF)	336	335	338	1009
ETDRS BCVA (letters) Mean (SD)	58.9 (14.0)	59.9 (13.4)	60.0 (12.4)	59.6 (13.3)
Snellen Equivalent	20/63	20/63	20/63	20/63
20/40 or worse (<73 letters)	287 (85.4%)	293 (87.5%)	290 (85.8%)	870 (86.2%)
20/32 (73 to 78 letters)	49 (14.6%)	42 (12.5%)	48 (14.2%)	139 (13.8%)
CRT(microns) Mean (SD)	367.1 (133.6)	370.6 (123.8)	370.7 (132.7)	369.4 (130.0)
Total Lesion Area (mm^2)	6.9 (5.41)	6.4 (5.07)	6.9 (5.65)	6.7 (5.38)
Lesion Type				
Occult	192 (57.1%)	197 (58.8%)	186 (55.0%)	575 (57.0%)
Predominantly Classic	71 (21.1%)	71 (21.2%)	67 (19.8%)	209 (20.7%)

Minimally Classic	61 (18.2%)	56 (16.7%)	68 (20.1%)	185 (18.3%)

Table 2-30. Patient Disposition at Week 96

	2q8	HDq12	HDq16	Total
# Randomized	337	337	338	1012
# Treated	336	335	338	1009
# Completing Week 96	286 (84.9%)	291 (86.4%)	292 (86.4%)	869 (85.9%)
# Not completing treatment to Week 96	50 (14.8%)	44 (13.1%)	46 (13.6%)	140 (13.8%)
Main reasons for discontinuation				
Adverse event	9 (2.7%)	5 (1.5%)	8 (2.4%)	22 (2.2%)
Lost to follow-up	3 (0.9%)	3 (0.9%)	4 (1.2%)	10 (1.0%)
Withdrawal by subject	14 (4.2%)	20 (5.9%)	20 (5.9%)	54 (5.3%)
Death	10 (3.0%)	7 (2.1%)	7 (2.1%)	24 (2.4%)

Table 2-32. Mean Number of Injections: Week 96 Completers

	2q8	HDq12	HDq16
Mean number of injections	12.8 (out of 13)	9.7 (out of 10)	8.2 (out of 8)

SAF, W96 completers:2q8 n=224; HDq12 n=230; HDq16 n=235

Table 2-33. Exposure to Study Treatment: Through Week 96 (safety analysis set)

	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)
Total number of active injections, n	4007	3090	2621	5711
Total number of sham injections, n	2867	3899	4372	8271
Number of active injections, n (%)				
0	0	0	1 (0.3%)	1 (0.1%)

1	1 (0.3%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
2	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
3	4 (1.2%)	3 (0.9%)	9 (2.7%)	12 (1.8%)
4	6 (1.8%)	7 (2.1%)	10 (3.0%)	17 (2.5%)
5	5 (1.5%)	4 (1.2%)	7 (2.1%)	11 (1.6%)
6	9 (2.7%)	5 (1.5%)	9 (2.7%)	14 (2.1%)
7	2 (0.6%)	11 (3.3%)	116 (34.3%)	127 (18.9%)
8	6 (1.8%)	19 (5.7%)	117 (34.6%)	136 (20.2%)
9	1 (0.3%)	163 (48.7%)	20 (5.9%)	183 (27.2%)
10	13 (3.9%)	59 (17.6%)	9 (2.7%)	68 (10.1%)
11	10 (3.0%)	25 (7.5%)	12 (3.6%)	37 (5.5%)
12	37 (11.0%)	19 (5.7%)	14 (4.1%)	33 (4.9%)
13	240 (71.4%)	16 (4.8%)	11 (3.3%)	27 (4.0%)
14	1 (0.3%)	0	0	0

Duration (weeks) = [(date of last study treatment) - (date of first study treatment) +28]/7; 28 days were added because of the minimum 4 week dosing interval in the study. (a) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 92] prior to Week 96. (b) All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 92] prior to Week 96. (c) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q20 or longer interval between Week 48 and prior to Week 96. (d) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q24 or longer interval between Week 48 and prior to Week 96. (e) Based on dose regimen modification (DRM) criteria assessed at the last visit with active injection before Week 96 [i.e. including DRM criteria until Week 92]. (f) All subjects on q12 or q16 interval for whom it was not planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (g) All subjects on q12 or q16 interval for whom it was planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (h) This includes also subjects who extended again after shortening back to q16 prior to Week 96. (i) This includes subjects whose extension to q20 was at their last active dosing visit prior to Week 96 and hence it is unknown if they were maintained, extended or shortened after that visit. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. All HD: Pooled high dose aflibercept 8 mg administered every 12 weeks or every 16 weeks, after 3 initial injections at 4 week intervals

Table 2-34. Summary of Exposure to Study Treatment: Through Week 96 (safety analysis set)

	2q8 N = 336 (100%)	**HDq12 N = 335 (100%)**	**HDq16 N = 338 (100%)**	**All HD N = 673 (100%)**
Number of active injections				
n	336	335	338	673
Mean (SD)	11.9 (2.4)	9.2 (1.9)	7.8 (2.1)	8.5 (2.1)
Median	13.0	9.0	8.0	9.0
Q1, Q3	12.0, 13.0	9.0, 10.0	7.0, 8.0	7.0, 9.0
Min, Max	1, 14	1, 13	0, 13	0, 13

Duration (weeks) = [(date of last study treatment) - (date of first study treatment) +28]/7; 28 days were added because of the minimum 4 week dosing interval in the study. (a) All subjects on q12

or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 92] prior to Week 96. (b) All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 92] prior to Week 96. (c) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q20 or longer interval between Week 48 and prior to Week 96. (d) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q24 or longer interval between Week 48 and prior to Week 96. (e) Based on dose regimen modification (DRM) criteria assessed at the last visit with active injection before Week 96 [i.e. including DRM criteria until Week 92]. (f) All subjects on q12 or q16 interval for whom it was not planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (g) All subjects on q12 or q16 interval for whom it was planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (h) This includes also subjects who extended again after shortening back to q16 prior to Week 96. (i) This includes subjects whose extension to q20 was at their last active dosing visit prior to Week 96 and hence it is unknown if they were maintained, extended or shortened after that visit. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. All HD: Pooled high dose aflibercept 8 mg administered every 12 weeks or every 16 weeks, after 3 initial injections at 4 week intervals.

Table 2-35. Exposure to Study Treatment: Through Week 96 (safety analysis set)

	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)
Number of sham injections, n (%)				
0	9 (2.7%)	7 (2.1%)	8 (2.4%)	15 (2.2%)
1	5 (1.5%)	4 (1.2%)	3 (0.9%)	7 (1.0%)
2	9 (2.7%)	2 (0.6%)	8 (2.4%)	10 (1.5%)
3	4 (1.2%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
4	8 (2.4%)	3 (0.9%)	4 (1.2%)	7 (1.0%)
5	5 (1.5%)	5 (1.5%)	3 (0.9%)	8 (1.2%)
6	9 (2.7%)	4 (1.2%)	2 (0.6%)	6 (0.9%)
7	15 (4.5%)	6 (1.8%)	3 (0.9%)	9 (1.3%)
8	24 (7.1%)	6 (1.8%)	5 (1.5%)	11 (1.6%)
9	56 (16.7%)	10 (3.0%)	7 (2.1%)	17 (2.5%)
10	192 (57.1%)	26 (7.8%)	15 (4.4%)	41 (6.1%)
11	0	28 (8.4%)	19 (5.6%)	47 (7.0%)
12	0	39 (11.6%)	18 (5.3%)	57 (8.5%)
13	0	83 (24.8%)	23 (6.8%)	106 (15.8%)
14	0	109 (32.5%)	46 (13.6%)	155 (23.0%)
15	0	0	90 (26.6%)	90 (13.4%)
16	0	0	82 (24.3%)	82 (12.2%)

Duration (weeks) = [(date of last study treatment) - (date of first study treatment) +28]/7; 28 days were added because of the minimum 4 week dosing interval in the study. (a) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 92] prior to Week 96. (b) All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 92] prior to Week 96. (c) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q20 or longer interval between Week 48 and prior to Week 96. (d) All subjects on q12 or q16 interval for whom

it was not planned to have their interval shortened anytime and who extended to q24 or longer interval between Week 48 and prior to Week 96. (e) Based on dose regimen modification (DRM) criteria assessed at the last visit with active injection before Week 96 [i.e. including DRM criteria until Week 92]. (f) All subjects on q12 or q16 interval for whom it was not planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (g) All subjects on q12 or q16 interval for whom it was planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (h) This includes also subjects who extended again after shortening back to q16 prior to Week 96. (i) This includes subjects whose extension to q20 was at their last active dosing visit prior to Week 96 and hence it is unknown if they were maintained, extended or shortened after that visit. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. All HD: Pooled high dose aflibercept 8 mg administered every 12 weeks or every 16 weeks, after 3 initial injections at 4 week intervals.

Table 2-36. Exposure to Study Treatment: Through Week 96 (safety analysis set)

	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)
Number of sham injections				
n	336	335	338	673
Mean (SD)	8.5 (2.6)	11.6 (3.2)	12.9 (4.0)	12.3 (3.7)
Median	10.0	13.0	15.0	13.0
Q1, Q3	8.0, 10.0	11.0, 14.0	12.0, 15.0	11.0, 15.0
Min, Max	0, 10	0, 14	0, 16	0, 16
Total amount (mg)				
n	336	335	338	673
Mean (SD)	23.8595 (4.8442)	73.7346 (15.5355)	61.9942 (16.5289)	67.8382 (17.0727)
Median	26.0000	72.0090	64.0080	72.0090
Q1, Q3	24.0000, 26.0000	72.0090, 80.0100	56.0070, 64.0080	56.0070, 72.0090
Min, Max	2, 30.001	8.001, 104.013	0, 104.013	0, 104.013
Duration of treatment (weeks)				
n	336	335	338	673
Mean (SD)	88.91 (19.89)	90.09 (18.36)	89.18 (20.33)	89.63 (19.36)
Median	96.00	96.00	96.00	96.00
Q1, Q3	95.70, 96.30	95.70, 96.30	95.70, 96.30	95.70, 96.30
Min, Max	4, 102	4, 101.9	0, 106	0, 106

Duration (weeks) = [(date of last study treatment) - (date of first study treatment) +28]/7; 28 days were added because of the minimum 4 week dosing interval in the study. (a) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 92] prior to Week 96. (b) All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 92] prior to Week 96. (c) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q20 or longer

interval between Week 48 and prior to Week 96. (d) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q24 or longer interval between Week 48 and prior to Week 96. (e) Based on dose regimen modification (DRM) criteria assessed at the last visit with active injection before Week 96 [i.e. including DRM criteria until Week 92]. (f) All subjects on q12 or q16 interval for whom it was not planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (g) All subjects on q12 or q16 interval for whom it was planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (h) This includes also subjects who extended again after shortening back to q16 prior to Week 96. (i) This includes subjects whose extension to q20 was at their last active dosing visit prior to Week 96 and hence it is unknown if they were maintained, extended or shortened after that visit. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. All HD: Pooled high dose aflibercept 8 mg administered every 12 weeks or every 16 weeks, after 3 initial injections at 4 week intervals.

Table 2-37. Exposure to Study Treatment: Through Week 96 (safety analysis set)

	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)
Subjects maintained with q12 or longer dosing interval (a), n (%)		254 (75.8%)	280 (82.8%)	534 (79.3%)
Subjects maintained with q16 or longer dosing interval (b), n (%)			242 (71.6%)	
Subjects maintained and extended to q20 or longer dosing interval (c), n (%)		113 (33.7%)	150 (44.4%)	263 (39.1%)
Subjects maintained and extended to q24 dosing interval (d), n (%)		72 (21.5%)	90 (26.6%)	162 (24.1%)
Subjects with q12 or longer dosing interval as the last intended dosing interval (e), n (%)		289 (86.3%)	302 (89.3%)	591 (87.8%)
Subjects with q16 or longer dosing interval as the last intended dosing interval (e), n (%)		197 (58.8%)	266 (78.7%)	463 (68.8%)
Subjects with q20 or longer dosing interval as the last intended dosing interval (e), n (%)		121 (36.1%)	163 (48.2%)	284 (42.2%)
Subjects with q24 dosing interval as the last intended dosing interval (e), n (%)		72 (21.5%)	93 (27.5%)	165 (24.5%)

Duration (weeks) = [(date of last study treatment) - (date of first study treatment) +28]/7; 28 days were added because of the minimum 4 week dosing interval in the study. (a) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 92] prior to Week 96. (b) All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 92] prior to Week 96. (c) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q20 or longer interval between Week 48 and prior to Week 96. (d) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q24 or longer interval between Week 48 and prior to Week 96. (e) Based on dose regimen modification (DRM) criteria assessed at the last visit with active injection before Week 96 [i.e. including DRM criteria until Week 92]. (f) All subjects on q12 or q16 interval for whom it was not planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (g) All subjects on q12 or q16 interval for whom it was planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (h) This includes also subjects who extended again after shortening back to q16 prior to Week 96. (i) This includes subjects whose extension to q20

was at their last active dosing visit prior to Week 96 and hence it is unknown if they were maintained, extended or shortened after that visit. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. All HD: Pooled high dose aflibercept 8 mg administered every 12 weeks or every 16 weeks, after 3 initial injections at 4 week intervals.

Table 2-38. Exposure to Study Treatment: Through Week 96 (safety analysis set)

	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)
Subjects shortened to q8 dosing interval at week 16, n (%)		18 (5.4%)	11 (3.3%)	29 (4.3%)
Subjects shortened to q8 dosing interval at week 20, n (%)		27 (8.1%)	22 (6.5%)	49 (7.3%)
Subjects shortened anytime, n (%)		86 (25.7%)	99 (29.3%)	185 (27.5%)
Subjects shortened to q8 dosing interval anytime, n (%)		81 (24.2%)	58 (17.2%)	139 (20.7%)
Subjects shortened to q12 dosing interval anytime without shortening to q8, n (%)			38 (11.2%)	
Subjects never extended dosing interval (f), n (%)		107 (31.9%)	143 (42.3%)	250 (37.1%)
Subjects extended dosing interval anytime (g), n (%)		228 (68.1%)	195 (57.7%)	423 (62.9%)
Subjects extended to q20 dosing interval, n (%)		122 (36.4%)	166 (49.1%)	288 (42.8%)
Subjects extended to q20 dosing interval and shortened back to q16 (h), n (%)		1 (0.3%)	3 (0.9%)	4 (0.6%)
Subjects extended to q20 dosing interval and maintained at q20, n (%)		18 (5.4%)	47 (13.9%)	65 (9.7%)
Subjects extended to q20 dosing interval and extended to q24, n (%)		72 (21.5%)	93 (27.5%)	165 (24.5%)
Subjects extended to q20 dosing interval at their last visit (i), n (%)		31 (9.3%)	23 (6.8%)	54 (8.0%)

Duration (weeks) = [(date of last study treatment) - (date of first study treatment) +28]/7; 28 days were added because of the minimum 4 week dosing interval in the study. (a) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 92] prior to Week 96. (b) All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 92] prior to Week 96. (c) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q20 or longer interval between Week 48 and prior to Week 96. (d) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q24 or longer interval between Week 48 and prior to Week 96. (e) Based on dose regimen modification (DRM) criteria assessed at the last visit with active injection before Week 96 [i.e. including DRM criteria until Week 92]. (f) All subjects on q12 or q16 interval for whom it was not planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (g) All subjects on q12 or q16 interval for whom it was planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (h) This includes also subjects who extended again after shortening back to q16 prior to Week 96. (i) This includes subjects whose extension to q20 was at their last active dosing visit prior to Week 96 and hence it is unknown if they were maintained, extended or shortened after that visit. 2q8: Aflibercept 2 mg administered every 8

weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. All HD: Pooled high dose aflibercept 8 mg administered every 12 weeks or every 16 weeks, after 3 initial injections at 4 week intervals.

Table 2-39. Exposure to study treatment through Week 96 – Dosing intervals (safety analysis set, only participants considered as completers for Week 96)

	HDq12 N = 291 (100%)	HDq16 N = 292 (100%)	All HD N = 583 (100%)
Subjects maintained with q12 or longer dosing interval (a), n (%)	219 (75.3%)	238 (81.5%)	457 (78.4%)
Subjects maintained with q16 or longer dosing interval (b), n (%)		205 (70.2%)	
Subjects maintained and extended to q20 or longer dosing interval (c), n (%)	110 (37.8%)	142 (48.6%)	252 (43.2%)
Subjects maintained and extended to q24 dosing interval (d), n (%)	72 (24.7%)	87 (29.8%)	159 (27.3%)
Subjects with q12 or longer dosing interval as the last intended dosing interval (e), n (%)	252 (86.6%)	260 (89.0%)	512 (87.8%)
Subjects with q16 or longer dosing interval as the last intended dosing interval (e), n (%)	185 (63.6%)	229 (78.4%)	414 (71.0%)
Subjects with q20 or longer dosing interval as the last intended dosing interval (e), n (%)	118 (40.5%)	155 (53.1%)	273 (46.8%)
Subjects with q24 dosing interval as the last intended dosing interval (e), n (%)	72 (24.7%)	90 (30.8%)	162 (27.8%)
Subjects shortened to q8 dosing interval at week 16, n (%)	17 (5.8%)	10 (3.4%)	27 (4.6%)
Subjects shortened to q8 dosing interval at week 20, n (%)	23 (7.9%)	20 (6.8%)	43 (7.4%)
Subjects shortened anytime, n (%)	77 (26.5%)	90 (30.8%)	167 (28.6%)
Subjects shortened to q8 dosing interval anytime, n (%)	72 (24.7%)	54 (18.5%)	126 (21.6%)
Subjects shortened to q12 dosing interval anytime without shortening to q8, n (%)		33 (11.3%)	
Subjects never extended dosing interval (f), n (%)	77 (26.5%)	105 (36.0%)	182 (31.2%)
Subjects extended dosing interval anytime (g), n (%)	214 (73.5%)	187 (64.0%)	401 (68.8%)
Subjects extended to q20 dosing interval, n (%)	119 (40.9%)	158 (54.1%)	277 (47.5%)
Subjects extended to q20 dosing interval and shortened back to q16 (h), n (%)	1 (0.3%)	3 (1.0%)	4 (0.7%)
Subjects extended to q20 dosing interval and maintained at q20, n (%)	17 (5.8%)	46 (15.8%)	63 (10.8%)

Subjects extended to q20 dosing interval and extended to q24, n (%)	72 (24.7%)	90 (30.8%)	162 (27.8%)
Subjects extended to q20 dosing interval at their last visit (i), n (%)	29 (10.0%)	19 (6.5%)	48 (8.2%)
Subjects with q8 as the last completed interval, n (%)	39 (13.4%)	33 (11.3%)	72 (12.3%)
Subjects with q12 as the last completed interval, n (%)	77 (26.5%)	29 (9.9%)	106 (18.2%)
Subjects with q16 as the last completed interval, n (%)	85 (29.2%)	89 (30.5%)	174 (29.8%)
Subjects with q20 as the last completed interval, n (%)	90 (30.9%)	141 (48.3%)	231 (39.6%)

DRM = dose regimen modification

a All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval (according to DRM criteria until Week 92) prior to Week 96.

b All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval (according to DRM criteria until Week 92) prior to Week 96.

c All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q20 or longer interval between Week 48 and prior to Week 96.

d All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q24 or longer interval between Week 48 and prior to Week 96.

e Based on DRM criteria assessed at the last visit with active injection before Week 96 (i.e. including DRM criteria until Week 92).

f All subjects on q12 or q16 interval for whom it was not planned to have their interval extended (according to DRM criteria until Week 92) prior to Week 96.

g All subjects on q12 or q16 interval for whom it was planned to have their interval extended (according to DRM criteria until Week 92) prior to Week 96.

h This includes also subjects who extended again after shortening back to q16 prior to Week 96.

i This includes subjects whose extension to q20 was at their last active dosing visit prior to Week 96 and hence it is unknown if they were maintained, extended or shortened after that visit.

Table 2-40. Exposure to Study Treatment: Through Week 96 (safety analysis set, Week 96 completers)

	2q8 N = 286 (100%)	**HDq12 N = 291 (100%)**	**HDq16 N = 292 (100%)**	**All HD N = 583 (100%)**
Total number of active injections, n	3653	2830	2404	5234
Total number of sham injections, n	2686	3665	4142	7807
Number of active injections, n (%)				
6	0	0	4 (1.4%)	4 (0.7%)
7	1 (0.3%)	0	108 (37.0%)	108 (18.5%)
8	0	16 (5.5%)	115 (39.4%)	131 (22.5%)

9	0	158 (54.3%)	19 (6.5%)	177 (30.4%)
10	4 (1.4%)	58 (19.9%)	9 (3.1%)	67 (11.5%)
11	6 (2.1%)	24 (8.2%)	12 (4.1%)	36 (6.2%)
12	36 (12.6%)	19 (6.5%)	14 (4.8%)	33 (5.7%)
13	238 (83.2%)	16 (5.5%)	11 (3.8%)	27 (4.6%)
14	1 (0.3%)	0	0	0

Duration (weeks) = [(date of last study treatment) - (date of first study treatment) +28]/7; 28 days were added because of the minimum 4 week dosing interval in the study. (a) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 92] prior to Week 96. (b) All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 92] prior to Week 96. (c) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q20 or longer interval between Week 48 and prior to Week 96. (d) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q24 or longer interval between Week 48 and prior to Week 96. (e) Based on dose regimen modification (DRM) criteria assessed at the last visit with active injection before Week 96 [i.e. including DRM criteria until Week 92]. (f) All subjects on q12 or q16 interval for whom it was not planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (g) All subjects on q12 or q16 interval for whom it was planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (h) This includes also subjects who extended again after shortening back to q16 prior to Week 96. (i) This includes subjects whose extension to q20 was at their last active dosing visit prior to Week 96 and hence it is unknown if they were maintained, extended or shortened after that visit. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. All HD: Pooled high dose aflibercept 8 mg administered every 12 weeks or every 16 weeks, after 3 initial injections at 4 week intervals.

Table 2-41. Exposure to Study Treatment: Through Week 96 (safety analysis set, Week 96 completers)

	2q8 N = 286 (100%)	**HDq12 N = 291 (100%)**	**HDq16 N = 292 (100%)**	**All HD N = 583 (100%)**
Number of active injections				
n	286	291	292	583
Mean (SD)	12.8 (0.6)	9.7 (1.2)	8.2 (1.6)	9.0 (1.6)
Median	13.0	9.0	8.0	9.0
Q1, Q3	13.0,13.0	9.0, 10.0	7.0, 8.0	8.0, 10.0
Min, Max	7,14	8, 13	6, 13	6, 13

Duration (weeks) = [(date of last study treatment) - (date of first study treatment) +28]/7; 28 days were added because of the minimum 4 week dosing interval in the study. (a) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 92] prior to Week 96. (b) All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 92] prior to Week 96. (c) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q20 or longer interval between Week 48 and prior to Week 96. (d) All subjects on q12 or q16 interval for whom

it was not planned to have their interval shortened anytime and who extended to q24 or longer interval between Week 48 and prior to Week 96. (e) Based on dose regimen modification (DRM) criteria assessed at the last visit with active injection before Week 96 [i.e. including DRM criteria until Week 92]. (f) All subjects on q12 or q16 interval for whom it was not planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (g) All subjects on q12 or q16 interval for whom it was planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (h) This includes also subjects who extended again after shortening back to q16 prior to Week 96. (i) This includes subjects whose extension to q20 was at their last active dosing visit prior to Week 96 and hence it is unknown if they were maintained, extended or shortened after that visit. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. All HD: Pooled high dose aflibercept 8 mg administered every 12 weeks or every 16 weeks, after 3 initial injections at 4 week intervals.

Table 2-42. Exposure to Study Treatment: Through Week 96 (safety analysis set, Week 96 completers)

	2q8 N = 286 (100%)	HDq12 N = 291 (100%)	HDq16 N = 292 (100%)	All HD N = 583 (100%)
Number of sham injections, n (%)				
3	1 (0.3%)	0	0	0
4	3 (1.0%)	0	0	0
5	2 (0.7%)	0	0	0
6	4 (1.4%)	1 (0.3%)	0	1 (0.2%)
7	8 (2.8%)	1 (0.3%)	0	1 (0.2%)
8	23 (8.0%)	2 (0.7%)	3 (1.0%)	5 (0.9%)
9	53 (18.5%)	9 (3.1%)	4 (1.4%)	13 (2.2%)
10	192 (67.1%)	25 (8.6%)	15 (5.1%)	40 (6.9%)
11	0	27 (9.3%)	16 (5.5%)	43 (7.4%)
12	0	38 (13.1%)	16 (5.5%)	54 (9.3%)
13	0	80 (27.5%)	22 (7.5%)	102 (17.5%)
14	0	108 (37.1%)	44 (15.1%)	152 (26.1%)
15	0	0	90 (30.8%)	90 (15.4%)
16	0	0	82 (28.1%)	82 (14.1%)

Duration (weeks) = [(date of last study treatment) - (date of first study treatment) +28]/7; 28 days were added because of the minimum 4 week dosing interval in the study. (a) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 92] prior to Week 96. (b) All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 92] prior to Week 96. (c) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q20 or longer interval between Week 48 and prior to Week 96. (d) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q24 or longer interval between Week 48 and prior to Week 96. (e) Based on dose regimen modification (DRM) criteria assessed at the last visit with active injection before Week 96 [i.e. including DRM criteria until Week 92]. (f) All subjects on q12 or q16 interval for whom it was not planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (g) All subjects on q12 or q16 interval for whom it was planned to have their interval extended [according to DRM

criteria until Week 92] prior to Week 96. (h) This includes also subjects who extended again after shortening back to q16 prior to Week 96. (i) This includes subjects whose extension to q20 was at their last active dosing visit prior to Week 96 and hence it is unknown if they were maintained, extended or shortened after that visit. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. All HD: Pooled high dose aflibercept 8 mg administered every 12 weeks or every 16 weeks, after 3 initial injections at 4 week intervals.

Table 2-43. Exposure to Study Treatment: Through Week 96 (safety analysis set, Week 96 completers)

	2q8 N = 286 (100%)	HDq12 N = 291 (100%)	HDq16 N = 292 (100%)	All HD N = 583 (100%)
Number of sham injections				
n	286	291	292	583
Mean (SD)	9.4 (1.2)	12.6 (1.6)	14.2 (1.9)	13.4 (1.9)
Median	10.0	13.0	15.0	14.0
Q1, Q3	9.0, 10.0	12.0, 14.0	13.0, 16.0	12.0, 15.0
Min, Max	3, 10	6, 14	8, 16	6, 16
Total amount (mg)				
n	286	291	292	583
Mean (SD)	25.5552 (1.3193)	77.7427 (9.9875)	65.8350 (13.0053)	71.7786 (13.0300)
Median	26.0000	72.0090	64.0080	72.0090
Q1, Q3	26.0000, 26.0000	72.0090, 80.0100	56.0070, 64.0080	64.0080, 80.0100
Min, Max	14, 30.001	54.864, 104.013	48.006, 104.013	48.006, 104.013
Duration of treatment (weeks)				
n	286	291	292	583
Mean (SD)	96.01 (3.33)	96.12 (1.10)	96.18 (1.17)	96.15 (1.14)
Median	96.00	96.00	96.00	96.00
Q1, Q3	96.00, 96.40	95.90, 96.40	96.00, 96.40	96.00, 96.40
Min, Max	48.1, 102	88.4, 101.9	87.3, 106	87.3, 106

Duration (weeks) = [(date of last study treatment) - (date of first study treatment) +28]/7; 28 days were added because of the minimum 4 week dosing interval in the study. (a) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 92] prior to Week 96. (b) All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 92] prior to Week 96. (c) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q20 or longer interval between Week 48 and prior to Week 96. (d) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q24 or longer interval between Week 48 and prior to Week 96. (e) Based on dose regimen modification (DRM) criteria assessed at the last visit with active injection before Week 96 [i.e. including DRM criteria until Week 92]. (f) All subjects on q12 or q16 interval for whom it was not planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (g) All subjects on

q12 or q16 interval for whom it was planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (h) This includes also subjects who extended again after shortening back to q16 prior to Week 96. (i) This includes subjects whose extension to q20 was at their last active dosing visit prior to Week 96 and hence it is unknown if they were maintained, extended or shortened after that visit. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. All HD: Pooled high dose aflibercept 8 mg administered every 12 weeks or every 16 weeks, after 3 initial injections at 4 week intervals.

[000727]The results of the exploratory endpoints, proportions of participants with a q16 or longer treatment interval through Week 96 in the HDq16 group, with a q12 or longer interval through Week 96 in the HDq12 and HDq16 groups, and with a q12 or q16 or longer treatment interval as the last intended interval at Week 96 in the HDq12 and HDq16 groups, respectively, in the SAF (safety analysis set), are presented in Table 2-44 and 2-45.

[000728]In addition, the proportions of participants who maintained and extended to q20 or longer treatment interval and to q24 treatment interval, proportions of participants with q20 and q24 treatment interval as the last intended interval in the HDq16 group, the proportion of participants who shortened treatment intervals in the HDq12 and HDq16 groups, and participants with q8, q12, q16 and q20 as the last completed intervals, are presented in Table 2-44 and 2-45.

[000729]Overall, the target treatment intervals of q12 or longer were maintained in more than 78% of all participants in the HD groups through Week 96.

[000730]The proportion of participants completing Week 96 who maintained q16 or longer treatment intervals through Week 96 was 70.2% in the HDq16 group (see Table 2-44 and 2-42).

[000731]The proportion of participants completing Week 96 who maintained q12 or longer treatment intervals through Week 96 was 75.3% and 81.5% in the HDq12 and HDq16 groups, respectively. In the pooled HD groups, 78.4% maintained q12 or longer treatment intervals (see Table 2-44 and 2-45).

[000732]The proportion of participants with q12 or longer treatment interval as the last intended interval at Week 96 was 86.6% in the HDq12 and 89.0% in the HDq16 group, and 87.8% in the pooled HD groups. The proportion of participants with q16 or longer treatment interval as the

last intended interval at Week 96 was 63.6% in the HDq12 and 78.4% in the HDq16 group, and 71.0% in the pooled HD groups (see Table 2-44 and 2-45).

[000733]The proportion of participants with q20 or longer and with q24 treatment intervals as the last intended interval at Week 96 was 40.5% and 24.7%, respectively, in the HDq12 group and 53.1% and 30.8%, respectively, in the HDq16 group (see Table 2-44 and 2-45).

[000734]The proportion of participants completing Week 96 in the HDq12 group whose dose intervals were shortened to q8 at any time through Week 96 was 24.7%. The corresponding proportion of participants completing Week 96 in the HDq16 group whose dose intervals were shortened to q8 at any time through Week 96 was 18.5%; 11.3% of participants in this group shortened to q12 treatment intervals (without shortening to q8) at any time through Week 96.

[000735]In the pooled HD groups, 28.6% of participants had their treatment intervals shortened at any time through Week 96 and 21.6% of participants had their treatment intervals shortened to q8 at any time through Week 96 (Table 2-44 and 2-45).

[000736]The proportion of participants completing Week 96 in the HDq12 group whose treatment intervals were extended at any time through Week 96 was 73.5%; 24.7% of participants in this group extended to q20 treatment intervals and subsequently to q24. The corresponding proportion of participants completing Week 96 in the HDq16 group whose treatment intervals were extended at any time through Week 96 was 64.0%; 30.8% of participants in this group extended to q20 treatment intervals and subsequently to q24.

[000737]In the pooled HD group, 68.8% of participants extended treatment intervals at any time through Week 96 (Table 2-44 and 2-45.

[000738]The proportion of participants with q8, q12, q16 and q20 as the last completed interval is presented in Table 2-44 and 2-45. The majority of participants had q16 or q20 as their last completed intervals in both the HDq12 (29.2% and 30.9%) and the HDq16 (30.5% and 48.3%) groups, respectively.

Table 2-44. Exposure to Study Treatment: Through Week 96 (safety analysis set, Week 96 completers)

	2q8 N = 286 (100%)	HDq12 N = 291 (100%)	HDq16 N = 292 (100%)	All HD N = 583 (100%)
Subjects maintained with q12 or longer dosing interval (a), n (%)		219 (75.3%)	238 (81.5%)	457 (78.4%)
Subjects maintained with q16 or longer dosing interval (b), n (%)			205 (70.2%)	
Subjects maintained and extended to q20 or longer dosing interval (c), n (%)		110 (37.8%)	142 (48.6%)	252 (43.2%)

Subjects maintained and extended to q24 dosing interval (d), n (%)		72 (24.7%)	87 (29.8%)	159 (27.3%)
Subjects with q12 or longer dosing interval as the last intended dosing interval (e), n (%)		252 (86.6%)	260 (89.0%)	512 (87.8%)
Subjects with q16 or longer dosing interval as the last intended dosing interval (e), n (%)		185 (63.6%)	229 (78.4%)	414 (71.0%)
Subjects with q20 or longer dosing interval as the last intended dosing interval (e), n (%)		118 (40.5%)	155 (53.1%)	273 (46.8%)
Subjects with q24 dosing interval as the last intended dosing interval (e), n (%)		72 (24.7%)	90 (30.8%)	162 (27.8%)

Duration (weeks) = [(date of last study treatment) - (date of first study treatment) +28]/7; 28 days were added because of the minimum 4 week dosing interval in the study. (a) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 92] prior to Week 96. (b) All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 92] prior to Week 96. (c) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q20 or longer interval between Week 48 and prior to Week 96. (d) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q24 or longer interval between Week 48 and prior to Week 96. (e) Based on dose regimen modification (DRM) criteria assessed at the last visit with active injection before Week 96 [i.e. including DRM criteria until Week 92]. (f) All subjects on q12 or q16 interval for whom it was not planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (g) All subjects on q12 or q16 interval for whom it was planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (h) This includes also subjects who extended again after shortening back to q16 prior to Week 96. (i) This includes subjects whose extension to q20 was at their last active dosing visit prior to Week 96 and hence it is unknown if they were maintained, extended or shortened after that visit. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. All HD: Pooled high dose aflibercept 8 mg administered every 12 weeks or every 16 weeks, after 3 initial injections at 4 week intervals.

Table 2-45. Exposure to Study Treatment: Through Week 96 (safety analysis set, Week 96 completers)

	2q8 N = 286 (100%)	**HDq12 N = 291 (100%)**	**HDq16 N = 292 (100%)**	**All HD N = 583 (100%)**
Subjects shortened to q8 dosing interval at week 16, n (%)		17 (5.8%)	10 (3.4%)	27 (4.6%)
Subjects shortened to q8 dosing interval at week 20, n (%)		23 (7.9%)	20 (6.8%)	43 (7.4%)
Subjects shortened anytime, n (%)		77 (26.5%)	90 (30.8%)	167 (28.6%)
Subjects shortened to q8 dosing interval anytime, n (%)		72 (24.7%)	54 (18.5%)	126 (21.6%)
Subjects shortened to q12 dosing interval anytime without shortening to q8, n (%)			33 (11.3%)	

Subjects never extended dosing interval (f), n (%)		77 (26.5%)	105 (36.0%)	182 (31.2%)
Subjects extended dosing interval anytime (g), n (%)		214 (73.5%)	187 (64.0%)	401 (68.8%)
Subjects extended to q20 dosing interval, n (%)		119 (40.9%)	158 (54.1%)	277 (47.5%)
Subjects extended to q20 dosing interval and shortened back to q16 (h), n (%)		1 (0.3%)	3 (1.0%)	4 (0.7%)
Subjects extended to q20 dosing interval and maintained at q20, n (%)		17 (5.8%)	46 (15.8%)	63 (10.8%)
Subjects extended to q20 dosing interval and extended to q24, n (%)		72 (24.7%)	90 (30.8%)	162 (27.8%)
Subjects extended to q20 dosing interval at their last visit (i), n (%)		29 (10.0%)	19 (6.5%)	48 (8.2%)
Subjects with q8 as the last completed interval, n (%)		39 (13.4%)	33 (11.3%)	72 (12.3%)
Subjects with q12 as the last completed interval, n (%)		77 (26.5%)	29 (9.9%)	106 (18.2%)
Subjects with q16 as the last completed interval, n (%)		85 (29.2%)	89 (30.5%)	174 (29.8%)
Subjects with q20 as the last completed interval, n (%)		90 (30.9%)	141 (48.3%)	231 (39.6%)

Duration (weeks) = [(date of last study treatment) - (date of first study treatment) +28]/7; 28 days were added because of the minimum 4 week dosing interval in the study. (a) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 92] prior to Week 96. (b) All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 92] prior to Week 96. (c) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q20 or longer interval between Week 48 and prior to Week 96. (d) All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened anytime and who extended to q24 or longer interval between Week 48 and prior to Week 96. (e) Based on dose regimen modification (DRM) criteria assessed at the last visit with active injection before Week 96 [i.e. including DRM criteria until Week 92]. (f) All subjects on q12 or q16 interval for whom it was not planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (g) All subjects on q12 or q16 interval for whom it was planned to have their interval extended [according to DRM criteria until Week 92] prior to Week 96. (h) This includes also subjects who extended again after shortening back to q16 prior to Week 96. (i) This includes subjects whose extension to q20 was at their last active dosing visit prior to Week 96 and hence it is unknown if they were maintained, extended or shortened after that visit. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. All

HD: Pooled high dose aflibercept 8 mg administered every 12 weeks or every 16 weeks, after 3 initial injections at 4 week intervals.

[000739]Mean treatment compliance through Week 96 was > 96% in each of the 3 treatment groups (Table 2-46).

Table 2-46. Compliance with study treatment: through Week 96 (safety analysis set)

	2q8 N = 336 (100%)	HDq12 N = 335 (100%)	HDq16 N = 338 (100%)	All HD N = 673 (100%)
Number of subjects receiving 100% planned injections within 96-week period	215 (64.0%)	221 (66.0%)	234 (69.2%)	455 (67.6%)
Treatment compliance (%)				
n	336	335	337	672
Mean (SD)	96.30 (7.44)	97.04 (5.72)	97.33 (5.27)	97.18 (5.50)
Median	100.00	100.00	100.00	100.00
Min, Max	47.8,100	60.9,100	66.7,100	60.9,100
Compliance categories, n (%)				
>90 to ≤100%	299 (89.0%)	309 (92.2%)	316 (93.5%)	625 (92.9%)
>80 to ≤90%	24 (7.1%)	16 (4.8%)	12 (3.6%)	28 (4.2%)
≤ 80 %	13 (3.9%)	10 (3.0%)	9 (2.7%)	19 (2.8%)

Max = maximum, Min = minimum, SD = standard deviation
Compliance = (Number of actual study interventions received during period before Week 96 or up to premature discontinuation)/ (Number of planned study interventions during period before Week 96 or up to premature discontinuation) x 100

[000740]Visual outcomes (BCVA) through week 96 are summarized in Tables 2-47 to 2-52. At Weeks 48 and 96, both aflibercept 8-mg groups maintained non-inferior BCVA gains to aflibercept 2q8. Nominal P-values for 8q12 and 8q16 were equal to 0.0006 and 0.0007 at week 96, respectively.

Table 2-47. Mean Change in BCVA through Week 96 (ETDRS letters)

Week	2q8	8q12	8q16
0	0.0	0.0	0.0
4	4.6	2.7	3.2
8	6.3	5	4.8
12	6.6	5.5	5.8
16	6.7	6	6.5
20	7.7	6	6.3
24	7.4	5.9	5.8
28	8.2	7.2	6.3
32	7.6	6.8	7.3
36	8.3	6.7	6.4

40	7.9	6.9	5.7
44	8.1	7.2	6
48	7.7	6.7	6.2
52	8	7.4	6.6
56	7.9	6.5	6.5
60	7.8	6.6	6.6
64	8	6.5	6.3
68	8.4	6.4	6.3
72	7.4	5.5	5.9
76	7.5	5.9	5.7
80	7.3	6	5.9
84	7.5	6	5.8
88	7.5	6.2	5.6
92	7.1	6	5.8
96	7.4	5.9	5.6

Exploratory EP: Mean change in BCVA at week 96
p-value for the one-sided non-inferiority (NI) test at a margin of 4 letters (based on adjusted means derived using an MMRM):
p = 0.0006 HDq12 vs. 2q8 -1.01 95% CI (-2.82, 0.80)
p = 0.0007 HDq16 vs. 2q8 -1.08 95% CI (-2.87, 0.71)
Observed values (censoring data post ICE); FAS:2q8 n=336; HDq12 n=335; HDq16 n=338 (at baseline)

Table 2-48. Least Squares Mean Change in BCVA (ETDRS letters) at Week 48 and 96

	Wk 48 LS_{Mean} Change	**Wk 96 LS_{Mean} Change**
2q8	7.0	6.6
8q12	6.1	5.6
8q16	5.9	5.5

Table 2-49. Change from Baseline in BCVA Measured by the ETDRS Letter Score at Week 96, MMRM (full analysis set)

Treatment	LS mean (SE) chg. from BL	Arith. mean (SD) chg. from BL (a)	Baseline mean(a)	Number of subjects with Week 96 data	DF	Contrast(b)	t-value	p-value of one-sided test for non-inferiority at a margin of 4 letters	p-value of one-sided test for superiority	Estimate for Contrast and two-sided 95% CI(c)
HDq12 (N = 335)	5.59 (0.77)	5.9 (14.2)	59.9	256	1006.4	HDq12 - 2q8	3.25	0.0006	0.8635	-1.01 (-2.82,0.80)
HDq16 (N = 338)	5.52 (0.75)	5.6 (13.7)	60.0	264	989.0	HDq16 - 2q8	3.21	0.0007	0.8823	-1.08 (-2.87,0.71)
2q8 (N = 336)	6.60 (0.73)	7.4 (13.8)	58.9	243						

BL Baseline. CI Confidence interval. DF Degrees of freedom. LS Least Square. SD Standard deviation. SE Standard error. A mixed model for repeated measurements (MMRM) was used with baseline BCVA measurement as a covariate, treatment group, visit and the stratification

variables (geographic region [Japan vs. Rest of World]; baseline BCVA [<60 vs. ≥60]) as fixed factors, and terms for the interaction between baseline BCVA and visit and the interaction between treatment and visit. A Kenward-Roger approximation was used for the denominator degrees of freedom. In order to model the within-subject error the following covariance structure was used: Toeplitz with heterogeneity. Intercurrent events (ICE) will be handled according to primary estimand strategy for continuous endpoints.
(a) based on observed assessments.
(b) The contrast also includes the interaction term for treatment x visit (at Week 96).
(c) Estimate based on the MMRM model, will be computed for the differences of HDq12 minus 2q8 and HDq16 minus 2q8, respectively with two-sided 95% CIs.
2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals.

Table 2-50. Summary Statistics for BCVA in ETDRS Letter Score by Visit, OC Prior to ICE (full analysis set)-2q8 treatment group

		Value at Visit							Change from Baseline (BL)					
Visit	n	Mean (SE)	SD	Q1	Med	Q3	Min, Max	n	Mean (SE)	SD	Q1	Med	Q3	Min, Max
BL	336	58.9 (0.8)	14.0	51.0	62.0	70.0	24,78							
Week 4	335	63.6 (0.8)	14.4	54.0	68.0	75.0	22, 87	335	4.6 (0.4)	7.3	1.0	4.0	9.0	-28, 34
Week 8	329	65.2 (0.8)	14.7	57.0	69.0	76.0	21, 92	329	6.3 (0.5)	8.5	1.0	5.0	11.0	-41, 43
Week 12	327	65.7 (0.9)	15.5	57.0	69.0	77.0	0, 93	327	6.6 (0.6)	10.0	1.0	6.0	12.0	-57, 40
Week 16	326	65.5 (0.8)	15.0	57.0	69.0	78.0	5, 89	326	6.7 (0.5)	9.8	1.0	6.0	13.0	-52, 39
Week 20	314	66.7 (0.9)	15.5	58.0	71.0	78.0	12, 93	314	7.7 (0.6)	10.4	3.0	8.0	14.0	-31, 42
Week 24	315	66.5 (0.9)	15.2	58.0	71.0	78.0	21, 90	315	7.4 (0.6)	10.7	1.0	7.0	13.0	-37, 40
Week 28	306	67.3 (0.9)	15.2	59.0	72.0	79.0	9, 91	306	8.2 (0.6)	10.8	2.0	8.0	14.0	-34, 45
Week 32	304	66.6 (0.9)	15.2	56.0	71.0	78.0	5, 92	304	7.6 (0.6)	10.9	2.0	8.0	13.5	-38, 45
Week 36	294	67.3 (0.9)	15.7	59.0	72.0	79.0	7, 93	294	8.3 (0.7)	11.8	2.0	9.0	14.0	-50, 45
Week 40	294	66.9 (0.9)	16.1	58.0	71.0	78.0	10, 93	294	7.9 (0.7)	11.9	2.0	8.0	14.0	-46, 47
Week 44	280	67.0 (0.9)	15.9	57.0	72.0	78.0	6, 94	280	8.1 (0.7)	11.8	2.0	9.0	14.0	-44, 49
Week 48	286	66.5 (1.0)	16.6	58.0	71.0	78.0	10, 94	286	7.7 (0.7)	12.3	1.0	8.0	14.0	-41, 49
Week 52	279	67.0 (1.0)	16.4	57.0	72.0	80.0	16, 94	279	8.0 (0.8)	12.6	2.0	9.0	15.0	-43, 54
Week 56	270	66.7 (1.0)	16.7	58.0	71.0	79.0	15, 91	270	7.9 (0.8)	12.8	1.0	8.0	15.0	-50, 52
Week 60	267	66.8 (1.0)	16.7	57.0	72.0	78.0	11, 93	267	7.8 (0.8)	12.6	2.0	8.0	14.0	-49, 53
Week 64	265	66.6 (1.0)	16.8	56.0	72.0	79.0	11, 94	265	8.0 (0.8)	13.0	3.0	8.0	15.0	-47, 52
Week 68	263	67.0 (1.0)	16.6	58.0	71.0	79.0	10, 92	263	8.4 (0.8)	12.9	2.0	9.0	15.0	-40, 50
Week 72	253	66.1 (1.1)	16.9	57.0	71.0	78.0	12, 94	253	7.4 (0.8)	13.2	1.0	8.0	15.0	-47, 46
Week 76	249	66.3 (1.1)	17.3	59.0	72.0	78.0	4, 95	249	7.5 (0.8)	13.3	0.0	8.0	15.0	-49, 50

Week 80	246	66.4 (1.1)	17.1	58.0	72.0	79.0	7, 95	246	7.3 (0.9)	13.6	0.0	8.0	15.0	-44, 55
Week 84	241	66.4 (1.1)	17.1	59.0	72.0	79.0	14, 95	241	7.5 (0.9)	13.5	0.0	8.0	15.0	-40, 55
Week 88	241	66.7 (1.1)	16.8	60.0	73.0	78.0	12, 94	241	7.5 (0.9)	13.4	0.0	8.0	14.0	-41, 53
Week 92	242	66.4 (1.1)	17.4	56.0	72.0	79.0	7, 93	242	7.1 (0.9)	14.2	1.0	8.0	15.0	-55, 53
Week 96	243	66.5 (1.1)	17.2	56.0	72.0	79.0	9, 93	243	7.4 (0.9)	13.8	0.0	9.0	15.0	-46, 53

OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded. Intercurrent events (ICE) will be handled according to primary estimand strategy for continuous endpoints. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. Med=median

Table 2-58. Summary Statistics for BCVA in ETDRS Letter Score by Visit, OC Prior to ICE (full analysis set)-HDq12 treatment group

		Value at Visit							Change from Baseline (BL)					
Visit	**n**	**Mean (SE)**	**SD**	**Q1**	**Med**	**Q3**	**Min, Max**	**n**	**Mean (SE)**	**SD**	**Q1**	**Med**	**Q3**	**Min, Max**
Baseline	335	59.9 (0.7)	13.4	52.0	62.0	71.0	24, 78							
Week 4	332	62.5 (0.8)	14.8	53.5	66.0	74.0	0, 87	332	2.7 (0.4)	8.1	-1.0	2.5	7.0	-55, 33
Week 8	331	64.8 (0.8)	15.0	57.0	68.0	77.0	10, 91	331	5.0 (0.5)	8.7	0.0	5.0	10.0	-25, 38
Week 12	328	65.5 (0.8)	15.2	56.0	70.0	77.0	7, 91	328	5.5 (0.5)	9.7	0.0	6.0	11.0	-33, 42
Week 16	325	65.9 (0.8)	14.9	57.0	70.0	77.0	17, 90	325	6.0 (0.5)	9.9	1.0	5.0	12.0	-31, 43
Week 20	322	66.0 (0.8)	15.0	57.0	70.0	78.0	18, 94	322	6.0 (0.6)	9.9	0.0	6.0	12.0	-29, 42
Week 24	319	66.0 (0.9)	15.8	58.0	70.0	78.0	0, 93	319	5.9 (0.7)	11.8	0.0	6.0	13.0	-61, 47
Week 28	317	67.1 (0.8)	15.0	59.0	71.0	78.0	22, 93	317	7.2 (0.6)	10.4	2.0	7.0	13.0	-35, 47
Week 32	314	66.7 (0.9)	15.1	58.0	71.0	78.0	25, 96	314	6.8 (0.6)	11.3	1.0	7.0	14.0	-44, 48
Week 36	304	66.7 (0.9)	15.4	57.5	71.0	78.0	23, 92	304	6.7 (0.6)	11.3	1.0	7.0	13.0	-47, 49
Week 40	300	67.1 (0.9)	15.2	59.0	72.0	78.0	2, 90	300	6.9 (0.7)	11.8	1.0	6.0	13.0	-70, 46
Week 44	298	67.6 (0.9)	14.7	60.0	72.0	78.0	24, 92	298	7.2 (0.7)	11.8	1.0	7.0	14.0	-48, 45
Week 48	299	66.9 (0.9)	15.5	60.0	71.0	77.0	2, 97	299	6.7 (0.7)	12.6	0.0	6.0	13.0	-70, 45
Week 52	293	67.6 (0.9)	15.3	61.0	72.0	78.0	9, 89	293	7.4 (0.7)	12.5	1.0	7.0	13.0	-63, 46
Week 56	287	66.8 (1.0)	16.1	58.0	71.0	77.0	2, 93	287	6.5 (0.8)	13.4	0.0	7.0	14.0	-70, 50
Week 60	284	66.9 (0.9)	15.9	58.0	70.5	78.5	2, 92	284	6.6 (0.8)	13.6	0.0	7.0	14.0	-70, 49
Week 64	278	67.1 (1.0)	16.7	58.0	71.0	78.0	0, 99	278	6.5 (0.8)	14.1	-1.0	7.0	15.0	-64, 52
Week 68	273	66.9 (1.0)	16.1	58.0	71.0	79.0	3, 92	273	6.4 (0.8)	13.4	-1.0	7.0	14.0	-69, 50
Week 72	272	66.1 (1.0)	16.8	57.0	70.0	78.5	4, 94	272	5.5 (0.8)	14.0	-1.0	6.0	13.0	-68, 48
Week 76	265	66.6 (1.0)	16.5	58.0	71.0	78.0	3, 98	265	5.9 (0.9)	14.0	-1.0	6.0	14.0	-69, 48

Week 80	266	66.7 (1.0)	16.3	59.0	71.0	78.0	2, 92	266	6.0 (0.8)	13.8	-1.0	6.0	13.0	-70, 45
Week 84	264	66.4 (1.0)	16.8	58.5	71.0	78.0	0, 91	264	6.0 (0.9)	14.1	-1.0	7.0	14.0	-67, 47
Week 88	259	66.5 (1.0)	16.5	58.0	69.0	79.0	4, 92	259	6.2 (0.9)	14.5	-1.0	7.0	15.0	-68, 46
Week 92	260	66.5 (1.0)	16.4	57.5	70.0	78.0	3, 90	260	6.0 (0.9)	14.4	-2.0	7.0	14.0	-68, 46
Week 96	256	66.6 (1.0)	16.1	58.0	70.0	79.0	4, 90	256	5.9 (0.9)	14.2	-2.0	6.0	14.0	-68, 48

OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded. Intercurrent events (ICE) will be handled according to primary estimand strategy for continuous endpoints. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. Med=median

Table 2-52. Summary Statistics for BCVA in ETDRS Letter Score by Visit, OC Prior to ICE (full analysis set)-HDq16 treatment group

		Value at Visit							Change from Baseline (BL)					
Visit	**n**	**Mean (SE)**	**SD**	**Q1**	**Med**	**Q3**	**Min, Max**	**n**	**Mean (SE)**	**SD**	**Q1**	**Med**	**Q3**	**Min, Max**
Baseline	338	60.0 (0.7)	12.4	52.0	61.0	70.0	24, 78							
Week 4	337	63.2 (0.8)	13.8	55.0	67.0	74.0	10, 86	337	3.2 (0.4)	7.3	0.0	3.0	7.0	-40, 35
Week 8	332	64.7 (0.8)	13.8	56.5	68.0	75.0	19, 90	332	4.8 (0.4)	7.9	0.0	5.0	9.0	-27, 31
Week 12	330	65.8 (0.8)	13.7	58.0	68.5	76.0	22, 89	330	5.8 (0.5)	8.7	1.0	5.0	11.0	-19, 40
Week 16	328	66.4 (0.8)	14.6	58.0	70.0	77.0	13, 93	328	6.5 (0.5)	9.4	2.0	6.0	12.0	-28, 36
Week 20	324	66.3 (0.8)	14.4	58.0	70.0	77.0	21, 91	324	6.3 (0.5)	9.4	1.0	6.0	12.0	-28, 35
Week 24	316	65.8 (0.9)	15.2	57.5	69.0	78.0	3, 93	316	5.8 (0.6)	10.5	1.0	6.0	12.0	-47, 34
Week 28	311	66.4 (0.9)	15.1	58.0	71.0	78.0	2, 93	311	6.3 (0.6)	10.7	0.0	7.0	13.0	-48, 39
Week 32	306	67.4 (0.9)	15.3	61.0	71.0	79.0	6, 95	306	7.3 (0.6)	11.1	1.0	8.0	15.0	-44, 43
Week 36	302	66.3 (0.9)	15.7	59.0	70.0	78.0	0, 93	302	6.4 (0.7)	12.1	1.0	7.0	13.0	-70, 40
Week 40	295	65.9 (0.9)	15.1	59.0	69.0	77.0	6, 93	295	5.7 (0.7)	11.7	0.0	6.0	12.0	-44, 40
Week 44	290	66.3 (0.9)	15.0	58.0	69.5	78.0	5, 95	290	6.0 (0.7)	11.4	0.0	5.5	12.0	-45, 41
Week 48	290	66.2 (0.9)	15.3	59.0	70.0	77.0	9, 95	290	6.2 (0.7)	11.7	1.0	6.5	13.0	-43, 37
Week 52	287	66.8 (0.9)	15.8	60.0	71.0	78.0	2, 91	287	6.6 (0.7)	12.0	1.0	8.0	14.0	-48, 40
Week 56	286	66.7 (0.9)	15.4	59.0	70.0	78.0	1, 92	286	6.5 (0.7)	11.8	1.0	7.0	13.0	-49, 37
Week 60	281	66.7 (0.9)	15.7	60.0	70.0	78.0	0, 94	281	6.6 (0.7)	11.7	1.0	7.0	14.0	-50, 33
Week 64	283	66.4 (1.0)	16.1	60.0	70.0	78.0	0, 91	283	6.3 (0.7)	12.4	1.0	7.0	14.0	-50, 37
Week 68	273	66.8 (1.0)	16.1	58.0	71.0	78.0	0, 93	273	6.3 (0.8)	12.6	0.0	7.0	14.0	-50, 36
Week 72	265	66.2 (1.0)	16.6	60.0	70.0	78.0	0, 94	265	5.9 (0.8)	12.9	0.0	7.0	14.0	-50, 37
Week 76	264	66.1 (1.0)	16.6	59.0	71.0	78.0	0, 92	264	5.7 (0.8)	13.1	0.0	6.0	14.0	-50, 41

Week 80	266	66.1 (1.1)	17.1	58.0	72.0	79.0	0, 97	266	5.9 (0.8)	13.5	0.0	7.0	14.0	-50, 42
Week 84	260	66.4 (1.0)	16.7	59.0	70.5	78.0	0, 93	260	5.8 (0.8)	13.6	-1.0	7.0	15.0	-50, 36
Week 88	264	66.0 (1.1)	17.3	58.0	70.0	78.0	0, 96	264	5.6 (0.8)	13.8	0.0	7.0	13.0	-50, 40
Week 92	261	66.0 (1.1)	17.4	58.0	70.0	79.0	0, 95	261	5.8 (0.8)	13.7	0.0	7.0	14.0	-50, 44
Week 96	264	65.9 (1.0)	16.9	58.0	70.0	78.0	0, 94	264	5.6 (0.8)	13.7	0.0	6.5	14.0	-50, 43

OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded. Intercurrent events (ICE) will be handled according to primary estimand strategy for continuous endpoints. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. Med=median

[000741]The proportion of participants with no IRF and no SRF in central subfield was a key secondary efficacy endpoint at Week 16, an additional secondary efficacy endpoint at Week 48 and an exploratory efficacy endpoint at Week 96. For the key secondary endpoint of proportion of participants with no IRF and no SRF in central subfield at Week 16, superiority in the pooled HD groups versus the comparator 2q8 was demonstrated.

[000742]At Week 96, the proportion of participants with no retinal fluid (no IRF and no SRF) in the central subfield was consistent with the results for the previous data releases. At Week 96, the proportion was numerically higher in the HDq12 group (69.6%) compared to the 2q8 and HDq16 groups (66.5% and 63.6%, respectively), based on LOCF in the FAS. The pairwise differences (95% CI) for the 2-sided tests, using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60) was 3.017% points (-4.076%, 10.109%) for HDq12 vs. 2q8 and -3.013% points (-10.249%, 4.222%) for HDq16 vs. 2q8 (Table 2-53).

[000743]Summary statistics for the proportion of participants with no IRF and no SRF in central subfield at baseline, Week 16, Week 48, Week 60, and Week 96 using LOCF for the FAS, are presented in Table 2-53. At Week 96, the proportions of participants with no retinal fluid decreased slightly compared to Week 60, but were still > 60% (63.6% to 69.6%) in all 3 treatment groups and the pooled HD groups.

Table 2-53. Summary Statistics for Proportion of Subjects with no IRF and no SRF in Central Subfield by Visit, LOCF (full analysis set)

Visit	Fluid Status	2q8 N = 336 Num/Den(%)	HDq12 N = 335 Num/Den(%)	HDq16 N = 338 Num/Den(%)	All HD N = 673 Num/Den(%)
Baseline	Dry	13/336 (3.9%)	8/335 (2.4%)	9/336 (2.7%)	17/671 (2.5%)

	Not Dry	323/336 (96.1%)	327/335 (97.6%)	327/336 (97.3%)	654/671 (97.5%)
	IRF only	48/336 (14.3%)	38/335 (11.3%)	28/336 (8.3%)	66/671 (9.8%)
	SRF only	170/336 (50.6%)	168/335 (50.1%)	172/336 (51.2%)	340/671 (50.7%)
	IRF and SRF	105/336 (31.3%)	121/335 (36.1%)	127/336 (37.8%)	248/671 (37.0%)
	Missing or undetermined	0	0	2	2
	IRF missing or undetermined (and SRF=No)	0	0	0	0
	SRF missing or undetermined (and IRF=No)	0	0	0	0
	Both missing or undetermined	0	0	2	2
Week 96	Dry	222/334 (66.5%)	231/332 (69.6%)	213/335 (63.6%)	444/667 (66.6%)
	Not Dry	112/334 (33.5%)	101/332 (30.4%)	122/335 (36.4%)	223/667 (33.4%)
	IRF only	39/334 (11.7%)	41/332 (12.3%)	50/335 (14.9%)	91/667 (13.6%)
	SRF only	65/334 (19.5%)	52/332 (15.7%)	58/335 (17.3%)	110/667 (16.5%)
	IRF and SRF	8/334 (2.4%)	8/332 (2.4%)	14/335 (4.2%)	22/667 (3.3%)
	Missing or undetermined	2	3	3	6
	IRF missing or undetermined (and SRF=No)	0	0	0	0
	SRF missing or undetermined (and IRF=No)	1	0	0	0
	Both missing or undetermined	1	3	3	6

LOCF method for the last available observed value prior to ICE will be carried forward to impute missing data. Intercurrent events (ICE) will be handled according to primary estimand strategy for binary endpoints. IRF Intraretinal fluid. SRF Subretinal fluid. Dry = defined as no IRF nor SRF detected; Not dry = defined as IRF and/or SRF detected. 2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals. HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals. HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals. All HD: Pooled high dose aflibercept 8 mg administered every 12 weeks or every 16 weeks, after 3 initial injections at 4-week intervals.

[000744]At Week 96, the proportion of participants without subRPE fluid in central subfield was > 90% in both HD groups and 88.0% in the 2q8 group. The proportion of participants with both no subRPE fluid and no retinal fluid (no IRF and no SRF) in central subfield at Week 96,

decreased slightly from Week 60 to values of approximately 60% to 64% in all treatment groups (Table 2-54); however, in general, these data were consistent with prior results.

Table 2-54. Proportion of participants without retinal fluid and subretinal pigment epithelium fluid in central subfield by visit, LOCF (full analysis set)

Visit	Fluid status	2q8 N = 336 Num/Den(%)	HDq12 N = 335 Num/Den(%)	HDq16 N = 338 Num/Den(%)
Baseline	No SubRPE fluid	237/335 (70.7%)	225/334 (67.4%)	236/336 (70.2%)
	Dry	7/335 (2.1%)	5/334 (1.5%)	6/336 (1.8%)
	Not dry (IRF and/or SRF)	230/335 (68.7%)	220/334 (65.9%)	230/336 (68.5%)
	Both IRF and SRF missing or undetermined	0/335	0/334	0/336
	SubRPE fluid present	98/335 (29.3%)	109/334 (32.6%)	100/336 (29.8%)
	Dry	6/335 (1.8%)	3/334 (0.9%)	3/336 (0.9%)
	Not dry (IRF and/or SRF)	92/335 (27.5%)	106/334 (31.7%)	97/336 (28.9%)
	Both IRF and SRF missing or undetermined	0/335	0/334	0/336
	SubRPE missing or undetermined	1	1	2
Week 48	No SubRPE fluid	281/326 (86.2%)	298/325 (91.7%)	308/330 (93.3%)
	Dry	178/326 (54.6%)	216/325 (66.5%)	206/330 (62.4%)
	Not dry (IRF and/or SRF)	103/326 (31.6%)	82/325 (25.2%)	101/330 (30.6%)
	Both IRF and SRF missing or undetermined	0/326	0/325	0/330
	SubRPE fluid present	45/326 (13.8%)	27/325 (8.3%)	22/330 (6.7%)
	Dry	17/326 (5.2%)	16/325 (4.9%)	14/330 (4.2%)
	Not dry (IRF and/or SRF)	28/326 (8.6%)	11/325 (3.4%)	8/330 (2.4%)
	Both IRF and SRF missing or undetermined	0/326	0/325	0/330
	SubRPE missing or undetermined	10	10	8
Week 60	No SubRPE fluid	296/326 (90.8%)	306/328 (93.3%)	309/331 (93.4%)
	Dry	226/326 (69.3%)	232/328 (70.7%)	227/331 (68.6%)
	Not dry (IRF and/or SRF)	70/326 (21.5%)	73/328 (22.3%)	82/331 (24.8%)
	Both IRF and SRF missing or undetermined	0/326	0/328	0/331
	SubRPE fluid present	30/326 (9.2%)	22/328 (6.7%)	22/331 (6.6%)
	Dry	18/326 (5.5%)	12/328 (3.7%)	13/331 (3.9%)
	Not dry (IRF and/or SRF)	12/326 (3.7%)	10/328 (3.0%)	9/331 (2.7%)
	Both IRF and SRF missing or undetermined	0/326	0/328	0/331
	SubRPE missing or undetermined	10	7	7
Week 96	No SubRPE fluid	292/332 (88.0%)	300/328 (91.5%)	311/333 (93.4%)
	Dry	207/332 (62.3%)	211/328 (64.3%)	200/333 (60.1%)
	Not dry (IRF and/or SRF)	85/332 (25.6%)	89/328 (27.1%)	111/333 (33.3%)
	Both IRF and SRF missing or undetermined	0/332	0/328	0/333
	SubRPE fluid present	40/332 (12.0%)	28/328 (8.5%)	22/333 (6.6%)
	Dry	13/332 (3.9%)	16/328 (4.9%)	12/333 (3.6%)
	Not dry (IRF and/or SRF)	27/332 (8.1%)	12/328 (3.7%)	10/333 (3.0%)
	Both IRF and SRF missing or undetermined	0/332	0/328	0/333
	SubRPE missing or undetermined	4	7	5

IRF = Intraretinal fluid, LOCF = Last observation carried forward, Num/Den = numerator/denominator, SAP = statistical analysis plan, SRF = Subretinal fluid, subRPE = subretinal pigment epithelium fluid
LOCF: last available observed value prior to ICE was used to impute missing data.
Intercurrent events (ICE) were handled according to primary estimand strategy for binary endpoints.
Dry = defined as no IRF and no SRF in central subfield detected; Not dry = defined as IRF and/or SRF in central subfield detected.

Table 2-55. Summary Statistics For Central Subfield Retinal Thickness (µm) by Visit, OC Prior to ICE (full analysis set)

		Value at visit							Change from Baseline						
Treatment	Visit	n	Mean (SE)	SD	Q1	Med	Q3	Min, Max	n	Mean (SE)	SD	Q1	Med	Q3	Min, Max
2q8 (N=336)	Baseline	335	367.1 (7.3)	133.6	275.0	343.0	423.0	142, 1116							
	Week 4	328	246.6 (4.1)	73.7	202.0	230.0	271.0	105, 762	328	-119.1 (5.8)	104.9	-168.0	-94.5	-48.0	-550, 223
	Week 8	322	235.7 (3.9)	70.1	194.0	220.0	254.0	118 695	322	-131.6 (6.4)	115.5	-184.0	-106.0	-54.0	-583, 188
	Week 12	319	231.0 (3.6)	65.0	192.0	218.0	255.0	120 657	319	-137.2 (6.7)	119.9	-192.0	-111.0	-53.0	-602, 216
	Week 16	319	252.0 (4.6)	82.5	199.0	231.0	289.0	126 655	319	-114.7 (6.9)	123.8	-176.0	-82.0	-26.0	-553, 182
	Week 20	306	228.7 (3.5)	61.7	192.0	218.0	253.0	120 613	306	-137.8 (7.0)	121.7	-195.0	-113.0	-50.0	-610, 147
	Week 24	307	247.3 (4.5)	78.4	200.0	228.0	271.0	125 605	307	-115.3 (6.9)	121.2	-180.0	-88.0	-30.0	-544, 187
	Week 28	298	224.8 (3.4)	59.1	192.0	216.0	248.0	112 589	298	-138.2 (6.8)	117.2	-196.0	-112.0	-53.0	-613, 127
	Week 32	296	242.8 (4.5)	77.4	195.0	224.5	272.5	113 591	296	-121.2 (7.1)	122.3	-183.0	-88.5	-37.0	-534, 130
	Week 36	284	224.1 (3.4)	57.4	190.5	216.0	244.5	101 572	284	-137.7 (6.9)	116.1	-198.5	-110.0	-54.0	-622, 136
	Week 40	280	240.3 (4.5)	74.9	192.5	224.5	265.0	118 576	280	-121.7 (7.4)	123.3	-184.5	-91.5	-33.5	-540, 169
	Week 44	270	221.0 (3.5)	57.5	187.0	215.5	246.0	99 567	270	-140.2 (7.2)	118.9	-205.0	-109.0	-56.0	-626, 154
	Week 48	274	236.3 (4.2)	70.0	189.0	223.0	267.0	118 568	274	-126.6 (7.5)	124.2	-190.0	-98.0	-39.0	-573, 145
	Week 52	268	217.6 (3.5)	56.5	185.0	211.0	238.0	102 572	268	-142.3 (7.3)	118.9	-198.5	-109.5	-58.5	-638, 124
	Week 56	260	233.2 (4.2)	67.9	189.5	224.0	262.0	113 555	260	-127.7 (7.8)	126.2	-186.0	-95.0	-43.0	-592, 180
	Week 60	257	215.6 (3.4)	54.7	184.0	211.0	236.0	110 554	257	-143.0 (7.6)	121.2	-201.0	-114.0	-61.0	-648, 181

	Week 64	258	229.5 (4.2)	68.0	188.0	217.0	255.0	107 573	258	-132.7 (7.9)	127.4	-197.0	-98.0	-44.0	-603, 202
	Week 68	254	216.4 (3.9)	61.6	182.0	209.0	237.0	111 585	254	-145.6 (7.8)	123.5	-204.0	-114.0	-60.0	-648, 173
	Week 72	244	233.0 (4.4)	69.1	190.0	219.5	258.5	110 558	244	-131.6 (8.4)	131.0	-195.0	-101.0	-44.0	-608, 246
	Week 76	242	213.7 (3.6)	55.5	180.0	208.0	239.0	89 507	242	-150.5 (8.2)	127.2	-214.0	-123.0	-59.0	-642, 163
	Week 80	236	227.0 (4.2)	65.2	185.5	219.0	252.5	99 523	236	-134.7 (8.6)	131.7	-199.5	-108.5	-43.5	-616, 280
	Week 84	233	211.4 (3.5)	53.9	177.0	206.0	235.0	100 522	233	-147.6 (7.8)	119.2	-209.0	-118.0	-63.0	-533, 185
	Week 88	233	225.2 (4.3)	66.2	186.0	217.0	252.0	91 538	233	-134.9 (8.6)	131.1	-201.0	-106.0	-45.0	-625, 324
	Week 92	232	213.4 (3.8)	58.3	180.0	208.0	238.0	95 520	232	-145.3 (8.4)	128.1	-205.5	-108.0	-54.0	-659, 211
	Week 96	233	224.3 (4.4)	66.7	181.0	217.0	248.0	103 606	233	-135.8 (8.7)	133.1	-204.0	-106.0	-46.0	-634, 392
HDq12 (N=335)	**Baseline**	335	370.3 (6.8)	123.7	280.0	348.0	428.0	151 840							
	Week 4	324	248.2 (4.1)	73.7	205.5	231.5	272.0	111 637	324	-119.8 (5.4)	96.6	-156.0	-99.0	-52.0	-493, 83
	Week 8	320	234.4 (3.7)	66.4	197.0	221.0	253.5	99 591	320	-132.5 (5.8)	103.1	-183.5	-110.5	-57.5	-559, 68
	Week 12	319	229.6 (3.4)	61.5	197.0	219.0	251.0	94 637	319	-136.2 (5.8)	103.1	-189.0	-116.0	-60.0	-551, 19
	Week 16	318	247.2 (4.5)	80.0	201.0	229.5	270.0	88 709	318	-119.6 (6.4)	113.6	-183.0	-103.5	-43.0	-501, 201
	Week 20	315	257.0 (5.0)	88.7	202.0	239.0	289.0	79 912	315	-110.6 (6.5)	115.4	-177.0	-84.0	-32.0	-546, 214
	Week 24	308	233.0 (4.2)	74.3	193.5	219.0	255.0	82 751	308	-134.5 (6.6)	116.5	-190.0	-114.0	-58.5	-545, 476
	Week 28	311	236.4 (4.1)	71.7	195.0	224.0	266.0	84 693	311	-130.6 (6.4)	113.7	-184.0	-107.0	-49.0	-545, 141
	Week 32	305	250.1 (4.9)	86.2	199.0	229.0	280.0	91 776	305	-118.0 (7.0)	121.6	-185.0	-94.0	-38.0	-548, 276
	Week 36	295	226.2 (3.7)	62.9	189.0	218.0	251.0	85 595	295	-142.3 (6.8)	116.6	-200.0	-119.0	-64.0	-591, 142
	Week 40	292	236.8 (4.1)	69.7	193.0	222.5	265.5	91 626	292	-130.9 (7.0)	119.4	-198.0	-102.0	-52.0	-553, 173
	Week 44	289	245.6 (4.3)	73.1	200.0	229.0	273.0	119 644	289	-120.2 (6.7)	113.9	-186.0	-98.0	-44.0	-518, 194
	Week 48	290	225.9 (3.8)	65.5	190.0	216.5	248.0	83 662	290	-142.7 (7.0)	119.9	-209.0	-119.0	-63.0	-549, 209
	Week 52	283	227.5 (4.0)	68.0	191.0	219.0	251.0	81 656	283	-139.2 (7.1)	120.2	-206.0	-111.0	-51.0	-551, 203

	Week 56	279	234.0 (4.4)	73.6	193.0	223.0	255.0	80 680	279	-133.3 (7.4)	123.3	-196.0	-106.0	-50.0	-556, 227
	Week 60	274	219.1 (3.7)	61.5	186.0	214.5	238.0	80 658	274	-149.3 (7.3)	120.9	-215.0	-120.5	-66.0	-559, 205
	Week 64	269	226.0 (4.0)	65.1	190.0	218.0	251.0	78 676	269	-140.3 (7.5)	123.3	-204.0	-115.0	-55.0	-559, 223
	Week 68	266	230.4 (4.3)	69.7	194.0	221.0	255.0	83 672	266	-136.8 (7.9)	128.3	-206.0	-107.5	-48.0	-562, 219
	Week 72	261	227.0 (4.3)	68.8	190.0	218.0	251.0	76 627	261	-140.2 (7.5)	121.4	-203.0	-109.0	-56.0	-567, 174
	Week 76	257	225.8 (4.1)	65.9	187.0	216.0	253.0	69 600	257	-141.2 (7.9)	126.7	-205.0	-114.0	-57.0	-554, 226
	Week 80	257	227.5 (4.2)	68.0	191.0	220.0	250.0	78 657	257	-138.6 (7.7)	123.7	-203.0	-116.0	-53.0	-565, 204
	Week 84	252	222.8 (4.0)	63.8	190.0	216.5	247.0	57 633	252	-148.0 (7.9)	125.0	-212.0	-117.0	-59.0	-559, 180
	Week 88	248	226.3 (3.9)	61.1	188.0	221.5	253.0	54 465	248	-142.3 (7.9)	124.0	-205.5	-110.0	-51.0	-566, 82
	Week 92	253	229.5 (4.5)	71.9	191.0	221.0	254.0	70 648	253	-139.2 (7.9)	125.4	-207.0	-110.0	-56.0	-540, 201
	Week 96	250	221.8 (4.1)	64.8	185.0	215.0	244.0	67 641	250	-143.9 (7.8)	123.6	-209.0	-115.5	-61.0	-572, 188
HDq16 (N=338)	**Baseline**	336	370.7 (7.2)	132.7	279.5	340.0	424.0	144 913							
	Week 4	329	244.0 (4.0)	72.3	202.0	231.0	271.0	104 714	329	-126.2 (5.7)	104.1	-166.0	-99.0	-53.0	-568, 51
	Week 8	326	231.2 (3.4)	61.0	195.0	222.0	255.0	105 624	326	-139.6 (6.3)	112.9	-186.0	-108.5	-60.0	-568, 10
	Week 12	324	226.7 (3.0)	53.4	194.0	216.0	252.5	108 561	324	-143.5 (6.4)	116.1	-200.0	-117.0	-59.5	-558, 85
	Week 16	322	238.6 (3.7)	66.6	196.0	225.5	264.0	100 534	322	-133.1 (6.8)	121.7	-188.0	-104.5	-48.0	-573, 143
	Week 20	318	254.9 (5.0)	89.7	200.0	232.5	282.0	97 732	318	-117.3 (7.0)	124.4	-168.0	-90.5	-31.0	-532, 274
	Week 24	309	265.1 (5.3)	92.6	204.0	251.0	299.0	88 870	309	-107.8 (7.4)	129.6	-165.0	-76.0	-17.0	-577, 182
	Week 28	305	225.9 (3.0)	52.8	188.0	217.0	253.0	114 492	305	-147.0 (7.2)	125.2	-203.0	-113.0	-59.0	-601, 100
	Week 32	300	229.2 (3.4)	59.0	188.0	221.0	256.0	81 497	300	-144.0 (7.5)	129.6	-199.5	-105.0	-50.5	-609, 69
	Week 36	294	244.2 (4.5)	77.6	194.0	228.5	279.0	79 684	294	-130.7 (7.6)	130.6	-180.0	-92.5	-42.0	-592, 84
	Week 40	289	243.6 (4.2)	71.8	197.0	233.0	281.0	78 570	289	-128.1 (7.9)	134.3	-183.0	-91.0	-37.0	-597, 111
	Week 44	283	227.7 (3.7)	63.0	188.0	217.0	256.0	85 650	283	-145.3 (7.8)	130.8	-199.0	-111.0	-57.0	-619, 80

	Week 48	282	226.9 (3.5)	58.2	188.0	216.5	258.0	69 449	282	-147.5 (7.8)	131.2	-207.0	-111.5	-58.0	-624, 89
	Week 52	280	231.0 (3.9)	66.0	189.5	223.0	263.0	80 608	280	-141.1 (8.1)	135.8	-199.5	-100.0	-52.0	-630, 130
	Week 56	278	233.2 (3.8)	63.0	196.0	227.0	270.0	84 548	278	-139.3 (8.0)	133.0	-196.0	-98.0	-49.0	-608, 90
	Week 60	272	221.9 (3.6)	58.6	184.0	213.0	251.0	107 462	272	-153.7 (8.1)	134.2	-207.5	-119.0	-63.0	-623, 158
	Week 64	275	221.5 (3.5)	58.2	183.0	214.0	250.0	89 421	275	-153.8 (8.2)	135.5	-212.0	-116.0	-59.0	-619, 98
	Week 68	266	228.3 (4.3)	69.6	186.0	220.5	261.0	87 568	266	-146.6 (8.3)	135.5	-208.0	-109.0	-54.0	-620, 142
	Week 72	258	233.5 (4.1)	66.1	190.0	226.0	268.0	83 552	258	-142.0 (8.8)	141.5	-207.0	-98.0	-47.0	-622, 125
	Week 76	254	218.4 (3.5)	55.9	182.0	211.0	250.0	85 419	254	-152.4 (8.0)	128.1	-202.0	-118.5	-65.0	-623, 74
	Week 80	259	220.5 (4.0)	64.0	182.0	216.0	249.0	87 641	259	-155.6 (8.3)	133.0	-205.0	-120.0	-65.0	-625, 90
	Week 84	252	223.1 (3.9)	62.0	182.0	215.5	257.5	83 476	252	-151.6 (8.8)	139.2	-215.5	-114.0	-55.0	-644, 121
	Week 88	257	224.3 (4.0)	63.6	182.0	220.0	258.0	76 503	257	-150.2 (8.8)	141.2	-207.0	-116.0	-56.0	-644, 122
	Week 92	256	217.7 (3.6)	58.0	179.0	211.5	252.0	78 380	256	-158.1 (8.6)	137.5	-215.5	-122.0	-64.5	-650, 72
	Week 96	257	221.3 (3.8)	60.9	181.0	210.0	259.0	83 405	257	-153.4 (8.8)	140.8	-209.0	-121.0	-59.0	-653, 93

NA Not available. OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded. Intercurrent events (ICE) will be handled according to primary estimand strategy for continuous endpoints.
2q8: Aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals.
HDq12: High dose aflibercept 8 mg administered every 12 weeks, after 3 initial injections at 4-week intervals.
HDq16: High dose aflibercept 8 mg administered every 16 weeks, after 3 initial injections at 4-week intervals.
Med=median

[000745] At week 96 in the full analysis set, 66.6% (444/667) and 66.5% (222/334) of patients receiving aflibercept 8 mg and aflibercept 2 mg were fluid-free in the central subfield. In patients with baseline CRT<400µm, 67.7% (306/452), 70.3% (317/451), and 66.2% (299/452) receiving aflibercept 8 mg and 54.3% (125/230), 61.3% (141/230), and 64.8% (149/230) receiving 2 mg were fluid-free at week 16, week 48, and week 96, respectively. In patients with baseline CRT ≥400µm, 54.0% (116/215), 65.6% (141/215), and 67.4% (145/215) receiving aflibercept 8 mg, and 45.2% (47/104), 54.8% (57/104), and 69.9% (72/103) receiving 2 mg were fluid-free at week 16, week 48, and week 96, respectively. In patients with baseline BCVA ≤54

letters, 60.5% (118/195), 65.1% (127/195), and 68.9% (135/196) receiving aflibercept 8 mg, and 54.3% (57/105), 58.1% (61/105), and 69.2% (72/104) receiving 2 mg were fluid-free at week 16, week 48, and week 96, respectively. In patients with baseline BCVA 55–73 letters, 65.8% (252/383), 69.7% (267/383), and 65.3% (250/383) receiving aflibercept 8mg, and 48.6% (88/181), 60.2% (109/181), and 65.2% (118/181) receiving 2 mg were fluid-free at week 16, week 48, and week 96, respectively. In patients with baseline BCVA ≥74 letters, 58.4% (52/89), 72.7% (64/88), and 67.0% (59/88) receiving aflibercept 8mg, and 57.1% (28/49), 59.2% (29/49), and 65.3% (32/49) receiving 2 mg were fluid-free at week 16, week 48, and week 96, respectively. In the overall PULSAR population, similar fluid control was achieved at week 16 and sustained through week 96 with aflibercept 8 mg with extended dosing intervals compared to aflibercept 2 mg every 8 weeks. Results in patients stratified by baseline BCVA and CRT are consistent with these findings. The observed data suggest rapid and sustained fluid control is achievable with aflibercept 8 mg in patients with treatment-naïve nAMD with extended dosing intervals.

[000746]Summary statistics for the CNV size at baseline, Week 12, Week 48, Week 60, and Week 96 based on OC prior to ICE in the FAS, are presented in Table 2-56.

[000747]The mean (SD) CNV size based on OC prior to ICE at baseline ranged from 5.9768 (4.8306) mm^2 to 6.5459 (5.5315) mm^2 across the 3 treatment groups. Numerical mean and median decreases from baseline were observed in all 3 treatment groups at Week 12, Week 48, Week 60, and Week 96. At Week 96, the mean (SD) decreases in CNV size from baseline were 4.6647 (5.9212) mm^2 in the HDq16 group compared to 3.8922 (5.5173) mm^2 and 3.9616 (5.4395) mm^2 in the HDq12 and 2q8 groups, respectively.

[000748]The mean CNV size using the MMRM at baseline was similar ranging from 6.0 to 6.5 mm^2 across the 3 treatment groups. Mean changes from baseline at Week 96 showed mean decreases in the HD groups and the 2q8 group. The estimated contrasts (95% CI) for the 2 sided test, using the MMRM in the FAS, were -0.25 (-0.96, -0.45) mm^2 for HDq12 vs. 2q8 and -0.57 (-1.23, 0.08) mm^2 for HDq16 vs. 2q8.

Table 2-56. Summary statistics for choroidal neovascularization size (mm^2) by visit, OC prior to ICE (full analysis set)

		Value at visit				Change from baseline			
Treatment	Visit	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
2q8 (N = 336)	Baseline	336	6.3593 (5.0394)	4.9970	0.148, 24.129				
	Week 12	314	5.2107 (5.4069)	3.7455	0.000, 29.362	314	-1.1702 (3.4604)	-0.4930	-22.149, 11.671

		Value at visit				Change from baseline			
Treatment	Visit	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
	Week 48	280	4.1366 (5.5680)	1.6195	0.000, 27.675	280	-2.3934 (5.2421)	-1.3125	-24.129, 16.636
	Week 60	254	2.8414 (4.8017)	0.0000	0.000, 26.866	254	-3.7845 (5.4744)	-2.4625	-24.129, 12.664
	Week 96	233	2.4473 (4.3969)	0.0000	0.000, 25.630	233	-3.9616 (5.4395)	-2.7730	-24.129, 11.092
HDq12 (N = 335)	Baseline	335	5.9768 (4.8306)	4.8990	0.115, 30.023				
	Week 12	312	4.3936 (4.6561)	3.0690	0.000, 30.212	312	-1.4886 (3.6500)	-0.5530	-21.998, 11.890
	Week 48	289	2.4930 (4.6860)	0.0000	0.000, 27.034	289	-3.5264 (5.0101)	-2.5380	-21.998, 15.501
	Week 60	257	2.1548 (4.2765)	0.0000	0.000, 26.051	257	-3.8819 (5.0293)	-2.7870	-21.998, 12.783
	Week 96	238	2.2188 (4.4501)	0.0000	0.000, 21.117	238	-3.8922 (5.5173)	-3.1335	-30.023, 15.040
HDq16 (N = 338)	Baseline	337	6.5459 (5.5315)	4.6980	0.000, 28.650				
	Week 12	313	4.8923 (5.1756)	3.3660	0.000, 27.081	313	-1.5729 (4.2200)	-0.4950	-25.133, 16.628
	Week 48	278	3.5401 (5.1806)	0.6930	0.000, 28.936	278	-2.9836 (5.3279)	-1.4035	-25.354, 15.869
	Week 60	261	2.6528 (4.7107)	0.0000	0.000, 30.991	261	-3.6663 (5.6510)	-2.1490	-26.231, 16.769
	Week 96	250	1.7848 (3.4328)	0.0000	0.000, 18.652	250	-4.6647 (5.9212)	-3.2500	-28.650, 6.883

Max = maximum, Min = minimum, SAP = statistical analysis plan, SD = standard deviation
OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded.
Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints

[000749]The proportion of participants without leakage on FA increased in all groups over time reaching values of > 55% in the HDq16 and the 2q8 groups and approximately 65% in the HDq12 group at Week 96. The number of participants with an undetermined leakage status was generally small and similar across the treatment groups over time (Table 2-57). The analysis for the same endpoint based on OC in the FAS provided results that were consistent with the results using LOCF

Table 2-57. Proportion of participants without leakage on FA by visit, LOCF (full analysis set)

Visit	Leakage status	2q8 N = 336 Num/Den(%)	HDq12 N = 335 Num/Den(%)	HDq16 N = 338 Num/Den(%)
Baseline	No leakage	0/336	0/335	1/337 (0.3%)
	Any leakage	336/336 (100%)	335/335 (100%)	336/337 (99.7%)
	Undetermined	0	0	1
Week 12	No leakage	61/308 (19.8%)	70/305 (23.0%)	67/307 (21.8%)
	Any leakage	247/308 (80.2%)	235/305 (77.0%)	240/307 (78.2%)
	Undetermined	9	8	7
Week 48	No leakage	135/321 (42.1%)	193/319 (60.5%)	140/319 (43.9%)
	Any leakage	186/321 (57.9%)	126/319 (39.5%)	179/319 (56.1%)
	Undetermined	8	9	7
Week 60	No leakage	177/318 (55.7%)	197/318 (61.9%)	168/315 (53.3%)
	Any leakage	141/318 (44.3%)	121/318 (38.1%)	147/315 (46.7%)
	Undetermined	11	10	11
Week 96	No leakage	180/320 (56.3%)	202/312 (64.7%)	180/313 (57.5%)
	Any leakage	140/320 (43.8%)	110/312 (35.3%)	133/313 (42.5%)

Visit	Leakage status	2q8 N = 336 Num/Den(%)	HDq12 N = 335 Num/Den(%)	HDq16 N = 338 Num/Den(%)
	Undetermined	9	16	13

ICE = Intercurrent events, FA = fluorescein angiography, LOCF = Last observation carried forward, Num/Den = numerator/denominator, SAP = statistical analysis plan
LOCF: last available observed value prior to ICE was used to impute missing data.
ICE were handled according to primary estimand strategy for binary endpoints

[000750]Summary statistics for the total lesion area by visit through Week 96 based on OC prior to ICE in the FAS, are presented in Table 2-58. The mean (SD) total lesion area at baseline ranged from 6.3820 (5.0664) mm^2 to 6.8814 (5.6514) mm^2 across the 3 treatment groups. Numerical mean and median decreases in total lesion area from baseline were observed in all 3 treatment groups through Week 96, except for a numerical mean increase in the 2q8 group at Week 48. The mean (SD) decreases in total lesion area from baseline were of similar extent in all 3 treatment groups ranging from -0.2070 (3.4153) mm^2 to 0.2923 (3.2702) mm^2 at Week 96.

Table 2-58. Summary statistics for total lesion area (mm^2) by visit, OC prior to ICE (full analysis set)

		Value at visit				Change from baseline			
Treatment	Visit	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
2q8 (N = 336)	Baseline	336	6.8647 (5.4145)	5.4120	0.148, 27.409	/	/	/	/
	Week 12	314	6.6722 (5.4651)	4.8480	0.271, 29.362	314	-0.2130 (2.4653)	-0.1510	-11.233, 13.520
	Week 48	281	7.2282 (6.1106)	5.5800	0.271, 35.332	281	0.1110 (3.5498)	-0.2690	-11.242, 24.641
	Week 60	254	6.9346 (5.8980)	5.1235	0.379, 30.953	254	-0.2633 (3.1821)	-0.3415	-11.494, 15.885
	Week 96	233	6.7911 (5.6210)	5.3020	0.288, 27.125	233	-0.2070 (3.4153)	-0.3510	-11.311, 17.339
HDq12 (N = 335)	Baseline	335	6.3820 (5.0664)	5.0260	0.185, 30.023	/	/	/	/
	Week 12	312	5.8133 (4.7055)	4.9645	0.154, 30.212	312	-0.4475 (2.2635)	-0.2345	-8.654, 10.872
	Week 48	289	6.0593 (5.2153)	4.9800	0.110, 30.259	289	-0.3675 (2.8935)	-0.2550	-8.719, 13.190
	Week 60	257	5.9091 (5.3831)	4.4750	0.138, 31.583	257	-0.5172 (2.8431)	-0.3390	-11.011, 14.006
	Week 96	239	6.1769 (5.2790)	4.6710	0.131, 28.272	239	-0.2923 (3.2702)	-0.1970	-12.950, 14.494
HDq16 (N = 338)	Baseline	336	6.8814 (5.6514)	5.0685	0.180, 28.650	/	/	/	/
	Week 12	312	6.3994 (5.2627)	5.0060	0.180, 27.081	312	-0.3923 (2.6320)	-0.1355	-11.856, 16.628
	Week 48	277	6.5375 (5.5805)	4.8820	0.137, 28.936	277	-0.2964 (3.1634)	-0.0570	-13.105, 15.869
	Week 60	260	6.3181 (5.6691)	4.4805	0.134, 34.294	260	-0.3205 (3.2568)	-0.1415	-12.755, 16.769

		Value at visit				Change from baseline			
Treatment	Visit	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
	Week 96	249	6.4962 (5.6298)	4.8820	0.135, 28.028	249	-0.2609 (3.1842)	-0.0720	-16.476, 17.414

Max = maximum, Min = minimum, SAP = statistical analysis plan, SD = standard deviation
OC (observed cases) prior to ICE: observations after an intercurrent event (ICE) defined for the primary estimand excluded.
Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints

[000751]The mean NEI-VFQ-25 total score at baseline was similar across the 3 treatment groups, ranging from 76.36 to 77.81. The mean (SD) increases from baseline at Week 96 ranged from 2.64 (12.39) in the HDq16 group to 4.16 (11.93) in the 2q8 group (Table 2-59).

Table 2-59. Summary statistics for NEI-VFQ-25 total score by visit, OC prior to ICE (full analysis set)

		Value at visit				**Change from baseline**			
Treatment	**Visit**	**n**	**Mean (SD)**	**Median**	**Min , Max**	**n**	**Mean (SD)**	**Median**	**Min , Max**
2q8 (N = 336)	Baseline	317	77.81 (14.42)	80.45	36.92, 99.43	/	/	/	/
	Week 48	269	82.47 (13.56)	85.87	31.38, 100.00	269	4.64 (11.01)	3.33	-33.79, 43.71
	Week 60	254	83.24 (13.52)	87.10	38.30, 100.00	254	5.19 (11.40)	3.44	-34.50, 45.95
	Week 96	229	82.43 (14.11)	85.79	38.11, 100.00	229	4.16 (11.93)	3.79	-38.67, 47.46
HDq12 (N = 335)	Baseline	321	76.36 (15.12)	79.51	24.21, 98.18	/	/	/	/
	Week 48	283	81.32 (14.95)	85.38	32.92, 100.00	283	4.02 (10.27)	3.07	-27.33, 38.92
	Week 60	268	81.46 (15.92)	86.10	18.67, 100.00	268	3.60 (12.01)	3.77	-58.00, 44.92
	Week 96	245	80.85 (15.98)	85.19	25.42, 100.00	245	2.72 (12.65)	3.41	-41.57, 38.88
HDq16 (N = 338)	Baseline	316	77.67 (15.40)	81.85	16.17, 98.18	/	/	/	/
	Week 48	268	81.82 (14.60)	85.79	16.71, 100.00	268	3.48 (10.67)	2.27	-37.38, 39.66
	Week 60	258	82.26 (14.83)	86.57	27.42, 99.43	258	3.82 (11.90)	2.30	-39.20, 47.50

Week 96	247	80.83 (15.30)	84.73	29.77, 100.00	247	2.64 (12.39)	2.27	-37.56, 50.30

Max = maximum, Min = minimum, NEI-VFQ25 = National Eye Institute Visual Functioning Questionnaire-25, OC = observed cases, SD = standard deviation
OC prior to intercurrent event (ICE): observations after an ICE defined for the primary estimand excluded. Intercurrent events (ICE) were handled according to primary estimand strategy for continuous endpoints

[000752]Overall, the proportions of participants gaining or losing at least 5 or 10 letters in BCVA from baseline at Week 96 were similar across the treatment groups, with minor numerical differences in favor of the 2q8 group, as can be seen from Table 2-60.

[000753]The proportion of participants gaining at least 10 letters or at least 5 letters in BCVA from baseline at Week 96 were numerically higher in the 2q8 group than in the HDq12 and HDq16 treatment groups, based on LOCF in the FAS. In contrast, the proportion of participants who showed any gain (> 0 letters) in BCVA from baseline was similar in the HDq16 and 2q8 groups and lower in the HDq12 group.

[000754]The proportions of participants gaining at least 15 letters in BCVA from baseline at Week 96, using LOCF in the FAS, were similar across the 3 treatment groups; the small numerical differences across the treatment groups were not clinically meaningful. The proportions and between-treatment differences obtained for the corresponding analysis based on OC prior to ICE were consistent with the results using LOCF.

[000755]The proportions of participants who gained at least 15 letters in BCVA from baseline remained at similar levels in all 3 treatment groups through Week 96 (22.2% to 24.2%).

[000756]The numerical differences in the proportion of participants who lost at least 5 or 10 letters across the treatment groups at Week 96 were generally small, with the lowest proportions of participants who lost at least 5 letters observed in the HDq12 group and of those who lost at least 10 letters in the 2q8 group. The results of the analysis for the same endpoint using OC prior to ICE at Week 96 were in line with those based on LOCF in the FAS.

[000757]The proportion of participants who lost at least 15 letters in BCVA from baseline was < 8.0% at Week 96 in all 3 treatment groups, based on LOCF in the FAS, with only small numerical differences across the treatment groups, as can be seen in Table 2-60. The analysis of the same endpoint using OC prior to ICE in the FAS provided proportions of participants who lost at least 15 letters in BCVA from baseline at Week 96 of 5.3%, 7.4% and 8.0% in the 2q8,

HDq12, and HDq16 group, respectively. This was generally consistent with the results based on LOCF in the FAS.

Table 2-60. Proportion of participants who gained or lost at least 5, 10 or 15 letters in BCVA from baseline at Week 96, LOCF (full analysis set)

Response category	Treatment	Subjects with response category, Num/Den (%)
Gained ≥ 15 letters	2q8 (N=336)	81/335 (24.2%)
	HDq12 (N=335)	74/334 (22.2%)
	HDq16 (N=338)	77/337 (22.8%)
Gained ≥ 10 letters	2q8 (N=336)	151/335 (45.1%)
	HDq12 (N=335)	129/334 (38.6%)
	HDq16 (N=338)	133/337 (39.5%)
Gained ≥ 5 letters	2q8 (N=336)	208/335 (62.1%)
	HDq12 (N=335)	182/334 (54.5%)
	HDq16 (N=338)	185/337 (54.9%)
Gained > 0 letters (any gain)	2q8 (N=336)	245/335 (73.1%)
	HDq12 (N=335)	225/334 (67.4%)
	HDq16 (N=338)	246/337 (73.0%)
Lost ≥ 5 letters	2q8 (N=336)	52/335 (15.5%)
	HDq12 (N=335)	50/334 (15.0%)
	HDq16 (N=338)	59/337 (17.5%)
Lost ≥ 10 letters	2q8 (N=336)	25/335 (7.5%)
	HDq12 (N=335)	34/334 (10.2%)
	HDq16 (N=338)	42/337 (12.5%)
Lost ≥ 15 letters	2q8 (N=336)	17/335 (5.1%)
	HDq12 (N=335)	26/334 (7.8%)
	HDq16 (N=338)	26/337 (7.7%)

BCVA = best corrected visual acuity, Num/Den = numerator/denominator, SAP = statistical analysis plan
LOCF (last observation carried forward): last available observed value prior to ICE was used to impute missing data.
Intercurrent events (ICE) were handled according to sensitivity estimand strategy for continuous endpoints.

[000758]The proportions of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent) at Week 96 using LOCF in the FAS were similar across the 3 treatment groups; the small numerical differences across the treatment groups were not clinically meaningful (Table 2-61). The proportions and between treatment differences obtained

for the corresponding analysis based on OC prior to ICE were consistent with the results using LOCF.

[000759]The proportions of participants achieving an ETDRS letter score of at least 69 was > 50% with similar values in all 3 treatment groups at Week 96 (53.1% to 56.7%). These data were consistent with previous results.

Table 2-61. Proportion of participants who achieved an ETDRS letter score of at least 69 at Week 96, LOCF (full analysis set)

	2q8 N = 336	HDq12 N = 335	HDq16 N = 338
Subjects who achieved ≥ 69 letters, Num/Den (%)	190/335 (56.7%)	178/334 (53.3%)	179/337 (53.1%)
Contrast	/	HDq12 - 2q8	HDq16 - 2q8
Difference (a) % (two-sided 95% CI)	/	-2.689 (-9.410, 4.031)	-2.448 (-9.120, 4.224)
CMH test (b) p-value	/	0.4324	0.4711

BCVA = best corrected visual acuity, CI = Confidence interval, CMH = Cochran-Mantel-Haenszel, ETDRS = Early Treatment Diabetic Retinopathy Study, LOCF = Last observation carried forward, Num/Den = numerator/denominator, SAP = statistical analysis plan
LOCF method for the last available observed value prior to ICE was carried forward to impute missing data
Intercurrent events (ICE) were handled according to sensitivity estimand strategy for continuous endpoints.
(a) Difference is HD groups minus 2q8 and CI was calculated using Mantel-Haenszel weighting scheme adjusted by geographical region and baseline BCVA (< 60 vs. ≥ 60) and is displayed with two-sided 95% Cis.
(b) Nominal p-value for the two-sided CMH test.

[000760]Table 2-62 summarizes the number of participants with ocular TEAEs in the study eye occurring in $\geq$ 2% of the participants in any treatment group through Week 96.

[000761]The frequencies of participants with ocular TEAEs of the study eye were similar across the treatment groups. There were no notable differences observed between treatment groups for any of the system organ classes or preferred terms reported.

[000762]Ocular TEAEs in the study eye were reported in 345 (51.3%) participants in the pooled HD groups (171 [51.0%] in the HDq12 group and 174 [51.5%] in the HDq16 group) and 181 (53.9%) participants in the 2q8 group. The most frequently (> 5% in any treatment group) reported ocular TEAEs in the study eye were Cataract (which was reported in 63 [9.4%] participants in the pooled HD groups and 22 [6.5%] participants in the 2q8 group), visual acuity reduced (which was reported in 44 [6.5%] participants in the pooled HD groups and 24 [7.1%] participants in the 2q8 group), and retinal haemorrhage (which was reported in 37 [5.5%]

participants in the pooled HD groups and 19 [5.7%] participants in the 2q8 group), all within the SOC Eye disorders. Ocular serious TEAEs are summarized in Table 2-63.

[000763]At week 96, the mean number of aflibercept injections per patient was 9.2, 7.8, and 11.9 in the 8q12, 8q16, and 2q8 arms respectively. The TEAE of IOP increased was reported in 3.6%, 3.3%, and 3.0% of patients in the 8q12, 8q16, and 2q8 arms, respectively, and the TEAE of ocular hypertension was reported in 1.2%, 1.2%, and 0.3%, respectively. Mean pre-dose IOP in the 8q12, 8q16, and 2q8 arms, respectively, was 14.9, 14.9, and 14.8 mmHg at baseline and 14.7, 15.0, and 14.5 mmHg at week 96. The proportion of patients with any pre-dose IOP ≥25mmHg through W96 was 2.7% (8q12), 2.1% (8q16), and 1.8% (2q8). At active dosing visits, mean±SD change from pre- to post-dose IOP was 3.4±3.8, 3.5±3.7, and 2.6±3.6 mmHg in the 8q12, 8q16, and 2q8 arms, respectively. Through week 96, the proportion of patients with any pre-dose or post-dose IOP ≥35 mmHg was 0.9% (8q12), 0.3% (8q16), and 0.6% (2q8).

[000764]Ocular TEAEs in the fellow eye were reported in similar proportions in the HD and the 2q8 groups, with 252 (37.4%) participants in the pooled HD groups (123 [36.7%] in the HDq12 group and 129 [38.2%] in the HDq16 group) and 132 (39.3%) participants in the 2q8 group. The most frequently (> 5% in any treatment group) reported ocular TEAEs in the fellow eye were Cataract, with 53 (7.9%) participants in the pooled HD groups (26 [7.8%] in the HDq12 group and 27 [8.0%] in the HDq16 group) and 18 (5.4%) participants in the 2q8 group, and Neovascular age-related macular degeneration, with 57 (8.5%) participants in the pooled HD groups (20 [6.0%] in the HDq12 group and 37 [10.9%] in the HDq16 group) and 23 (6.8%) participants in the 2q8 group. These ocular TEAEs in the fellow eye were also reported in similar proportions in the HD and the 2q8 groups.

[000765]Ocular TEAEs in the study eye judged to be related to study drug were reported in 40 (5.9%) participants in the pooled HD groups (21 [6.3%] in the HDq12 group and 19 [5.6%] in the HDq16 group) and 16 (4.8%) participants in the 2q8 group. The only ocular TEAEs in the study eye judged to be related to study drug that were reported for more than 2 participants in any treatment group were visual acuity reduced, Retinal pigment epithelial tear, and Intraocular pressure increased. Visual acuity reduced was reported in 6 (0.9%) participants in the pooled HD groups (4 [1.2%] in the HDq12 group and 2 (0.6%) in the HDq16 group) and no participants in the 2q8 group. Retinal pigment epithelial tear was reported in 4 (0.6%) participants in the pooled HD groups (3 [0.9%] in the HDq12 group and 1 (0.3%) in the HDq16 group) and 1 (0.3%) participant in the 2q8 group. Intraocular pressure increased was reported in 4 (0.6%) participants in the pooled HD groups (2 [0.6%] in the HDq12 group and 2 (0.6%) in the HDq16

group) and 3 (0.9%) participants in the 2q8 group. All events of visual acuity reduced judged to be related to study drug resolved or were resolving through Week 96.

[000766]Ocular TEAEs in the fellow eye judged to be related to study drug through Week 96 were reported in 3 (0.4%) participants in the pooled HD groups (1 [0.3%] in the HDq12 group and 2 [0.6%] in the HDq16 group) and 2 (0.6%) participants in the 2q8 group. These TEAEs were Visual acuity tests abnormal in the HDq12 group, cataract and iridocyclitis in the HDq16 group, and neovascular age-related macular degeneration and endophthalmitis in the 2q8 group.

[000767]Non-ocular TEAEs judged to be related to study drug through Week 96 were reported in 6 (0.9%) participants in the pooled HD groups (3 [0.9%] in the HDq12 group and 3 [0.9%] in the HDq16 group) and 7 (2.1%) participants in the 2q8 group. The only TEAEs that were reported in 2 (0.6%) participants were observed in the HDq16 group (myocardial infarction) and 2q8 group (cerebrovascular accident). No other non ocular TEAEs were reported for more than 1 participant in any treatment group.

[000768]Overall, the proportions of ocular TEAEs related to IVT injection procedure in the study eye were similar between the HD groups and the 2q8 group.

[000769]These IVT injection procedure-related TEAEs were reported in 82 (12.2%) of the participants in the pooled HD groups (39 [11.6%] in the HDq12 group and 43 [12.7%] in the HDq16 group) and 51 (15.2%) participants in the 2q8 group. The most common of these TEAEs in the pooled HD groups, reported in 5 or more participants, were intraocular pressure increased, conjunctival haemorrhage, vitreous floaters, ocular hypertension, eye irritation, eye pain, and sensation of foreign body. All other IVT injection procedure-related TEAEs in the study eye were reported in less than 5 participants in each treatment group.

[000770]Ocular IVT injection procedure-related TEAEs in the fellow eye through Week 96 were reported in 13 (1.9%) of the participants in the pooled HD groups (6 [1.8%] in the HDq12 group and 7 [2.1%] in the HDq16 group) and 10 (3.0%) participants in the 2q8 group. No IVT injection procedure-related TEAEs in the fellow eye were reported in more than 2 participants in any treatment group, except for conjunctival haemorrhage (4 participants in the HDq12 group and 2 participants in the 2q8 group).

[000771]Non-ocular IVT injection procedure-related TEAEs through Week 96 were reported in 6 (0.9%) of the participants in the pooled HD groups (4 [1.2%] in the HDq12 group and 2 [0.6%]

in the HDq16 group) and 1 (0.3%) participant in the 2q8 group. Non-ocular IVT injection procedure-related TEAEs were reported only in single participants in each treatment group.

Table 2-62. Ocular TEAEs in the Study Eye ≥2% through Week 96

	2q8	HDq12	HDq16	All HD
N (SAF)	336	335	338	673
Number of Patients ≥ 1 AE, n (%)	181 (53.9%)	172 (51.3%)	175 (51.8%)	347 (51.6%)
Cataract	22 (6.5%)	31 (9.3%)	32 (9.5%)	63 (9.4%)
Conjunctival haemorrhage	9 (2.7%)	10 (3.0%)	8 (2.4%)	18 (2.7%)
Dry age-related macular degeneration	7 (2.1%)	5 (1.5%)	3 (0.9%)	8 (1.2%)
Dry eye	11 (3.3%)	8 (2.4%)	8 (2.4%)	16 (2.4%)
Macular oedema	10 (3.0%)	3 (0.9%)	11 (3.3%)	14 (2.1%)
Macular thickening	7 (2.1%)	10 (3.0%)	9 (2.7%)	19 (2.8%)
Neovascular age-related macular degeneration	3 (0.9%)	10 (3.0%)	8 (2.4%)	18 (2.7%)
Posterior capsule opacification	2 (0.6%)	5 (1.5%)	7 (2.1%)	12 (1.8%)
Retinal haemorrhage	19 (5.7%)	18 (5.4%)	19 (5.6%)	37 (5.5%)
Subretinal fluid	16 (4.8%)	14 (4.2%)	9 (2.7%)	23 (3.4%)
Visual acuity reduced	24 (7.1%)	21 (6.3%)	25 (7.4%)	46 (6.8%)
Vitreous detachment	7 (2.1%)	8 (2.4%)	12 (3.6%)	20 (3.0%)
Vitreous floaters	16 (4.8%)	5 (1.5%)	17 (5.0%)	22 (3.3%)
Sensation of foreign body	7 (2.1%)	3 (0.9%)	4 (1.2%)	7 (1.0%)
Conjunctivitis	9 (2.7%)	9 (2.7%)	4 (1.2%)	13 (1.9%)
Intraocular pressure increased	10 (3.0%)	12 (3.6%)	11 (3.3%)	23 (3.4%)

Table 2-63. Ocular Serious TEAEs in the Study Eye through Week 96

	2q8	HDq12	HDq16	All HD
N (SAF)	336	335	338	673
Number of Patients ≥ 1 AE, n (%)	4 (1.2%)	10 (3.0%)	10 (3.0%)	20 (3.0%)

Angle closure glaucoma	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
Cataract	0	2 (0.6%)	2 (0.6%)	4 (0.6%)
Dry age-related macular degeneration	0	1 (0.3%)	0	1 (0.1%)
Macular detachment	0	1 (0.3%)	0	1 (0.1%)
Retinal detachment	1 (0.3%)	2 (0.6%)	3 (0.9%)	5 (0.7%)
Retinal haemorrhage	1 (0.3%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
Retinal tear	0	0	1 (0.3%)	1 (0.1%)
Vitreous haemorrhage	0	0	1 (0.3%)	1 (0.1%)
Endophthalmitis	1 (0.3%)	0	0	0
Skin laceration	0	0	1 (0.3%)	1 (0.1%)
Intraocular pressure increased	0	2 (0.6%)	0	2 (0.3%)

[000772]The proportion of participants with increases in pre-dose IOP from baseline ≥ 10 mmHg, with IOP values > 21 or ≥ 25 mmHg at pre-dose, or ≥ 35 mmHg at pre- or post-dose assessments was generally low (< 12.5%) and similar across the treatment groups.

Table 2-64. Intraocular Pressure Criteria through Week 96

	2q8	**HDq12**	**HDq16**	**All HD**
N (SAF)	336	335	338	673
Subjects with increase ≥ 10 mmHg in pre-dose IOP from baseline	11/336 (3.3%)	8/335 (2.4%)	10/338 (3.0%)	18/673 (2.7%)
Subjects with > 21 mmHg pre-dose measurement	35/336 (10.4%)	40/335 (11.9%)	42/338 (12.4%)	82/673 (12.2%)
Subjects with ≥ 25 mmHg pre-dose measurement	6/336 (1.8%)	9/335 (2.7%)	7/338 (2.1%)	16/673 (2.4%)
Subjects with ≥ 35 mmHg pre-dose or post-dose measurement	2/336 (0.6%)	3/335 (0.9%)	1/338 (0.3%)	4/673 (0.6%)

[000773] The number (proportion) of participants with TEAEs related to intraocular inflammation in the study eye was low and similar among the treatment groups.

Table 2-65. Intraocular Inflammation in the Study Eye through Week 96

	2q8	HDq12	HDq16	All HD
N (SAF)	336	335	338	673
Number of Patients with IOI AE, n (%)	7 (2.1%)	6 (1.8%)	3 (0.9%)	9 (1.3%)
Anterior chamber cell	0	1 (0.3%)	0	1 (0.1%)
Eye inflammation	1 (0.3%)	0	0	0
Iridocyclitis	1 (0.3%)	0	3 (0.9%)	3 (0.4%)
Iritis	0	1 (0.3%)	0	1 (0.1%)
Uveitis	1 (0.3%)	1 (0.3%)	0	1 (0.1%)
Vitreal cells	2 (0.6%)	1 (0.3%)	0	1 (0.1%)
Vitritis	0	1 (0.3%)	0	1 (0.1%)
Chorioretinitis	0	1 (0.3%)	0	1 (0.1%)
Endophthalmitis	2 (0.6%)	0	0	0
Hypopyon	1 (0.3%)	0	0	0

[000774]Non-ocular TEAEs were reported in 500 (74.3%) participants in the pooled HD groups (253 [75.5%] in the HDq12 group and 247 [73.1%] in the HDq16 group) and 257 (76.5%) participants in the 2q8 group. The most frequently reported non ocular TEAE was COVID 19, with 130 (19.3%) participants in the pooled HD groups (58 [17.3%] in the HDq12 group and 72 [21.3%] in the HDq16 group) and 60 (17.9%) participants in the 2q8 group.

Table 2-66. Non-Ocular Safety Summary through Week 96

	2q8	HDq12	HDq16	All HD

N (SAF)	336	335	338	673
Patients with ≥ 1 AE (%)				
Hypertension events	8.0%	8.1%	8.3%	8.2%
APTC events	3.3%	1.5%	2.1%	1.8%
Non-ocular SAEs	19.6%	21.8%	18.9%	20.4%
Deaths	3.6%	3.0%	2.1%	2.5%

Table 2-67. Non-Ocular TEAEs ≥2% through Week 96

	2q8	**HDq12**	**HDq16**	**All HD**
N (SAF)	336	335	338	673
Number of Patients ≥ 1 AE, n (%)	257 (76.5%)	253 (75.5%)	247 (73.1%)	500 (74.3%)
Atrial fibrillation	7 (2.1%)	7 (2.1%)	6 (1.8%)	13 (1.9%)
Diarrhoea	6 (1.8%)	12 (3.6%)	6 (1.8%)	18 (2.7%)
Gastrooesophageal reflux disease	2 (0.6%)	6 (1.8%)	8 (2.4%)	14 (2.1%)
Nausea	5 (1.5%)	6 (1.8%)	9 (2.7%)	15 (2.2%)
Pyrexia	10 (3.0%)	8 (2.4%)	3 (0.9%)	11 (1.6%)
Bronchitis	10 (3.0%)	8 (2.4%)	5 (1.5%)	13 (1.9%)
COVID-19	60 (17.9%)	58 (17.3%)	72 (21.3%)	130 (19.3%)
Nasopharyngitis	30 (8.9%)	18 (5.4%)	27 (8.0%)	45 (6.7%)
Pneumonia	8 (2.4%)	7 (2.1%)	10 (3.0%)	17 (2.5%)
Sinusitis	7 (2.1%)	2 (0.6%)	3 (0.9%)	5 (0.7%)
Upper respiratory tract infection	12 (3.6%)	11 (3.3%)	8 (2.4%)	19 (2.8%)
Urinary tract infection	21 (6.3%)	13 (3.9%)	16 (4.7%)	29 (4.3%)
Contusion	6 (1.8%)	7 (2.1%)	2 (0.6%)	9 (1.3%)

Fall	13 (3.9%)	6 (1.8%)	6 (1.8%)	12 (1.8%)
Arthralgia	8 (2.4%)	12 (3.6%)	11 (3.3%)	23 (3.4%)
Back pain	22 (6.5%)	18 (5.4%)	15 (4.4%)	33 (4.9%)
Osteoarthritis	9 (2.7%)	8 (2.4%)	10 (3.0%)	18 (2.7%)
Dizziness	9 (2.7%)	5 (1.5%)	6 (1.8%)	11 (1.6%)
Headache	9 (2.7%)	8 (2.4%)	8 (2.4%)	16 (2.4%)
Insomnia	2 (0.6%)	7 (2.1%)	1 (0.3%)	8 (1.2%)
Benign prostatic hyperplasia	4 (1.2%)	5 (1.5%)	7 (2.1%)	12 (1.8%)
Cough	10 (3.0%)	9 (2.7%)	13 (3.8%)	22 (3.3%)
Eczema	2 (0.6%)	2 (0.6%)	7 (2.1%)	9 (1.3%)
Hypertension	18 (5.4%)	23 (6.9%)	23 (6.8%)	46 (6.8%)

Table 2-68. Non-Ocular Serious TEAEs ≥1% through Week 96

	2q8	**HDq12**	**HDq16**	**All HD**
N (SAF)	336	335	338	673
Number of Patients ≥ 1 AE, n (%)	66 (19.6%)	73 (21.8%)	64 (18.9%)	137 (20.4%)
Angina pectoris	1 (0.3%)	0	4 (1.2%)	4 (0.6%)
Pneumonia	2 (0.6%)	5 (1.5%)	5 (1.5%)	10 (1.5%)
Urinary tract infection	5 (1.5%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Osteoarthritis	3 (0.9%)	5 (1.5%)	3 (0.9%)	8 (1.2%)

[000775]The number (proportion) of participants with TEAEs related to hypertension was low and similar among the treatment groups. By comparison, approximately 62% of the participants in all treatment groups had a medical history of Hypertension. See Table 2-69.

Table 2-69. Hypertension events through Week 96

	2q8	**HDq12**	**HDq16**	**All HD**
N (SAF)	336	335	338	673
# of Patients with ≥ 1 AE, n (%)	27 (8.0%)	27 (8.1%)	28 (8.3%)	55 (8.2%)
Retinopathy hypertensive	1 (0.3%)	0	0	0

Blood pressure diastolic increased	1 (0.3%)	0	0	0
Blood pressure increased	5 (1.5%)	3 (0.9%)	6 (1.8%)	9 (1.3%)
Blood pressure systolic increased	1 (0.3%)	2 (0.6%)	0	2 (0.3%)
Blood pressure inadequately controlled	0	1 (0.3%)	0	1 (0.1%)
Diastolic hypertension	0	0	1 (0.3%)	1 (0.1%)
Essential hypertension	1 (0.3%)	0	0	0
Hypertension	18 (5.4%)	23 (6.9%)	23 (6.8%)	46 (6.8%)
Systolic hypertension	0	1 (0.3%)	0	1 (0.1%)
White coat hypertension	1 (0.3%)	0	0	0

[000776]The number (proportion) of participants with adjudicated APTC events was low and similar among the treatment groups. See Table 2-70.

Table 2-70. APTC Events through Week 96

	2q8	**HDq12**	**HDq16**	**All HD**
N (SAF)	336	335	338	673
# of Patients with ≥ 1 APTC AE, n (%)	11 (3.3%)	5 (1.5%)	7 (2.1%)	12 (1.8%)
Acute coronary syndrome	1 (0.3%)	0	0	0
Acute myocardial infarction	2 (0.6%)	1 (0.3%)	0	1 (0.1%)
Arteriosclerosis coronary artery	0	1 (0.3%)	0	1 (0.1%)
Cardiac arrest	1 (0.3%)	0	0	0
Myocardial infarction	2 (0.6%)	0	4 (1.2%)	4 (0.6%)
Myocardial ischaemia	1 (0.3%)	0	0	0
Death	0	1 (0.3%)	2 (0.6%)	3 (0.4%)
Carotid aneurysm rupture	0	1 (0.3%)	0	1 (0.1%)

Cerebral haematoma	1 (0.3%)	0	0	0
Cerebral infarction	2 (0.6%)	0	0	0
Cerebrovascular accident	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Stroke in evolution	0	1 (0.3%)	0	1 (0.1%)

[000777]The death rate (number [percentage] of AEs with fatal outcome) was low and similar across the treatment groups. None of these AEs have been assessed to be related to study drug. Of note, 2 participants had end of study dates after their death dates.

Table 2-71. Deaths through Week 96

	2q8	**HDq12**	**HDq16**	**All HD**
N (SAF)	336	335	338	673
Number of Deaths, n (%)	12 (3.6%)	10 (3.0%)	7 (2.1%)	17 (2.5%)
Acute myocardial infarction	1 (0.3%)	0	0	0
Arteriosclerosis coronary artery	0	1 (0.3%)	0	1 (0.1%)
Cardiac arrest	1 (0.3%)	0	0	0
Cardiac failure	1 (0.3%)	0	1 (0.3%)	1 (0.1%)
Myocardial infarction	0	1 (0.3%)	0	1 (0.1%)
Myocardial ischaemia	1 (0.3%)	0	0	0
Abdominal strangulated hernia	1 (0.3%)	0	0	0
Death	1 (0.3%)	1 (0.3%)	2 (0.6%)	3 (0.4%)
Abdominal strangulated hernia	1 (0.3%)	0	0	0
COVID-19	0	0	1 (0.3%)	1 (0.1%)
COVID-19 pneumonia	0	1 (0.3%)	0	1 (0.1%)
Pneumonia	0	1 (0.3%)	0	1 (0.1%)

Pneumonia aspiration	1 (0.3%)	0	0	0
Sepsis	0	0	1 (0.3%)	1 (0.1%)
Skull fracture	1 (0.3%)	0	0	0
Adenocarcinoma of colon	0	1 (0.3%)	0	1 (0.1%)
Lung carcinoma cell type unspecified stage IV	0	1 (0.3%)	0	1 (0.1%)
Lung neoplasm malignant	1 (0.3%)	0	0	0
Metastatic neoplasm	0	1 (0.3%)	0	1 (0.1%)
Non-small cell lung cancer	0	1 (0.3%)	0	1 (0.1%)
Carotid aneurysm rupture	0	1 (0.3%)	0	1 (0.1%)
Cerebral haematoma	1 (0.3%)	0	0	0
Cerebral infarction	1 (0.3%)	0	0	0
Intracranial mass	1 (0.3%)	0	0	0
Chronic obstructive pulmonary disease	0	0	1 (0.3%)	1 (0.1%)
Hypoxia	1 (0.3%)	0	0	0
Pulmonary embolism	0	0	1 (0.3%)	1 (0.1%)

[000778]Samples for ADA examinations were taken at baseline and subsequently at Week 48 and Week 96 and the results are presented based on the Week 96 database. The samples were analyzed using a validated, electrochemiluminescence bridging assay to detect the presence of ADA.

[000779]Out of the 874 participants in the AAS, a total of 54 participants had positive samples in the ADA assay through at Week 96; 15 participants in the 2q8 group, 23 participants in the HDq12 group, and 16 participants in the HDq16 group, of whom 7, 9, and 3 participants were positive at baseline, respectively (Table 2-72).

[000780]A total of 34 participants participating in this study exhibited a treatment-emergent ADA response; 8 participants in the 2q8 group, 14 participants in the HDq12 group, and 12 participants in the HDq16 group. The incidence of treatment-emergent immunogenicity in the 2q8, HDq12 and HDq16 groups was 2.8%, 4.7%, and 4.1%, respectively. Treatment boosted

ADA was observed in 1 participant in the HDq16 group and all treatment emergent responses were low titer (< 1000). None of the samples that were positive in the ADA assay demonstrated neutralizing activity (Table 2-72).

Table 2-72. Summary of ADA status, ADA category and NAb status through Week 96 (AAS analysis set)

Category	Number (%)	2q8 N = 284 (100%)	HDq12 N = 295 (100%)	HDq16 N = 295 (100%)	All HD N = 590 (100%)
Total ADA subjects	n (%)	284 (100%)	295 (100%)	295 (100%)	590 (100%)
Negative(a)	n (%)	269 (94.7%)	272 (92.2%)	278 (94.2%)	550 (93.2%)
Pre-existing immunoreactivity(b)	n (%)	7 (2.5%)	9 (3.1%)	3 (1.0%)	12 (2.0%)
Treatment-boosted(c)	n (%)	0	0	1 (0.3%)	1 (0.2%)
Treatment-emergent positive(d)	n (%)	8 (2.8%)	14 (4.7%)	12 (4.1%)	26 (4.4%)
Persistent Response(e)	n (%)	1 (0.4%)	3 (1.0%)	3 (1.0%)	6 (1.0%)
Indeterminate Response(f)	n (%)	0	2 (0.7%)	1 (0.3%)	3 (0.5%)
Transient Response(g)	n (%)	7 (2.5%)	9 (3.1%)	8 (2.7%)	17 (2.9%)
Missing	n (%)	0	0	1 (0.3%)	1 (0.2%)
Number in NAbAS analysis set	n (%)	284	295	295	590
Number of subjects ADA negative(h)	n (%)	269 (94.7%)	272 (92.2%)	278 (94.2%)	550 (93.2%)
Number of subjects treatment-emergent ADA positive(h)	n (%)	8 (2.8%)	14 (4.7%)	12 (4.1%)	26 (4.4%)
Number of subjects treatment-emergent NAb ADA positive(h)	n (%)	0	0	0	0

AAS = ADA Analysis Set, ADA = anti-drug antibody, NAb = neutralizing antibody, NAbAS = NAb analysis set

(a) ADA Negative: negative response in the ADA assay at all time points and those that exhibited a pre-existing response, as defined in (b), regardless of any missing samples.

(b) Pre-existing immunoreactivity: either a positive response in the ADA assay at baseline with all post first dose ADA results negative OR a positive response at baseline with all post first dose ADA responses less than 4-fold of baseline titer levels.

(c) Treatment-boosted ADA response: positive response post first dose that is greater than or equal to 4-fold over baseline titer level, when baseline results were positive.

(d) Treatment-emergent positive: ADA-positive response post first dose when baseline results were negative or missing.

(e) Persistent Response - Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points (Week 48 and Week 96), separated by at least 12/16-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.

(f) Indeterminate Response -Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples (either ADA

positive at Week 48, when Week 96 sample is missing or ADA positive at Week 96, when Week 48 sample is missing).
(g) Transient Response -Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.
(h) Percentages are calculated out of the NAbAS analysis set. Samples that tested negative for ADA were not assayed in the NAb assay and the corresponding NAb result were imputed as negative and included as such in the NAbAS analysis set. Participants in the NAbAS with multiple post-dose ADA results which consisted of both imputed NAb-negative result(s) for ADA negative samples and only missing NAb results for all ADA-positive result(s), were set to NAb negative. Participants in the NAbAS that had at least one post-dose positive NAb analysis result were set to NAb positive even if other NAb results were missing.
Treatment-emergent ADA positive: ADA positive response post first dose when baseline results are negative or missing, or ADA positive response more than 4-fold of a positive baseline titer.

[000781]Overall, the low level of immunogenicity was not considered clinically relevant.

[000782]In participants with treatment-emergent ADA, one participant in the HDq12 group had an AE of mild iritis which was not considered to be related to study treatment by the investigator.

[000783]*Pharmacokinetic evaluation.* The PKS was used for the descriptive statistics of the general (sparse) PK assessment and included 934 (92.4%) participants in total and 641 (63.4%) participants with unilateral treatment. A subset of the PKS was used for the analysis of the PK sub-study (DPKS) with dense sampling and included 19 (1.9%) participants with unilateral treatment assessed after the first administration of aflibercept up to Week 48. Data for the PK sub-study were analyzed using non-compartmental analysis (NCA).
[000784]Summary of free aflibercept concentrations for participants in the DPKS are presented by treatment in Table 2-73. After initial IVT administration of 2 mg or 8 mg (HDq12 pooled with HDq16) aflibercept, the concentration-time profiles of free aflibercept were characterized by an initial phase of increasing concentrations reflecting initial absorption from the ocular space and initial distribution into the systemic circulation from the ocular space into systemic circulation followed by a mono-exponential elimination phase.
[000785]For participants with unilateral treatment up to Week 48 enrolled in the dense PK substudy and receiving aflibercept 2 mg (N = 6), plasma concentrations of free aflibercept were detectable in 4 participants on Day 8 but in only 1 single participant on Day 15 with values only twice the LLOQ. For the aflibercept 8 mg treatment (N = 13), free aflibercept concentrations were detectable in 38% the participants (N = 5) at the end of dense PK sampling on Day 29 (Table 2-73). Most of the participants in the 2q8 DPKS had concentrations of free aflibercept < 0.04 mg/L on Day 2 which corresponds to the expected maximum concentration. However, there was 1 participant in the DPKS (2q8) with implausibly high concentrations (up to 15 times

higher than the rest of the participants in this group). These high values in a single participant influence the arithmetic mean considerably. These values appeared pharmacokinetically implausible but were left in this data presentation, since an analytical artifact was not proven. Therefore, the median was more meaningful and was used for comparison, although arithmetic means remained the general base for data presentation.

Table 2-73. Summary of Concentration of Free Aflibercept (mg/L) in Plasma by Time and Treatment in Participants with nAMD With Unilateral Treatment Up To Day 29 – Dense PK Substudy (DPKS)

		Free aflibercept				
Treatment	Time	n total	n ≥ LLOQ	Geom. Mean ± SD	Arithm. Mean ± SD	Median
2q8 (N = 6)	Day 1, Pre-dose	4	0	N.C	0.00 (0.00)	0.00
2q8 (N = 6)	Day 1, 4 Hours Post-dose	6	3	N.C	0.0182 (0.0210)	0.0127
2q8 (N = 6)	Day 1, 8 Hours Post-dose	5	4	0.03 (3.31)	0.0549 (0.0742)	0.0282
2q8 (N = 6)	Day 2	6	6	0.04 (2.68)	0.0734 (0.105)	0.0357
2q8 (N = 6)	Day 3	6	6	0.04 (2.49)	0.0622 (0.0835)	0.0320
2q8 (N = 6)	Day 5	6	5	0.03 (2.67)	0.0451 (0.0580)	0.0283
2q8 (N = 6)	Day 8	5	4	0.02 (1.66)	0.0187 (0.0110)	0.0212
2q8 (N = 6)	Day 15	5	1	N.C	0.00624 (0.0140)	0.00
2q8 (N = 6)	Day 22	5	0	N.C	0.00 (0.00)	0.00
2q8 (N = 6)	Day 29	5	1	N.C	0.00330 (0.00738)	0.00
HDq12 +HDq16 (N = 13)	Day 1, Pre-dose	12	0	N.C	0.00 (0.00)	0.00
HDq12 +HDq16 (N = 13)	Day 1, 4 Hours Post-dose	13	6	N.C	0.0409 (0.0605)	0.00
HDq12 +HDq16 (N = 13)	Day 1, 8 Hours Post-dose	12	9	0.05 (3.78)	0.0973 (0.102)	0.0672
HDq12 +HDq16 (N = 13)	Day 2	12	12	0.11 (2.21)	0.146 (0.110)	0.0903
HDq12 +HDq16 (N = 13)	Day 3	12	12	0.11 (2.06)	0.137 (0.0947)	0.112
HDq12 +HDq16 (N = 13)	Day 5	11	11	0.08 (1.86)	0.0933 (0.0481)	0.0854
HDq12 +HDq16 (N = 13)	Day 8	13	13	0.07 (1.75)	0.0794 (0.0413)	0.0682
HDq12 +HDq16 (N = 13)	Day 15	13	12	0.04 (1.76)	0.0435 (0.0199)	0.0385
HDq12 +HDq16 (N = 13)	Day 22	11	9	0.02 (1.76)	0.0213 (0.0148)	0.0232
HDq12 +HDq16 (N = 13)	Day 29	12	5	N.C	0.00766 (0.00958)	0.00

Arithm. = arithmetic, DPKS = dense pharmacokinetic analysis set, LLOQ = lower level of quantification, geom. = geometric, N = Number of participants with unilateral treatment up to Week 48, n = Number of observations, nAMD = neovascular (wet) age-related macular degeneration, PK = pharmacokinetic, SD = standard deviation; N.C.: not calculated (less than 2/3 of values per time point are ≥ LLOQ for geometric mean calculation). Values below LLOQ (0.0156 mg/L) were substituted by 1/2 LLOQ for the calculation of geometric statistics and 0 for arithmetic statistics and median. Minimum and Maximum have been rounded to 4 decimal places.

[000786]Summaries of PK parameters for free aflibercept for participants in the DPKS are presented by treatment in Table 2-74 for non-Japanese (rest of world) participants and in Table 2-75 for Japanese participants.

[000787]After the initial monthly aflibercept dose of 2 mg (2q8) or 8 mg (HDq12 pooled with HDq16) in non-Japanese participants, free aflibercept median time to peak concentration (t_{max}) was 1.05 and 1.93 days for the aflibercept 2 mg and 8 mg treatments, respectively. As the IVT dose of aflibercept increased from 2 mg to 8 mg (4-fold ratio), the median peak concentration (C_{max}) for free aflibercept increased in a slightly less than dose-proportional manner (about 3-fold) and in a greater than dose-proportional manner (about 7-fold) for median area under the plasma concentration-time curve from time zero to the time of the last measurable concentration (AUC_{last}).

[000788]Following the third initial monthly IVT dose of aflibercept, based on the ratio of aflibercept concentration at Week 12 to Week 4 (C_{Week12}/C_{Week4}), the accumulation ratio of free aflibercept was 1.17 for HDq12 + HDq16 (Table 2-74). The accumulation ratio of free aflibercept could not be determined for 2q8 since all aflibercept concentration values at Week 12 were below LLOQ.

[000789]In general, concentrations of free aflibercept as well as PK parameters (C_{max}, AUC_{last}) in a single Japanese participant (in the HDq12 + HDq16 group) were in the same range of values seen in non-Japanese participants after administration of aflibercept 8 mg.

Table 2-74. Summary Statistics of Free Aflibercept Pharmacokinetic Parameters in Plasma in Participant with Unilateral Treatment from Pooled Region: Rest Of The World – Dense PK Substudy (DPKS)

Pooled region	PK parameter (unit)	Treatment	n	Geom. mean (SD)	Geom. Mean 95% CI	Geom. CV (%)	Arithm. mean (SD)	Arithm. CV (%)	Median	Min, Max
Rest of the World	Cmax (mg/L)	2q8 (N = 6)	6	0.0469 (2.51)	0.02, 0.12	116	0.0758 (0.103)	136	0.0357	0.0223, 0.286
		HDq12+HDq16 (N = 11)	11	0.115 (1.95)	0.06, 0.22	74.8	0.137 (0.0755)	55.0	0.111	0.0288, 0.231
	Cmax/Dose (mg/L/mg)	2q8 (N = 6)	6	0.0235 (2.51)	0.01, 0.06	116	0.0379 (0.0517)	136	0.0179	0.0112, 0.143
		HDq12+HDq16 (N = 11)	11	0.0144 (1.95)	0.01, 0.03	74.8	0.0171 (0.00943)	55.0	0.0139	0.0036, 0.0289
	Clast (mg/L)	2q8 (N = 6)	6	0.0202 (1.12)	0.02, 0.02	11.5	0.0203 (0.00226)	11.1	0.0202	0.0165, 0.0235
		HDq12+HDq16 (N = 11)	11	0.0217 (1.44)	0.02, 0.03	37.6	0.0233 (0.0113)	48.7	0.0183	0.0164, 0.0549
	Ctrough (mg/L) Day 29	2q8 (N = 6)	5	0.0165 (NE)	NE	NE	0.00330 (0.00738)	224	0.00	0.00, 0.0165
		HDq12+HDq16 (N = 11)	10	0.0186 (1.14)	0.02, 0.02	13.3	0.00750 (0.00980)	131	0.00	0.00, 0.0226
	AUClast (day*mg/L)	2q8 (N = 6)	6	0.188 (3.17)	0.06, 0.60	167	0.362 (0.538)	149	0.18	0.0532, 1.45
		HDq12+HDq16 (N = 11)	11	1.12 (1.99)	0.56, 2.23	78.0	1.28 (0.476)	37.1	1.31	0.156, 1.85
	AUCinf (day*mg/L)	2q8 (N = 6)	0	/	/	/	/	/	/	/

		HDq12+HDq16 (N = 11)	7	1.73 (1.19)	1.46, 2.05	17.2	1.749 (0.26879)	15.4	1.83	1.22, 1.98
	AUCinf/Dose (day*mg/L/mg)	2q8 (N = 6)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 11)	7	0.216 (1.19)	0.18, 0.26	17.2	0.219 (0.0336)	15.4	0.229	0.153, 1.98
	AUC(0-28d) Norm by WT (day*mg/L/kg)	2q8 (N = 6)	3	0.0059 (2.26)	0.00, 0.01	96.9	0.00753 (0.00656)	87.1	0.00413	0.0034, 0.0151
		HDq12+HDq16 (N = 11)	9	0.0172 (1.32)	0.01, 0.02	27.9	0.0177 (0.00441)	24.9	0.0161	0.0098, 0.0232
	Accumulation Ratio (C_{Week12}/C_{Week4})	2q8 (N = 6)	1	NE (NE)	NE	NE	0.00 (NE)	NE	0.00	0.00, 0.00
		HDq12+HDq16 (N = 11)	4	1.16 (1.11)	1.05, 1.29	10.2	1.165 (0.118)	10.1	1.17	1.04, 1.28
	t1/2 (day)	2q8 (N = 6)	2	5.93 (1.04)	5.72, 6.16	3.71	5.94 (0.220)	3.71	5.94	5.78, 6.09
		HDq12+HDq16 (N = 11)	9	10.3 (1.95)	5.30, 20.1	74.7	13.3 (13.1)	98.6	10.6	5.21, 47.3
	tmax (day)	2q8 (N = 6)	6	/	/	/	/	/	1.05	0.333, 1.95
		HDq12+HDq16 (N = 11)	11	/	/	/	/	/	1.93	0.333, 4.03
	tlast (day)	2q8 (N = 6)	6	/	/	/	/	/	6.98	2.00, 26.9
		HDq12+HDq16 (N = 11)	11	/	/	/	/	/	21.1	7.05, 28.1

Arithm. = arithmetic, AUC_{inf} = Area under the curve from time zero to infinity, AUC_{last} = Area under the curve to the last quantifiable concentration, CI = confidence interval, C_{last} = Last concentration, C_{max} = Maximum concentration, C_{trough} = trough concentration, CV = coefficient of variation, geom. = geometric, DPKS = dense pharmacokinetic analysis set, LLOQ = Lower level of quantification, Max = Maximum, Min = Minimum, N = Number of participants with unilateral treatment up to Week 48, n = Number of observations, NE = Not Evaluable, PK = pharmacokinetic, SD = Standard deviation, $t_{1/2}$ = half-life, t_{last} = time to last concentration, t_{max} = time to maximum concentration, WT = weight. / indicates categories that do not apply.
For C_{last}, values below LLOQ were substituted by 1/2 LLOQ for the calculation of geometric statistics and 0 for arithmetic statistics.

Table 2-75. Summary Statistics of Free Aflibercept Pharmacokinetic Parameters in Plasma in Participants with Unilateral Treatment from Pooled Region: Japan – Dense PK Substudy (DPKS)

Pooled region	PK parameter (unit)	Treatment	n	Geom. mean (SD)	Geom. Mean 95% CI	Geom. CV (%)	Arithm. mean (SD)	Arthm. CV (%)	Median	Min, Max
Japan	Cmax (mg/L)	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	1	0.393 (NE)	NE	NE	0.393 (NE)	NE	0.39300	0.393, 0.393
	Cmax/Dose (mg/L/mg)	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	1	0.0491 (NE)	NE	NE	0.0491 (NE)	NE	0.0491	0.0491, 0.0491
	Clast (mg/L)	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	1	0.0169 (NE)	NE	NE	0.0169 (NE)	NE	0.01690	0.0169, 0.0169
	Ctrough (mg/L)	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	1	0.0169 (NE)	NE	NE	0.0169 (NE)	NE	0.01690	0.0169, 0.0169
	AUClast (day*mg/L)	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	1	3.51 (NE)	NE	NE	3.51 (NE)	NE	3.51	3.51, 3.51
	AUCinf (day*mg/L)	2q8	0	/	/	/	/	/	/	/

	(N = 0)								
	HDq12+HDq16 (N = 2)	1	3.66 (NE)	NE	NE	3.66 (NE)	NE	3.66	3.66, 3.66
AUCinf/Dose (day*mg/L/mg)	2q8 (N = 0)	0	/	/	/	/	/	/	/
	HDq12+HDq16 (N = 2)	1	0.457 (NE)	NE	NE	0.457 (NE)	NE	0.457	0.457, 0.457
AUC(0-28d) Norm by WT (day*mg/L/kg)	2q8 (N = 0)	0	/	/	/	/	/	/	/
	HDq12+HDq16 (N = 2)	1	0.0807 (NE)	NE	NE	0.0807 (NE)	NE	0.0807	0.0807, 0.0807
Accumulation Ratio (C_{Week12}/C_{Week4})	2q8 (N = 0)	0	/	/	/	/	/	/	/
	HDq12+HDq16 (N = 2)	1	1.37 (NE)	NE	NE	1.37 (NE)	NE	1.37	1.37, 1.37
t1/2 (day)	2q8 (N = 0)	0	/	/	/	/	/	/	/
	HDq12+HDq16 (N = 2)	1	6.03 (NE)	NE	NE	6.03 (NE)	NE	6.03	6.03, 6.03
tmax (day)	2q8 (N = 0)	0	/	/	/	/	/	/	/
	HDq12+HDq16 (N = 1)	1	/	/	/	/	/	1.02	1.02, 1.02
tlast (day)	2q8 (N = 0)	0	/	/	/	/	/	/	/
	HDq12+HDq16 (N = 1)	1	/	/	/	/	/	27.9	27.9, 27.9

Arithm. = arithmetic, AUC_{inf} = Area under the curve from time zero to infinity, AUC_{last} = Area under the curve to the last quantifiable concentration, CI = confidence interval, C_{last} = Last concentration, C_{max} = Maximum concentration, C_{trough} = trough concentration, CV = coefficient of variation, geom. = geometric, DPKS = dense pharmacokinetic analysis set, geom. = geometric, LLOQ = lower level of quantification, Max = maximum, Min = minimum, N = Number of participants with unilateral treatment up to Week 48, n = Number of observations, NE = Not Evaluable, PK = pharmacokinetic, SD = standard deviation, $t_{1/2}$ = half-life, t_{last} = time to last concentration, t_{max} = time to maximum concentration, WT = weight.
/ indicates categories that do not apply. For C_{last}, values below LLOQ were substituted by 1/2 LLOQ for the calculation of geometric statistics and 0 for arithmetic statistics.

[000790]Summary of adjusted bound aflibercept concentrations for participants in the DPKS are presented by treatment in Table 2-76. After the initial IVT administration of aflibercept of 2 mg or 8 mg (HDq12 pooled with HDq16), the concentration-time profiles of adjusted bound aflibercept were characterized by a slower attainment of peak concentration compared to free aflibercept. Following attainment of C_{max}, a slight decrease of the concentration-time profiles was observed until the end of the dosing interval of 4 weeks for both dose groups.

[000791]For unilaterally treated participants enrolled in the dense PK substudy who received aflibercept 2 mg (N = 6), concentrations of adjusted bound aflibercept were detectable in almost all participants until the end of the dense PK sampling. For the aflibercept 8 mg treatment (N = 13), adjusted bound aflibercept concentrations were detectable in almost all participants until the end of the dense PK sampling at Day 29 (Table 2-76).

Table 2-76. Concentration of Adjusted Bound Aflibercept (mg/L) in Plasma by Time and Treatment in Participants with Unilateral Treatment Group up to Day 29 – Dense PK substudy (DPKS)

Treatment	Time	n total	n ≥ LLOQ	Geom. Mean ± SD	Arithm. Mean ± SD
2q8 (N = 6)	Day 1, Pre-dose	4	0	N.C	0.00 (0.00)
2q8 (N = 6)	Day 1, 4 Hours Post-dose	6	0	N.C	0.00 (0.00)
2q8 (N = 6)	Day 1, 8 Hours Post-dose	5	0	N.C	0.00 (0.00)
2q8 (N = 6)	Day 2	6	4	0.02 (1.91)	0.0249 (0.0216)
2q8 (N = 6)	Day 3	6	6	0.06 (1.57)	0.0638 (0.0343)
2q8 (N = 6)	Day 5	6	6	0.10 (1.52)	0.104 (0.0518)
2q8 (N = 6)	Day 8	5	5	0.16 (1.55)	0.179 (0.0990)
2q8 (N = 6)	Day 15	5	5	0.16 (1.65)	0.181 (0.108)
2q8 (N = 6)	Day 22	5	5	0.16 (1.53)	0.169 (0.0773)
2q8 (N = 6)	Day 29	5	5	0.12 (1.90)	0.149 (0.124)
HDq12 +HDq16 (N = 13)	Day 1, Pre-dose	12	0	N.C	0.00 (0.00)
HDq12 +HDq16 (N = 13)	Day 1, 4 Hours Post-dose	13	0	N.C	0.00 (0.00)
HDq12 +HDq16 (N = 13)	Day 1, 8 Hours Post-dose	12	0	N.C	0.00 (0.00)
HDq12 +HDq16 (N = 13)	Day 2	12	10	0.06 (3.50)	0.124 (0.186)
HDq12 +HDq16 (N = 13)	Day 3	12	12	0.13 (2.07)	0.173 (0.155)
HDq12 +HDq16 (N = 13)	Day 5	11	11	0.18 (1.88)	0.223 (0.157)
HDq12 +HDq16 (N = 13)	Day 8	13	13	0.31 (1.56)	0.334 (0.135)
HDq12 +HDq16 (N = 13)	Day 15	13	13	0.37 (1.50)	0.393 (0.130)
HDq12 +HDq16 (N = 13)	Day 22	11	10	0.25 (3.00)	0.335 (0.155)
HDq12 +HDq16 (N = 13)	Day 29	12	12	0.32 (1.39)	0.331 (0.0953)

Arithm. = arithmetic, DPKS = dense pharmacokinetic analysis set, geom. = geometric, LLOQ = Lower level of quantification, N = Number of participants with unilateral treatment up to Week 48, n = Number of observations, PK = pharmacokinetic, SD = standard deviation
N.C.: not calculated (less than 2/3 of values per time point are ≥ LLOQ for geometric mean calculation). Values below LLOQ (0.022442 mg/L) were substituted by 1/2 LLOQ for the calculation of geometric statistics and 0 for arithmetic statistics and median.

[000792]Summaries of PK parameters for adjusted bound aflibercept for participants in the DPKS are presented by treatment in Table 2-77 for non-Japanese participants and in Table 2-78 for Japanese participants.

[000793]After the initial monthly aflibercept dose of 2 mg (2q8) or 8 mg (HDq12 pooled with HDq16), adjusted bound aflibercept median tmax was 14 days for the aflibercept 2 mg and 8 mg treatments. As the IVT dose of aflibercept increased from 2 mg to 8 mg (4-fold dose), the mean C_{max} and mean AUC_{last} for adjusted bound aflibercept increased in a less than dose-proportional manner (about 2 to 2.5-fold) (Table 2-77).

[000794]Following the third initial monthly IVT dose of aflibercept, based on the ratio of aflibercept concentration at Week 12 to Week 4 (C_{Week12}/C_{Week4}), the accumulation ratio of

adjusted bound aflibercept was 1.83 and 1.72 for 2q8, and HDq12+HDq16, respectively (Table 2-77).

[000795]In general, concentrations of adjusted bound aflibercept as well as PK parameters (C_{max}, AUC_{last}) in the 2 Japanese participants (one each in the HDq12 + HDq16 groups, with only one of them providing data for PK parameters) were in the same range of values seen in non- Japanese participants after administration of aflibercept 8 mg.

Table 2-77. Summary statistics of adjusted bound aflibercept pharmacokinetic parameters in plasma in participants with unilateral treatment for pooled region: Rest of the World – Dense PK substudy (DPKS)

Pooled region	PK parameter (unit)	Treatment	n	Geom. mean (SD)	Geom. Mean 95% CI	Geom. CV (%)	Arithm. mean (SD)	Arthm. CV (%)	Median	Min, Max
Rest of the World	Cmax (mg/L)	2q8 (N = 6)	6	0.164 (1.54)	0.11, 0.25	44.9	0.179 (0.0950)	53.0	0.158	0.108, 0.368
		HDq12+HDq16 (N = 11)	11	0.415 (1.50)	0.28, 0.62	42.6	0.441 (0.138)	31.3	0.424	0.143, 0.611
	Cmax/Dose (mg/L/mg)	2q8 (N = 6)	6	0.0821 (1.54)	0.05, 0.13	44.9	0.0897 (0.0475)	53.0	0.0789	0.0541, 0.184
		HDq12+HDq16 (N = 11)	11	0.0519 (1.50)	0.03, 0.08	42.6	0.0552 (0.0173)	31.3	0.0531	0.0178, 0.0764
	Clast (mg/L)	2q8 (N = 6)	6	0.120 (1.78)	0.07, 0.21	63.1	0.142 (0.112)	78.5	0.106	0.0739, 0.368
		HDq12+HDq16 (N = 11)	11	0.325 (1.40)	0.23, 0.46	34.8	0.341 (0.0966)	28.4	0.338	0.143, 0.512
	Ctrough (mg/L) Day 29	2q8 (N = 6)	5	0.122 (1.90)	0.06, 0.23	71.8	0.149 (0.124)	82.7	0.105	0.0739, 0.368
		HDq12+HDq16 (N = 11)	10	0.317 (1.41)	0.22, 0.45	35.4	0.332 (0.0970)	29.3	0.336	0.143, 0.512
	AUClast (day*mg/L)	2q8 (N = 6)	6	3.42 (1.66)	2.06, 5.68	54.2	3.84 (2.21)	57.6	3.34	1.77, 8.08
		HDq12+HDq16 (N = 11)	11	7.98 (1.47)	5.43, 11.7	39.8	8.45 (2.64)	31.3	8.00	3.12, 12.3
	AUCinf (day*mg/L)	2q8 (N = 6)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 11)	0	/	/	/	/	/	/	/
	AUCinf/Dose (day*mg/L/mg)	2q8 (N = 6)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 11)	0	/	/	/	/	/	/	/
	AUC(0-28d) Norm by WT (day*mg/L/kg)	2q8 (N = 6)	2	0.0379 (1.19)	0.03, 0.05	17.9	0.0382 (0.00673)	17.6	0.0382	0.0334, 0.0429
		HDq12+HDq16 (N = 11)	5	0.118 (1.55)	0.08, 0.18	46.2	0.127 (0.0514)	40.3	0.140	0.069, 0.190
	Accumulation Ratio (C_{Week12}/C_{Week4})	2q8 (N = 6)	5	1.68 (1.63)	1.04, 2.74	51.6	1.83 (0.766)	41.8	1.66	0.790, 2.75
		HDq12+HDq16 (N = 11)	10	1.59 (1.53)	1.04, 2.42	44.2	1.72 (0.774)	45.0	1.58	0.707, 3.55
	t1/2 (day)	2q8 (N = 6)	1	25.3 (NE)	NE	NE	25.3 (NE)	NE	25.3	25.3, 25.3
		HDq12+HDq16 (N = 11)	1	281 (NE)	NE	NE	281 (NE)	NE	281	281, 281
	tmax (day)	2q8 (N = 6)	6	/	/	/	/	/	14.0	7.05, 21.0
		HDq12+HDq16 (N = 11)	11	/	/	/	/	/	14.1	1.03, 28.1
	tlast (day)	2q8 (N = 6)	6	/	/	/	/	/	28.0	21.0, 29.2
		HDq12+HDq16 (N = 11)	11	/	/	/	/	/	27.9	21.0, 32.0

Arithm. = arithmetic, AUC_{inf} = Area under the curve from time zero to infinity, AUC_{last} = Area under the curve to the last quantifiable concentration, CI = confidence interval, C_{last} = Last concentration, C_{max} = Maximum concentration, C_{trough} = trough concentration, CV = coefficient of variation, geom. = geometric, DPKS = dense pharmacokinetic analysis set, LLOQ = Lower level of quantification, Max = maximum, Min = minimum, N = Number of participants with unilateral treatment up to Week 48, n = Number of observations, NE = Not Evaluable, PK = pharmacokinetic, SD = standard deviation, t1/2 = half-life, t_{last} = time to last concentration, t_{max} = time to maximum concentration, WT = weight. / indicates categories that do not apply.
For C_{last}, values below LLOQ were substituted by 1/2 LLOQ for the calculation of geometric statistics and 0 for arithmetic statistics

Table 2-78. Summary Statistics of Adjusted Bound Aflibercept Pharmacokinetic Parameters in Plasma in Participants with Unilateral Treatment for Pooled Region: Japan – Dense PK Substudy (DPKS)

Pooled region	PK parameter (unit)	Treatment	n	Geom. mean (SD)	Geom. Mean 95% CI	Geom. CV (%)	Arithm. mean (SD)	Arthm. CV (%)	Median	Min, Max
Japan	Cmax (mg/L)	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	1	0.567 (NE)	NE	NE	0.567 (NE)	NE	0.567	0.567, 0.567
	Cmax/Dose (mg/L/mg)	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	1	0.0709 (NE)	NE	NE	0.0709 (NE)	NE	0.0709	0.0709, 0.0709
	Clast (mg/L)	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	1	0.412 (NE)	NE	NE	0.412 (NE)	NE	0.412	0.412, 0.412
	Ctrough (mg/L) Day 29	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	1	0.412 (NE)	NE	NE	0.412 (NE)	NE	0.412	0.412, 0.412
	AUClast (day*mg/L)	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	1	11.7 (NE)	NE	NE	11.7 (NE)	NE	11.7	11.7, 11.7
	AUCinf (day*mg/L)	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	0	/	/	/	/	/	/	/
	AUCinf/Dose (day*mg/L/mg)	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	0	/	/	/	/	/	/	/
	AUC(0-28d) Norm by WT (day*mg/L/kg)	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	0	/	/	/	/	/	/	/
	Accumulation Ratio (C_{Week12}/C_{Week4})	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	1	1.47 (NE)	NE	NE	1.47 (NE)	NE	1.47	1.47, 1.47
	t1/2 (day)	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	0	/	/	/	/	/	/	/
	tmax (day)	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	1	/	/	/	/	/	14.0	14.0 14.0
	tlast (day)	2q8 (N = 0)	0	/	/	/	/	/	/	/
		HDq12+HDq16 (N = 2)	1	/	/	/	/	/	27.9	27.9 27.9

Arithm. = arithmetic, AUC_{inf} = Area under the curve from time zero to infinity, AUC_{last} = Area under the curve to the last quantifiable concentration, CI = confidence interval, C_{last} = Last concentration, C_{max} = Maximum concentration, C_{trough} = trough concentration, CV = coefficient of variation, geom. = geometric, DPKS = dense pharmacokinetic analysis set, LLOQ = Lower level of quantification, Max = Maximum, Min = Minimum, N = Number of participants with unilateral treatment up to Week 48, n = Number of observations, NE = Not Evaluable, PK = pharmacokinetic, SD = standard deviation, $t_{1/2}$ = half-life, t_{last} = time to last concentration, t_{max} = time to maximum concentration, WT = weight. / indicates categories that do not apply.
For C_{last}, values below LLOQ were substituted by 1/2 LLOQ for the calculation of geometric statistics and 0 for arithmetic statistics.

[000796]Table 2-79 shows an overview of sampling time points for the sparse sampling in the 3 different dosing groups. Table 2-80 summarizes the plasma concentration-time data for free aflibercept in participants with unilateral treatment (sparse PK sampling, PKS) after IVT administration of aflibercept in the 2q8, HDq12, and HDq16 regimens, respectively.

[000797]Concentrations of free aflibercept concentration in plasma were, on average, higher for the HDq12 and HDq16 treatment groups than the 2q8 treatment group. Mean free aflibercept concentrations increased from baseline to Visit 5 (60-64 days after first administration). Thereafter, mean concentrations of free aflibercept declined in all 3 dose groups. In the 2q8 treatment group, mean concentrations of free aflibercept declined to values close to or below LLOQ in almost all participants 4 weeks after treatment, in the HD groups 8 weeks after treatment (Week 28 for HDq12, Week 48 for HDq16) (Table 2-80).

Table 2-79. Overview of Sampling Time Points for the Different Dosing Groups (PKS)

Sampling time point	2q8	HDq12	HDq16
Baseline	Prior to first administration		
Week 4	4 weeks after first administration		
Visit 5	4-7 days after third monthly administration		
Week 12	4 weeks after third montly administration		
Week 28	4 weeks after Week 24 administration	8 weeks after Week 20 administration	4 weeks after Week 24 administration
Week 48	4 weeks after Week 40 administration	4 weeks after Week 44 administration	8 weeks after Week 40 administration

[000798]Comparison of mean concentrations of free aflibercept at Visit 5 which could be considered a time point around an expected C_{max} rather than a trough value, showed that concentrations increased about 6-fold as the IVT dose of aflibercept increased from 2 mg to 8 mg (4-fold dose). Based on the ratio of aflibercept concentration at Week 12 to Day 29 (C_{Week12}/C_{Day29}), the accumulation ratio of free aflibercept was 1.06, 1.69, and 1.92 for 2q8, HDq12, and HDq16, respectively.

[000799]Exploratory analysis of subgroups with respect to age, body mass index (BMI), medical history of renal impairment (as determined by creatinine clearance), medial history of

hepatic impairment, ethnicity (Latino/Hispanic vs not Latino/Hispanic), race (White vs. Asian), and treatment-emergent antibody status did not reveal any meaningful differences for free aflibercept concentrations.

Table 2-80. Summary of Concentration of Free Aflibercept (mg/L) in Plasma by Time and Treatment in Participants with Unilateral Treatment and without DRMs upto Week 48 – General PK (PKS)

			Free aflibercept		
Time	Treatment	n total	n ≥ LLOQ	Geom. Mean ± SD	Arithm. Mean ± SD
Baseline (Visit 2)	2q8 (N = 237)	228	3	N.C	0.00033 (0.00303)
	HDq12 (N = 203)	189	0	N.C	0.00 (0.00)
	HDq16 (N = 193)	178	0	N.C	0.00 (0.00)
Week 4 (Visit 3)	2q8 (N = 237)	219	4	N.C	0.00044 (0.00371)
	HDq12 (N = 203)	192	121	N.C	0.0172 (0.0157)
	HDq16 (N = 193)	182	117	N.C	0.0170 (0.0163)
Visit 5	2q8 (N = 237)	203	167	0.02 (1.83)	0.0256 (0.0165)
	HDq12 (N = 203)	176	173	0.13 (1.97)	0.157 (0.101)
	HDq16 (N = 193)	165	161	0.13 (2.02)	0.151 (0.0810)
Week 12 (Visit 6)	2q8 (N = 237)	221	11	N.C	0.00133 (0.00654)
	HDq12 (N = 203)	191	155	0.02 (1.98)	0.0284 (0.0227)
	HDq16 (N = 193)	188	149	0.02 (2.02)	0.0293 (0.0226)
Week 28 (Visit 10)	2q8 (N = 237)	203	4	N.C	0.00068 (0.00601)
	HDq12 (N = 203)	187	6	N.C	0.00088 (0.00525)
	HDq16 (N = 193)	179	101	N.C	0.0152 (0.0160)
Week 48 (Visit 15)	2q8 (N = 237)	202	2	N.C	0.00087 (0.0100)
	HDq12 (N = 203)	180	87	N.C	0.0136 (0.0179)
	HDq16 (N = 193)	165	4	N.C	0.00056 (0.00375)

Arithm. = arithmetic, DRM = dose regimen modification, geom. = geometric, LLOQ = Lower level of quantification, N = Number of participants with unilateral treatment and without DRMs up to Week 48, n = Number of observations, PKS = pharmacokinetic analysis set, SD = standard deviation; N.C.: not calculated (less than 2/3 of values per time point are ≥ LLOQ for geometric mean calculation). Values below LLOQ (0.0156 mg/L) were substituted by 1/2 LLOQ for the calculation of geometric statistics and 0 for arithmetic statistics and median.

[000800]Table 2-81 summarizes the plasma concentration-time data for adjusted bound aflibercept in all participants (sparse PK sampling, PKS) after IVT administration of aflibercept in the 2q8, HDq12, and HDq16 regimens, respectively. Concentrations of adjusted bound aflibercept in plasma were, on average, higher for the HDq12 and HDq16 treatment groups than the 2q8 treatment group. Mean adjusted bound aflibercept concentrations increased from baseline to Visit 5 (60-64 days after first administration). Thereafter, a slight decrease of the concentration-time profiles was observed until the end of the observation period (Week 48).

[000801]Evaluation of mean concentrations of adjusted bound aflibercept at Visit 5 which could be considered a time point around an expected C_{max} rather than a trough value, showed that concentrations increased about 3-fold as the IVT dose of aflibercept increased from 2 mg to 8 mg (4-fold dose). Based on the ratio of aflibercept concentration at Week 12 to Day 29

(C_{Week12}/C_{Day29}), the accumulation ratio of adjusted bound aflibercept was 1.83, 2.03, and 2.22 for 2q8, HDq12, and HDq16, respectively.

[000802]Exploratory analysis of subgroups with respect to age, BMI, medical history of renal impairment (as determined by creatinine clearance), medial history of hepatic impairment, ethnicity (Latino/Hispanic vs not Latino/Hispanic), race (White vs. Asian), and treatment-emergent antibody status did not reveal any meaningful differences for adjusted bound aflibercept concentrations.

Table 2-81. Summary of Concentration of Adjusted Bound Aflibercept (mg/L) in Plasma by Time and Treatment in Participants with Unilateral Treatment and Without DRMs upto Week 48 – General PK (PKS)

		Adjusted Bound Aflibercept			
Time	Treatment	n total	n ≥ LLOQ	Geom. Mean ± SD	Arithm. Mean ± SD
Baseline (Visit 2)	2q8 (N = 237)	228	7	N.C	0.0109 (0.0915)
	HDq12 (N = 203)	189	1	N.C	0.00029 (0.00404)
	HDq16 (N = 193)	178	2	N.C	0.00081 (0.00923)
Week 4 (Visit 3)	2q8 (N = 237)	219	215	0.12 (1.67)	0.130 (0.0839)
	HDq12 (N = 203)	192	191	0.34 (1.65)	0.375 (0.132)
	HDq16 (N = 193)	182	181	0.33 (1.72)	0.362 (0.141)
Visit 5	2q8 (N = 237)	203	201	0.24 (1.59)	0.255 (0.0920)
	HDq12 (N = 203)	176	174	0.65 (1.77)	0.710 (0.249)
	HDq16 (N = 193)	165	164	0.64 (1.63)	0.687 (0.222)
Week 12 (Visit 6)	2q8 (N = 237)	221	219	0.18 (1.72)	0.208 (0.119)
	HDq12 (N = 203)	191	191	0.58 (1.46)	0.615 (0.216)
	HDq16 (N = 193)	188	187	0.56 (1.63)	0.610 (0.220)
Week 28 (Visit 10)	2q8 (N = 237)	203	203	0.15 (1.57)	0.168 (0.107)
	HDq12 (N = 203)	187	185	0.19 (1.81)	0.222 (0.119)
	HDq16 (N = 193)	179	174	0.32 (2.04)	0.372 (0.145)
Week 48 (Visit 15)	2q8 (N = 237)	202	184	0.06 (2.10)	0.0775 (0.0703)
	HDq12 (N = 203)	180	171	0.30 (2.44)	0.375 (0.178)
	HDq16 (N = 193)	165	161	0.17 (1.97)	0.204 (0.107)

Arithm. = arithmetic, DRM = dose regimen modification, geom. = geometric, LLOQ = Lower level of quantification, N = Number of participants with unilateral treatment and without DRMs up to Week 48, n = Number of observations, PKS = pharmacokinetic analysis set, SD = standard deviation; N.C.: not calculated (less than 2/3 of values per time point are ≥ LLOQ for geometric mean calculation). Values below LLOQ (0.022442 mg/L) were substituted by 1/2 LLOQ for the calculation of geometric statistics and 0 for arithmetic statistics and median.

Expanded Population PK Analysis (referred to as the Population PK model, or PopPK).

[000803]With availability of the free and adjusted bound aflibercept concentration data from the CANDELA, PULSAR, and PHOTON along PK data from the other studies listed herein, a comprehensive PopPK model was developed, In this latter PopPK model, the PK of free and adjusted bound aflibercept following IV, SC, or IVT administration was adequately described by a 3-compartment PopPK model with the binding of free aflibercept from the central compartment to VEGF described by Michaelis-Menten kinetics. An additional tissue compartment that could represent platelets (Sobolewska *et al.*, Human Platelets Take up Anti-VEGF Agents. J

Ophthalmol 2021; 2021:8811672) was added where the rate of elimination from the central compartment of free aflibercept to the platelet compartment was dependent on the number of platelets that were able to uptake anti-VEGF agents such as ranibizumab, bevacizumab, and aflibercept (Figure 31).

[000804]Although PK parameters for free and adjusted bound aflibercept in plasma were determined by noncompartmental analysis (NCA) and reported at the level of the individual study reports, the PK parameters determined by population PK analysis are considered to be the more accurate estimate and therefore the definitive PK parameters are those assessed by the population PK model.

[000805]Across all 3 studies (CANDELA, PULSAR, and PHOTON), the pharmacokinetic analysis set (PKAS) includes all treated participants who received any amount of study drug (aflibercept or HD aflibercept) and had at least 1 non-missing aflibercept or adjusted bound aflibercept measurement following the first dose of study drug. The PKAS is based on the actual treatment received (as treated), rather than as randomized. The PKAS-dense (PK-dense) analysis set is a subset of the PKAS and includes participants who had dense blood sample collection for systemic drug concentrations.

[000806]CANDELA, PULSAR, and PHOTON each included a PK substudy where drug concentration data were collected using dense blood sample collection schedules during the first dosing interval and sparse PK sampling thereafter in up to approximately 30 participants. Drug concentration data were also collected in each study for all participants using a sparse sampling schedule throughout the 44 weeks (CANDELA) or 48 weeks (PHOTON, PULSAR) of treatment.

[000807]Pharmacokinetic parameters for individual studies were calculated by non-compartmental analysis for free and adjusted bound aflibercept concentration data collected from participants with dense sampling schedules in these 3 studies.

[000808]Additionally, all concentration data from these 3 studies were incorporated into the Population PK data set.

[000809]The concentration time profiles of free and adjusted bound aflibercept in plasma after the initial dose of HD aflibercept by IVT administration were consistent between all studies in participants with nAMD or DME. The consistency of the concentration-time profiles for free and adjusted bound aflibercept in plasma between the nAMD and DME populations is further supported by population PK analysis (Figure 33 and Figure 34).

[000810]Population PK estimated post-hoc concentration-time profiles and PK parameters for combined nAMD and DME populations following single IVT administration of 2 mg aflibercept or HD aflibercept are provided in Figure 33 and Figure 34 and in Table 2-82 and Table 2-85.

[000811]Following single IVT administration of aflibercept 2 mg or HD aflibercept, the concentration-time profiles of free and adjusted bound aflibercept in plasma in participants who underwent dense sample collection for systemic drug concentrations (dense PK substudy) after the initial dosing of aflibercept 2 mg or HD aflibercept, respectively, were consistent between the 3 studies in participants with nAMD or DME (Figure 32). Notably, there was one excluded participant in the PULSAR dense-sampling PK substudy that had free aflibercept concentrations over time that were approximately 10-fold higher than the mean concentration-time profiles in that study.

[000812]The consistency of the concentration-time profiles for free and adjusted bound aflibercept between the nAMD and DME populations is further supported by Population PK analysis (Figure 33). Population PK estimated post-hoc concentration-time profiles and PK parameters for combined nAMD and DME populations following single IVT administration of 2 mg aflibercept or HD aflibercept are provided below in Figure 33 and in Table 2-83 and Table 2-84.

[000813]The corresponding observed and Population PK estimated post-hoc concentration-time profiles and PK parameters for participants with nAMD and DME are provided in Figure 36, Figure 37, and Figure 38 and Table 2-85, Table 2-86.

[000814]Following single IVT administration of 2 mg aflibercept or HD aflibercept, the concentration-time profiles of free aflibercept are characterized by an initial phase of increasing concentrations, as the drug moved from the ocular space into systemic circulation, followed by a mono-exponential elimination phase. The concentration time profiles of adjusted bound aflibercept in plasma are characterized by a slower attainment of Cmax compared to free aflibercept. Following attainment of C_{max}, a sustained plateau of the concentration-time profiles of adjusted bound aflibercept in plasma was observed until approximately the end of the first dosing interval (Figure 32, Figure 33).

[000815]For participants who underwent dense blood sample collection for systemic drug concentrations across the CANDELA, PULSAR, and PHOTON studies, after the initial dosing of 2 mg IVT aflibercept (n = 34), observed concentrations of free aflibercept were detectable in 15 (44.1%) participants by week 1 and in 3 (8.8%) participants by week 2.

[000816]For participants who underwent dense blood sample collection for systemic drug concentrations after the initial dosing of 8 mg IVT aflibercept (n = 54), observed concentrations

of free aflibercept were detectable in 46 (85.2%) participants by week 1 and in 44 (77.8%) participants by week 2. The observed and Population PK simulated free and adjusted bound aflibercept concentrations in plasma for up to 48 weeks are presented for the combined nAMD and DME population (Figure 34), and the nAMD (Figure 39) and DME (Figure 40) populations. Based on the Population PK analysis, the median time for free aflibercept concentrations to reach LLOQ in plasma following HDq12 or HDq16 was more than double (3.50 weeks versus 1.5 weeks) the median time needed to reach LLOQ following aflibercept 2q8 (Table 2-87).

[000817]The longer duration of systemic exposure to free aflibercept following HDq12 and HDq16 compared to the 2 mg aflibercept is attributed to not only a higher administered dose and nonlinear systemic target-mediated elimination, but also to a 34% slower ocular clearance of free aflibercept. The slower ocular clearance of free aflibercept for HD aflibercept is attributed to a HD drug product effect which was identified as a statistically significant covariate in the Population PK model.

[000818]Population PK analysis confirmed no relevant differences in PK between the nAMD and DME populations, and therefore all subsequent analyses are presented for the combined nAMD and DME population.

[000819]The pharmacokinetic (PK) data set forth above summarize the observed systemic concentration-time profiles and associated PK parameters for free and adjusted bound aflibercept for each individual study. The analyses utilized to estimate the PK parameters in each individual study were performed by non-compartmental analysis. While the individual PHOTON study results describe the observed systemic concentration-time profiles and associated PK parameters of free and adjusted bound aflibercept in plasma, they do not specifically identify PK characteristics of the HD 8 mg aflibercept drug product contributing to the unexpected pharmacodynamic (PD) and efficacy results for HD aflibercept observed in the CANDELA (NCT04126317), PULSAR (NCT04423718), and PHOTON (European Clinical Trials Database (EudraCT): 2019-003851-12) studies.

[000820]An expanded PopPK analysis that utilized free and adjusted bound concentration in plasma data from the HD clinical studies, as well as 13 prior studies:

<u>DME population</u>

- VGFT-OD-0307: A double-blind, randomised, dose-escalating study evaluating safety, tolerability and bio-effect after intravenous (IV) administration of VEGF Trap in subjects with DME. Subjects were planned to receive 4 IV infusions of VEGF Trap, once every 2 weeks (day 1, day 15, day 29, and day 43), at dose levels of 0.3 mg/kg, 1 mg/kg, or 3 mg/kg, or placebo. However, dosing was stopped before the planned sequential dose escalation when dose-

limiting toxicities (grade 2 proteinuria in a single subject and grade 4 treatment-related malignant hypertension in a single subject) were observed in another phase 1 dose-escalation study in subjects with AMD (VGFT-OD-0305). The dose limiting toxicities observed in study VGFT-OD-0305 occurred at the 3 mg/kg IV dose. Therefore, only the lowest dose (0.3 mg/kg) of study drug was investigated. Nine subjects were randomised and treated (3 placebo, 6 VEGF Trap 0.3 mg/kg). Concentrations of free and bound VEGF Trap were determined at selected time intervals following dose administration (screening, day 1[pre-dose], day 8, day 15, day 29, day 43, day 57, day 71, day 85, and day 133 [3 months post-last dose]);

- VGFT-OD-0512: An open-label, proof-of-concept study evaluating safety, tolerability and bio-effect of VEGF Trap IVT administration in subjects with DME. Five (5) subjects with DME were enrolled. Subjects received a single IVT injection of 4 mg VEGF Trap into the study eye. During the first 6 weeks after the injection, vital signs as well as ocular and systemic adverse events (AEs) were recorded. Blood samples for analysis of free and bound VEGF Trap concentrations in plasma were collected at screening, day 1 (pre-dose), day 3, day 8, day 15, day 29, day 43 and day 155 following the single IVT administration;
- VGFT-OD-0706.PK (PK sub-study of VGFT-OD- 0706): DME And VEGF Trap-Eye [Intravitreal Aflibercept Injection (IAI;EYLEA®;BAY86-5321)] INvestigation of Clinical Impact (DA VINCI)-Clinicaltrials.gov Identifier NCT00789477; and
- 91745: Intravitreal Aflibercept Injection in Vision Impairment Due to DME (VIVID-DME)-ClinicalTrials.gov Identifier NCT01331681;

<u>AMD population</u>

- VGFT-OD-0305: A double-masked, placebo controlled, sequential group, dose escalating, (0.3 mg/kg, 1 mg/kg, 3 mg/kg, 5 mg/kg, 7 mg/kg, and 10 mg/kg) study of safety and bioeffect. The study included subjects with a diagnosis of visual impairment associated with neovascular AMD. Subjects were required to have visual loss due to subfoveal choroidal neovascularization (CNV) secondary to AMD, be 50 years of age or older, with no history of Type I or Type II diabetes, without significant cardiac, liver or kidney disease, or congestive heart failure (CHF); and without confounding ophthalmic issues. The study treatments were: 1. VEGF Trap 0.3 mg/kg. 2. VEGF Trap 1 mg/kg, and 3. VEGF Trap 3 mg/kg;
- VGFT-OD-0306: An open label, long term safety and tolerability extension study of intravenous VEGF Trap in subjects with neovascular AMD who had been included in Study VEGF-OD-0305. The study treatments were VEGF Trap at the same dose level the subjects had been treated with in Study VEGF-OD-0305: either 0.3 mg/kg or 1 mg/kg, by intravenous administration every 2 weeks. Placebo patients from Study VGFT-OD-0305 were assigned to

VEGF Trap at the dose level at which they were enrolled in Study VGFT-OD-0305. The efficacy outcome measures were: Visual acuity (ETDRS), Retinal thickness (OCT), Funduscopic examination, Fundus photography, and FA. The safety outcome measures were: AEs, Clinical laboratory tests, and Ophthalmic exam. Treatment duration was for up to 106 days. There were seven subjects: four subjects treated with 0.3 mg/kg, 3 subjects treated with 1 mg/kg. There were five females, two males and the age range was 68 to 84 years. Six of the seven subjects had a slight reduction in ERT in the study eye and six of seven subjects had slight reductions in macular volume in the study eye;

- VGFT-OD-0502 Part A: Safety and Tolerability Study of Intravitreal VEGF-Trap Administration in Patients With Neovascular AMD-ClinicalTrials.gov Identifier: NCT00320775;
- VGFT-OD-0502 Part C: ClinicalTrials.gov Identifier: NCT00320775;
- VGFT-OD-0603: Safety and Tolerability of Intravitreal VEGF Trap Formulations in Subjects With Neovacular AMD-ClinicalTrials.gov Identifier: NCT00383370;
- VGFT-OD-0702.PK (PK sub-study of VGFT-OD-0702): Randomized, Single-Masked, Long-Term, Safety and Tolerability Study of VEGF Trap-Eye in AMD-ClinicalTrials.gov Identifier: NCT00527423; and
- 311523 (VIEW2): A multicentre, double masked, randomised, active controlled, parallel group, non-inferiority efficacy and safety study. The study was almost identical in design to Study VGFT-OD-0605/14393 (VIEW 1). The submission contained the report of the first 52 weeks of the study. The study was conducted at 186 centres in 26 countries.

The inclusion criteria, exclusion criteria and study treatments were identical to Study VGFT-OD-0605/14393 (VIEW 1). The efficacy outcome measures were the same, except for the additional outcome measure: change in scores of the EQ-5D questionnaire from screening at Week 52;

<u>Oncology population</u>

- VGFT-ST-0103, (also known as TED6113): VEGF Trap in Treating Patients With Relapsed or Refractory Solid Tumors or Non-Hodgkin's Lymphoma-ClinicalTrials.gov Identifier: NCT00036946;

<u>Healthy participant population</u>

- PDY6655: A Phase I, single centre, randomised, single dose, crossover, pharmacokinetic (PK) study in healthy volunteers to compare the pharmacokinetics and pharmacodynamic (PD) of intravenous and subcutaneous administration of aflibercept. The study included 40 healthy male subjects aged 18 to 45 years. The study treatments were: aflibercept 2.0 mg/kg as an intravenous infusion over 1 hour, and as a subcutaneous injection.

The aflibercept was presented as 4 mL of 25 mg/mL solution. The treatments were administered as single doses followed by 6 week observation period. The treatment periods were separated by 1 to 2 weeks. The PK outcome measures were: Cmax, AUC, apparent volume of distribution at steady state (Vss), clearance and half life ($t_{1/2}$). The PD outcome measures were: systolic blood pressure, diastolic blood pressure, heart rate, mean arterial pressure, plasma renin activity, angiotensin I, aldosterone, and free endogenous VEGF. The safety outcome measures were: AEs, clinical laboratory test, injection site reactions, and anti-aflibercept antibodies. AUC and Cmax were slightly higher for Period 2, indicating some carry over. For Period 1, for free aflibercept mean (co-variance (CV%)) AUC was 177 (33) µg•day/mL and peak plasma concentration (Cmax) was 44.4 (36) µg/mL for intravenous and AUC was 84.9 (30) µg•day/mL and Cmax was 7.76 (39) µg/mL for subcutaneous. For Period 1, for bound aflibercept mean (CV%) AUC was 57.7 (19) µg•day/mL and Cmax was 1.84 (22) µg/mL for intravenous and AUC was 47.3 (27) µg•day/mL and Cmax was 1.60 (27) µg/mL for subcutaneous. The mean (90% CI) ratio for AUC, subcutaneous/ intravenous, was 0.51 (0.46 to 0.56) [(range)], and

- PDY6656: A single centre, Phase I, randomised, double blind, placebo controlled, sequential ascending dose study of intravenous aflibercept. The study included healthy male subjects 18 to 45 years of age; non-smoker; 18≤ body mass index (BMI) ≤28 kg/m²; with normal vital signs and no symptomatic hypotension. The study treatments were aflibercept 1 mg/kg, 2 mg/kg and 4 mg/kg, and placebo. There were three cohorts of 16 subjects: twelve treated with aflibercept and four treated with placebo. The treatments were administered as a single dose by intravenous infusion over 1 hour. The pharmacodynamic outcome measures were: systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), plasma active renin, aldosterone and angiotensin I; markers of endothelium dysfunction (plasma endothelin-1, E-selectin, cyclic guanosine 3'5' monophosphate (cGMP), and urine nitrites/nitrates); renal function; and VEGF. The safety outcome measures were: AEs and laboratory tests. The study included 48 subjects: 12 treated with 1 mg/kg, 12 with 2 mg/kg, 12 with 4 mg/kg and 12 with placebo. The age range was 21 to 45 years. For free aflibercept mean (CV%) Cmax was 18.2 (18) µg/mL for the 1 mg/kg dose, 39.7 (27) µg/mL for the 2 mg/kg dose and 78.6 (15) µg/mL for the 4 mg/kg dose; and mean (CV%) AUC was 64.8 (20) µg.day/mL for the 1 mg/kg dose, 180 (20) for the 2 mg/kg dose and 419 (21) for the 4 mg/kg dose. Bound aflibercept concentrations were not dose dependent and the proportion of bound aflibercept decreased with increasing dose. However, Cmax and AUC for total aflibercept were dose proportional [(range)]; (See Australian Public Assessment Report for Afibercept, AusPAR Eylea Aflibercept Bayer Australia Ltd; PM-2010-03802-3-5 Final 30 July 2012; and Assessment

Report, Eylea, Committee for Medicinal Products for Human Use (CHMP) 26 June 2014 EMA/430291/2014; FDA, Center for Drug Evaluation and Research, Approval Package for: APPLICATION NUMBER: 125387Orig1s048, Eylea, March 25, 2015)
of aflibercept 2 mg in the DME and nAMD populations, healthy participants, and participants with oncology diseases after intravenous (IV), subcutaneous (SC), or intravitreal (IVT) administration was performed to: characterize the concentration-time profiles of free and adjusted bound aflibercept in plasma; estimate population and individual PK parameters of aflibercept in patients with nAMD and DME; investigate the effects of relevant covariates which may explain variability in aflibercept PK parameters; and derive *post-hoc* estimates of individual exposure metrics in the nAMD and DME patients from the final PopPK model that formed the basis for pharmacokinetic/pharmacodynamic (PK/PD) analyses.

[000821]A key finding from this expanded PopPK analysis is that clearance of free aflibercept from the ocular compartment (ocular clearance) is 34.3% slower for HD drug product than for 2 mg IVT aflibercept reference drug product, and is attributed to an "HD aflibercept drug product effect". Ultimately, it is this HD drug product effect on slowing the ocular clearance that resulted in a longer than expected ocular residence time, and the greater than expected proportion of patients able to be maintained on the longer dosing intervals of q12 and q16.

[000822]The consequences of the slower ocular clearance for HD (8 mg) aflibercept, as identified in the PopPK analysis, were further evaluated via PopPK model-based simulations to predict the time-course of free aflibercept in the eye (ocular compartment) under different dosing scenarios, and via exposure-response analyses to assess whether PopPK estimates of ocular clearance are predictive of the time required for dose regimen modification (DRM).

[000823]Efficacy data from the phase 3 PULSAR study in the nAMD population confirmed that the HDq12 and HDq16 regimens provide durable efficacy over the 48-week treatment period, as both regimens met the primary endpoint for efficacy of non-inferior change from baseline in BCVA at week 48 compared to 2q8. A majority of participants randomized to HDq12 or HDq16 maintained their 12-week (79%) and 16-week (77%) dosing intervals, without the need for DRM, through 48 weeks.

[000824]Results from the phase 2/3 PHOTON study also confirmed efficacy of the HDq12 and HDq16 regimens in participants with DME and DR as both met the primary endpoint for efficacy of noninferior change from baseline in BCVA at week 48 compared to 2q8, with a majority of participants maintaining their HDq12 (91%) and HDq16 (89%) regimens, without the need for DRM, through the end of the 48-week treatment period.

[000825]As the vast majority of participants enrolled in the PHOTON study had underlying DR, they were also assessed for efficacy endpoints associated with the improvement of their underlying retinopathy. The HDq12 regimen met the key secondary efficacy endpoint of noninferiority for the proportion of participants with a ≥2-step improvement in DRSS score compared to 2q8 at the prespecified margin of 15%. Additionally, noninferiority was demonstrated using the FDA recommended 10% margin. Non-inferiority was not established for HDq16 at the 15% margin. The HDq16 group had more participants with mild to moderate disease than both the HDq12 and the 2q8 group, which may have contributed to these findings.

[000826]Regarding safety, similar ocular and systemic safety profiles for HDq12 and HDq16 compared to 2q8 aflibercept were observed in all 3 studies, with no new safety signals identified for HD aflibercept.

[000827]Residual variability was modeled separately for free and adjusted bound aflibercept using an additive + proportional error model. Estimated bioavailability for free aflibercept was 71.9% following IVT administration (Table 2-82). Parameter estimates for the Population PK model are presented in Table 2-82.

Table 2-83. Population Pharmacokinetic Parameter Estimates for the Final Model for Aflibercept

Parameter	Estimate	C.I.95	RSE %	CV %
K20 (1/day) [run431 Estimate]	0.0807	0.0438 — 0.136	29.5	—
V2 V4 (L) [run431 Estimate]	4.99	4.71 — 5.25	2.79	—
V3 (L) [run431 Estimate]	1.08	0.816 — 1.58	17	—
QF1 (L/day) [run431 Estimate]	0.849	0.435 — 1.33	29.2	—
V8 (L) [run431 Estimate]	1.18	0.281 — 0.541	16.8	—
QF2 (L/day) [run431 Estimate]	0.0763	0.147 — 0.186	5.93	—
KM (mg/L) [run431 Estimate]	0.411	0.293 — 0.442	10.5	—
VMK24 (mg/day/L) [run431 Estimate]	0.167	0.482 — 0.593	—	—
K40 (1/day) [run463 Estimate]	0.035	—	—	—
F1 & F5	0.719	0.706 — 0.731	—	—
QE (L/day)	0.000624	0.000577 — 0.000674	3.97	—
K62 (1/day) [run431 Estimate]	0.368	0.0165 — 0.0632	35.3	—
F6 [run431 Estimate]	0.536	0.00584 — 0.149	99	—
VMK27 (mg/day/L) [run431 Estimate]	0.031	4.17 — 340	159	—
K70 (1/day) [run431 Estimate]	0.0265	0.632 — 2.84	39.8	—
KMK27 (mg) [run431 Estimate]	42.7	0.0481 — 0.12	23.7	—
TWGT V2+V4 [run431 Estimate]	0.872	0.55 — 1.22	19.3	—
TWGT V3 [run431 Estimate]	1.08	-0.00762 — 2.45	51.3	—
TWGT V8 [run431 Estimate]	1.16	-2.97 — 6.58	135	—

TWGT K20 [run431 Estimate]	-0.192	-1.28 — 0.819	234	—
TWGT K40 [run463 Estimate]	-0.153	—	—	—
HD QE	0.657	0.607 — 0.712	4.08	—
AGE QE	-1.53	-1.76 — -1.3	7.68	—
TALB K40 [run463 Estimate]	-0.767	—	—	—
IIV K20 [run431 Estimate]	0.207	-0.0147 — 0.508	54.1	48
IIV covariance(K20, V2 & V4) [run431 Estimate]	-0.0727	-0.136 — -0.0183	38.9	—
IIV V2 & V4 [run431 Estimate]	0.0618	0.0198 — 0.105	34.7	25.3
IIV VMK24 [run431 Estimate]	0.305	-0.083 — 0.67	65.4	59.8
IIV K40 [run463 Estimate]	0.0452	—	—	21.5
IIV QE	0.297	0.257 — 0.336	6.86	58.8
IIV K62 [run431 Estimate]	0.852	0.124 — 1.45	43	116
IIV F6 [run431 Estimate]	0.629	0.288 — 0.905	26.4	93.6
SD ADD LLOQ 0.0313 (Free,IV+SC) [run463 Estimate]	0.025	—	—	—
SD PROP LLOQ 0.0313 (Free,IV+SC) [run463 Estimate]	0.403	—	—	—
SD ADD LLOQ 0.0156 (Free)	0.00779	0.00624 — 0.00973	11.4	—
SD PROP LLOQ 0.0156 (Free)	0.433	0.418 — 0.448	1.72	—
SD ADD LLOQ 0.0315 (Adj.Bound)	0.0216	0.0177 — 0.0264	10.2	—
SD PROP LLOQ 0.0315 (Adj.Bound)	0.159	0.12 — 0.197	12.4	—
SD ADD LLOQ 0.0224 (Adj.Bound)	0.0291	0.0202 — 0.0419	18.8	—
SD PROP LLOQ 0.0224 (Adj.Bound)	0.214	0.194 — 0.234	4.83	

ADD = additive, age = baseline age, C.I.95 = 95% confidence intervals, CV = coefficient of variation, F1 and F5 = bioavailability of intravitreal injections in ocular compartments, F6 = bioavailability of subcutaneous injections, HD = high dose (8 mg IVT cohorts), IIV = inter-participant variability, IV = intravenous, K20 = elimination rate of free aflibercept, K40 = elimination rate constant for adjusted bound aflibercept, K62 = rate of absorption from subcutaneous injection dosing compartment, K70 = elimination rate from tissue (platelet) compartment, KM = concentration of free aflibercept at half of maximum binding capacity with VEGF; KMK27 = concentration of free aflibercept at half of maximum binding capacity to platelets, LLOQ = lower limit of quantification, PROP = proportional, QE = inter-compartmental clearance between ocular compartment and central compartment of free aflibercept, QF1 and QF2 = inter-compartmental clearances of free aflibercept, RSE% = percent relative standard error, SC = subcutaneous, TALB = time varying albumin, TWGT = time varying body weight, V2 = central volume of free aflibercept in plasma, V3 and V8 = peripheral volumes of free aflibercept in tissues, V4 = central volume of adjusted bound aflibercept in plasma, VMK24 = maximum binding rate of free aflibercept to VEGF, VMK27 = maximum binding rate of aflibercept to platelets Estimates of fixed-effect parameters are presented in the natural scale; IIV are reported as variances around the log of the parameters or the logit of F6. Residual errors of IV and SC data not presented in the table for LLOQ=0.0156 (σ additive=0.00786, σproportional= 0.357) and LLOQ=0.0315 (σadditive=0.0206, σproportional=0.167) were fixed in the final model to estimates from run463. C.I.95 and %RSE% for run431 were calculated from bootstrap. η-shrinkage: ηK20= 54.2%, ηV2,V4= 15.2%, ηVMK24= 42.2%, ηK40= 39.1%, ηQE= 31.6%, ηK62= 1e-10%, ηF6= 17.7%.

[000828]Concentrations of free and bound aflibercept in plasma were measured using validated enzyme-linked immunosorbent assay (ELISA) methods. The assay for bound aflibercept is calibrated using the VEGF:aflibercept standards, and the results are reported for bound aflibercept as weight per volume (*e.g.*, ng/mL or mg/L) of the VEGF:aflibercept complex. Therefore, to account for the difference in molecular weight and normalize the relative concentrations between free and bound aflibercept, the concentration of the bound aflibercept complex is adjusted by multiplying the bound aflibercept concentration by 0.717. This is to account for the presence of VEGF in the bound complex and report the complex in terms of mg/L (i.e., mass/volume) that are corrected for, and consistent with, the molar concentrations (referred to as adjusted bound aflibercept in this module). Herein, concentrations of aflibercept:VEGF complex are limited to the adjusted bound concentrations.

[000829]The concentration of bound aflibercept was normalized to determine the amount of aflibercept present in the bound aflibercept complex. The bound aflibercept complex consisted of 71.7% aflibercept and 28.3% human $VEGF_{165}$ based on the molecular weight of each component. Therefore, the concentration of the bound aflibercept complex was multiplied by 0.717 to yield the concentration of adjusted bound aflibercept (Equation 1). Total aflibercept was calculated by summing the plasma concentrations of free and adjusted bound aflibercept (Equation 2).

Equation 1: Adjusted bound aflibercept (mg/L) = Bound aflibercept (mg/L) x 0.717

Equation 2: Total aflibercept (mg/L) = Sum of adjusted bound aflibercept (mg/L) + free aflibercept (mg/L)

[000830]Time-varying body weight was a predictor of the central volumes for free and adjusted bound aflibercept (V2=V4), the peripheral volumes of free aflibercept in tissues (V3, and V8), and elimination rate of free aflibercept (K20) and adjusted bound aflibercept (K40). The effect of time-varying albumin was also a predictor of elimination rate of adjusted bound aflibercept (K40). Age and the effect of HD drug product versus aflibercept groups with doses ≤4 mg presented as the reference drug product were predictors of clearance from the ocular compartment (QE). The clearance of free aflibercept from the ocular compartment slowed with age, with an estimated exponent in the relationship of -1.53, resulting in clearance from the ocular compartment being approximately 25% slower for an 86 year-old (95th percentile of age in the analysis population) participant than a 71 year-old (median age in analysis population) participant.

[000831]Following IVT administration, HD drug product was estimated to have 34.3% slower clearance from the ocular compartment compared to the reference IVT aflibercept drug product

for doses ≤4 mg. This slower ocular clearance resulted in a longer duration of ocular exposure to free aflibercept in the ocular compartment for the HD drug product. Through PopPK covariate analysis, the 34% slower ocular clearance (QE) and longer duration of free aflibercept ocular exposure for HD drug product is statistically attributed to an "HD aflibercept drug product effect". The exact nature or attributes of the HD drug product responsible for the attenuated ocular clearance cannot be fully explained by increasing the dose alone.

[000832]Exposure-Response Analyses. An exposure-response analysis was conducted using the time to dose regimen modification (TTDRM). A KM (Kaplan-Meier) plot of TTDRM stratified by indication showed a statistically significant ($p < 0.00001$) difference in TTDRM between participants with AMD and participants with DME, per the logrank test. KM plots of TTDRM, stratified by quartiles of ocular clearance (QE) within indication, showed rank ordering of longer TTDRM by lower ocular clearance percentile. A Cox proportional hazard model that included indication, baseline CRT, and ocular clearance as predictors of DRM showed that the rate of DRM due to the HD drug product effect is 20.6% lower than would have been expected if the HD drug product had the same ocular clearance as the 2 mg aflibercept presented as the reference drug product.

[000833]The need for DRM is determined by the clinician objective measurements obtained during an office visit, at which time a participant's dosing regimen can be shortened due to suboptimal efficacy. Faster transit of aflibercept from the eye into the systemic circulation leads to earlier depletion of the drug from the ocular space and therefore a more rapid loss of efficacy. While there may be other factors affecting efficacy, such as disease progression, comorbidities, or variability in response, this analysis shows a statistically significant relationship between an independently determined PK parameter (ocular clearance) that describes the transit of aflibercept from the eye and a reduction in efficacy as indicated by an earlier retreatment (DRM) than anticipated based on clinical assessment via BCVA and CRT.

[000834]For those participants requiring a DRM, Cox proportional hazard modeling was performed to evaluate factors that may contribute to the need for a reduction in the dosing interval. The results of these analyses estimate a 260% higher rate for DRMs for participants with nAMD compared to participants with DME and DR. After accounting for indication (nAMD or DME and DR), ocular clearance of free aflibercept and baseline CRT were identified as significant covariates contributing to the need for DRM. Within an indication (nAMD or DME and DR), for participants with the same ocular clearance of free aflibercept, a 52.8% higher rate of DRM is predicted for participants at the 75th percentile vs 25th percentile of baseline CRT. Similarly, for participants with the same baseline CRT, a 32.9% higher rate of DRM is predicted

for participants at the 75th vs 25th percentile of ocular clearance of free aflibercept. The results of these analyses also estimate that the lower ocular clearance for HD drug product resulted in a 20.6% lower rate of DRM than would have been expected if the HD drug product had the same ocular clearance as 2 mg aflibercept.

[000835]Comparison of Pharmacokinetics Across Studies in Participants with Neovascular Age-Related Macular Degeneration or Diabetic Macular Edema. In the clinical development of HD aflibercept for treatment of AMD and DME, a dosage regimen of 8 mg IVT (3 initial monthly doses followed by q12w or q16w IVT dosing) was evaluated and compared to an aflibercept 2 mg IVT dosage regimen (3 or 5 initial monthly doses followed by q8w or q12w IVT dosing) in the clinical studies CANDELA, PULSAR, and PHOTON. This allowed for a direct comparison of the systemic exposures of free and adjusted bound aflibercept across the 3 studies. CANDELA and PULSAR studies included participants with nAMD while PHOTON study included participants with DME and DR.

[000836]Following single IVT administration of aflibercept 2 mg or HD aflibercept, the concentration-time profiles of free and adjusted bound aflibercept in plasma in participants who underwent dense sample collection for systemic drug concentrations (dense PK sub-study) after the initial dosing of aflibercept 2 mg or HD aflibercept presented as the HD drug product, respectively, were consistent between the 3 studies in participants with nAMD or DME (Figure 32).

[000837]The consistency of the concentration-time profiles for free and adjusted bound aflibercept between the nAMD and DME populations is further supported by Population PK analysis (Figure 33). Population PK estimated *post-hoc* concentration-time profiles and PK parameters for combined nAMD and DME populations following single IVT administration of 2 mg aflibercept or HD aflibercept are provided in Figure 33 and in Table 2-83 and Table 2-84.

Table 2-83. Summary of *Post-hoc* Simulated Pharmacokinetic Parameters for Free Aflibercept in Plasma after Single Dose IVT Administration in the Combined nAMD and DME Population Treated Only in the Study Eye and Without Study Eye Dosing Modifications in the Dense PK Sub-studies (DPKS)

		Aflibercept 2 mg IVT (N = 31)		HD Aflibercept 8 mg IVT (N = 50)	
PK Parameters	**Unit**	**Mean (SD)**	**Median**	**Mean (SD)**	**Median**
$AUC_{0\text{-}28}$	mg x day/L	0.282 (0.189)	0.238	2.55 (2.31)	2
C_{max}	mg/L	0.0394 (0.0391)	0.0251	0.304 (0.267)	0.222
$C_{trough,28}$	mg/L	< LLOQ (0)	< LLOQ	< LLOQ (0.00853)	< LLOQ
t_{max}	day	2.26 (0.783)	2.16	2.8 (1.08)	2.89

AUC = area under the concentration-time curve, C_{max} = maximum (peak) concentration for a 28-day interval following dosing, C_{trough} = trough concentration, DME = diabetic macular edema, DPKS = dense pharmacokinetic sub-studies, IVT = intravitreally, LLOQ = lower limit of quantitation, n = number of participants, nAMD = neovascular age-related macular degeneration, PK = pharmacokinetics, SD = Standard deviation, t_{max} = median time to peak concentration; Note: Participants who had fellow eye treatment before day 28 are excluded.

Table 2-84. Summary of *Post-hoc* Simulated Pharmacokinetic Parameters for Adjusted Bound Aflibercept in Plasma after Single Dose IVT administration in the Combined nAMD and DME Population Treated Only in the Study Eye and Without Study Eye Dosing Modifications in the Dense PK Sub-studies (DPKS)

		Aflibercept		HD Aflibercept	
		2 mg IVT (N = 31)		8 mg IVT (N = 50)	
PK Parameters	**Unit**	**Mean (SD)**	**Median**	**Mean (SD)**	**Median**
AUC_{0-28}	**mg x day/L**	3.07 (1.31)	3.05	10.8 (6.14)	9.03
C_{max}	**mg/L**	0.142 (0.0616)	0.139	0.507 (0.282)	0.434
$C_{trough,28}$	**mg/L**	0.105 (0.0393)	0.0994	0.386 (0.21)	0.338
t_{max}	**day**	14.8 (5.65)	13.7	15.5 (5.22)	15.8

AUC = area under the concentration-time curve, C_{max} = maximum (peak) concentration for a 28-day interval following dosing, C_{trough} = trough concentration, DME = diabetic macular edema, DPKS = dense pharmacokinetic sub-studies, IVT = intravitreally, nAMD = neovascular age-related macular degeneration, PK = pharmacokinetics , SD = standard deviation, t_{max} = median time to peak concentration; Note: Participants who had fellow eye treatment before day 28 are excluded.

[000838]The corresponding observed and Population PK estimated *post-hoc* concentration-time profiles and PK parameters for participants with nAMD or DME are provided in Figure 36, Figure 37, Figure 38, Table 2-85 and Table 2-86.

Table 2-85. Summary of Simulated Pharmacokinetic Parameters for Free Aflibercept in Plasma after Single Dose IVT Administration in Participants with nAMD or DME Treated Only in the Study Eye and Without Study Eye Dosing Modifications in the Dense PK Sub-studies (DPKS)

		2 mg IVT			8 mg IVT		
PK Parameters	**Unit**	**N**	**Mean (SD)**	**Median**	**N**	**Mean (SD)**	**Median**
nAMD participants							
AUC_{0-28}	mg x day/L	21	0.302 (0.223)	0.258	29	2.77 (2.77)	1.95
C_{max}	mg/L		0.0419 (0.0439)	0.0258		0.306 (0.302)	0.172
$C_{trough,28}$	mg/L		< LLOQ (0)	< LLOQ		< LLOQ (0.0094)	< LLOQ
t_{max}	day		2.19 (0.606)	2.16		2.97 (1.08)	3.05
DME participants							
AUC_{0-28}	mg x day/L	10	0.238 (0.0732)	0.236	21	2.25 (1.45)	2.17
C_{max}	mg/L		0.0343 (0.0275)	0.0212		0.302 (0.216)	0.265

$C_{trough,28}$	mg/L		< LLOQ (0)	< LLOQ		< LLOQ (0.00732)	< LLOQ
t_{max}	day		2.41 (1.09)	2.23		2.56 (1.06)	2.36

AUC_{0-28} = area under the concentration-time curve, C_{max} = maximum (peak) concentration for a 28-day interval following dosing, $C_{trough,28}$ = trough concentration, DME = diabetic macular edema, DPKS = dense pharmacokinetic sub-studies, IVT = intravitreally, LLOQ = lower limit of quantitation, n = number of participants, nAMD = neovascular age-related macular degeneration, PK = pharmacokinetic, SD = Standard deviation, t_{max} = median time to peak concentration. Note: Participants who had fellow eye treatment before day 28 are excluded.

Table 2-86. Summary of Simulated Pharmacokinetic Parameters for Adjusted Bound Aflibercept in Plasma after Single Dose IVT administration in Participants with nAMD or DME Treated Only in the Study Eye and Without Study Eye Dosing Modifications in the Dense PK Sub-studies (DPKS)

		Adjusted Bound Aflibercept					
		2 mg IVT			8 mg IVT		
PK Parameters	Unit	N	Mean (SD)	Median	N	Mean (SD)	Median
nAMD participants							
AUC_{0-28}	mg x day/L	21	3.35 (1.44)	3.16	29	11.8 (7.17)	11
C_{max}	mg/L		0.155 (0.0686)	0.144		0.558 (0.329)	0.51
$C_{trough,28}$	mg/L		0.113 (0.0418)	0.113		0.439 (0.23)	0.415
t_{max}	day		14.4 (4.89)	13.1		16.9 (5.26)	17.2
DME participants							
AUC_{0-28}	mg x day/L	10	2.46 (0.726	2.43	21	9.33 (4.06)	8.39
C_{max}	mg/L		0.115 (0.0317)	0.117		0.438 (0.187)	0.4
$C_{trough,28}$	mg/L		0.088 (0.0281)	0.09		0.314 (0.156)	0.25
t_{max}	day		15.6 (7.21)	15.4		13.7 (4.65)	12.9

AUC_{0-28} = area under the concentration-time curve, C_{max} = maximum (peak) concentration for a 28-day interval following dosing, $C_{trough,28}$ = trough concentration, DME = diabetic macular edema, DPKS = dense pharmacokinetic sub-studies, IVT = intravitreally, LLOQ = lower limit of quantitation, n = number of participants, nAMD = neovascular age-related macular degeneration, SD = standard deviation, t_{max} = median time to peak concentration; Note: Participants who had fellow eye treatment before day 28 are excluded.

[000839]Following single IVT administration of 2 mg aflibercept or HD aflibercept presented as HD drug product, the concentration-time profiles of free aflibercept are characterized by an initial phase of increasing concentrations, as the drug moved from the ocular space into systemic circulation, followed by a mono-exponential elimination phase. The concentration time profiles of adjusted bound aflibercept in plasma are characterized by a slower attainment of C_{max} compared to free aflibercept. Following attainment of C_{max}, a sustained plateau of the

concentration-time profiles of adjusted bound aflibercept in plasma was observed until approximately the end of the first dosing interval (Figure 32, Figure 33).

[000840]For participants who underwent dense blood sample collection for systemic drug concentrations across the CANDELA, PULSAR, and PHOTON studies, after the initial dosing of 2 mg IVT aflibercept (n = 34), observed concentrations of free aflibercept were detectable in 15 (44.1%) participants by week 1 and in 3 (8.8%) participants by week 2. For participants who underwent dense blood sample collection for systemic drug concentrations after the initial dosing of 8 mg IVT aflibercept (n = 54), observed concentrations of free aflibercept were detectable in 46 (85.2%) participants by week 1 and in 44 (77.8%) participants by week 2.

[000841]The observed and Population PK simulated free and adjusted bound aflibercept concentrations in plasma for up to 48 weeks are presented for the combined nAMD and DME population (Figure 34), and the nAMD (Figure 39) and DME (Figure 40) populations. Based on the Population PK analysis, the median time for free aflibercept concentrations to reach LLOQ following HDq12 or HDq16 was 3.5 weeks, which is more than double the median time needed to reach LLOQ (1.5 weeks) following aflibercept 2q8 (Table 2-87).

Table 2-87. Summary of Model-Predicted Time to LLOQ of Free Aflibercept in Plasma Following IVT for Participants With nAMD and DME, Combined

Regimen	**Mean (SD)** Week	**Median (90% PI)** Week
2q8	1.58 (0.712)	1.5 (0.524, 2.82)
HDq12	3.81 (1.61)	3.51 (1.83, 6.81)
HDq16	3.79 (1.58)	3.50 (1.83, 6.73)

Model-predicted time = time after a single IVT dose of the 2q8, HDq12 or HDq16 regimens. 2q8 = aflibercept 2 mg administered every 8 weeks, after 3 initial injections at 4-week intervals, DME = diabetic macular edema, HDq12 = aflibercept 8 mg administered every 12 weeks following 3 initial monthly injections, HDq16 = aflibercept 8 mg administered every 16 weeks following 3 initial monthly injections, IVT = intravitreally, LLOQ = lower limit of quantification, nAMD = neovascular age related macular degeneration, PI = prediction interval, SD = standard deviation

[000842]The longer duration of systemic exposure to free aflibercept following HDq12 and HDq16 compared to the 2 mg aflibercept is attributed to not only a higher administered dose and nonlinear systemic target-mediated elimination, but also to a 34% slower ocular clearance of free aflibercept. The 34% slower ocular clearance of free aflibercept for HD aflibercept is attributed to a HD drug product effect which was identified as a statistically significant covariate in the Population PK model.

[000843]Ocular Elimination. Based on the Population PK analysis, HD aflibercept, presented as the HD drug product, was estimated to have a 34% slower clearance from the ocular

compartment compared to the lower IVT doses of aflibercept (≤ 4 mg doses) that was presented as the standard, or reference drug product. The median time for the amount of free aflibercept to reach the adjusted LLOQ [the adjusted LLOQ imputes the LLOQ of free aflibercept in from the assay in plasma (that is, 0.0156 mg/L) times the assumed volume of the study eye compartment in the PK model (that is, 4 mL)] in the ocular compartment was estimated using Population PK simulation analyses, after a single 2 mg or 8 mg IVT dose. In the combined nAMD and DME population, the median time for the amount of free aflibercept to reach the adjusted LLOQ in the ocular compartment increased from 8.71 weeks after a 2 mg IVT dose to 15 weeks after an 8 mg IVT dose (i.e., the duration of free aflibercept ocular exposure following HD drug product is extended by approximately 6 weeks relative to 2 mg drug product). The slower ocular clearance and longer duration of free aflibercept ocular exposure for HD aflibercept are attributed to an HD aflibercept drug product effect. Assuming no HD aflibercept drug product effect (*i.e.*, that the 8 mg IVT dose has the same ocular clearance as the 2 mg IVT dose), the Population PK simulated median time for the amount of free aflibercept to reach the adjusted LLOQ in the ocular compartment was only 10 weeks for 8 mg aflibercept, which is only 1.3 weeks longer than that for 2 mg aflibercept (Figure 35).

[000844]As the PULSAR and PHOTON studies were designed to assess non-inferiority of the HDq12 and HDq16 regimens versus the 2q8 regimen, it was of interest to estimate how long it takes for the amount of free aflibercept in the ocular compartment for the HDq12 and HDq16 regimens to reach the same amount of free aflibercept remaining in the ocular compartment for the 2q8 regimen at the end of an 8-week dosing interval (2q8 target). Using a modified approach, using Population PK simulation analyses in the combined nAMD and DME population, the median time for HDq12 and HDq16 regimens to reach the 2q8 target in the ocular compartment after single IVT administration was 14 weeks, suggesting that the HD aflibercept regimens may provide a 6-week longer duration of efficacy than the 2q8 regimen. In contrast, if there were no HD aflibercept drug product effect, the Population PK simulated median time for the amount of free aflibercept to reach the 2q8 target in the ocular compartment would be only 9.21 weeks for an 8 mg dose, representing an extension of only 1.21 weeks relative to the 2q8 regimen, and is consistent with the prior example.

[000845]High-Dose Aflibercept Drug Product. The totality of the composition of the HD drug product used to deliver the 8 mg dose is different from that for the 2 mg aflibercept IVT dose. Based on Population PK analysis, the HD aflibercept drug product is a statistically significant predictor of ocular clearance of free aflibercept that results in a slower ocular clearance for the HD aflibercept versus 2 mg aflibercept when administered by the IVT route. (Table 2-88). The

slower ocular clearance and higher molar dose for the HD aflibercept drug product results in a longer duration of ocular exposure to free aflibercept compared to the 2 mg IVT dose. The slower ocular clearance of the HD aflibercept drug product is predicted to provide a 6-week longer duration of efficacy compared to 2q8, as the time to achieve the free aflibercept amount in the ocular compartment for the 2q8 regimen at the end of an 8-week dosing interval occurs 6 weeks later for the HD aflibercept drug product. Consistent with these predictions, the HDq12 and HDq16 regimens demonstrated noninferiority to the 2q8 regimen in the PHOTON (for DME only) and PULSAR studies. Correspondingly, a slower ocular clearance for the HD aflibercept drug product contributes in part to a longer duration of systemic exposure to free aflibercept for HD aflibercept versus the 2 mg IVT dose. The slower ocular clearance for HD aflibercept is attributed to a difference in the HD aflibercept drug product, not just an increase in the IVT dose from 2 mg to 8 mg. These results were further confirmed by a sensitivity analysis conducted in the final model.

Table 2-88. Comparison of Clearance from the Ocular Compartment (QE) (Mean [95% CI]) of Aflibercept for HD Aflibercept and 2 mg Aflibercept

Dose Group	Clearance from the Ocular Compartment (QE) Mean (95% CI) (mL/day)	k = QE/0.004 Mean (95% CI (day^{-1})
2 mg Aflibercept	0.624 (0.577 - 0.674)	0.156 (0.144 - 0.169)
HD 8 mg Aflibercept	0.41 (0.367 - 0.458)	0.102 (0.0916 - 0.115)

QE = inter-compartmental clearance between ocular compartment and central compartment of free aflibercept, 95% CI of parameters are provided.

[000846]Pharmacokinetic Conclusions. The concentration time profiles of free and adjusted bound aflibercept in plasma after the initial dose of HD aflibercept by IVT administration were consistent between all studies in participants with nAMD or DME. Population PK analysis confirmed no relevant differences in PK between the nAMD and DME populations, and therefore all subsequent analyses are presented for the combined nAMD and DME population.

[000847]Following the initial monthly IVT dose, the observed concentration-time profile of free aflibercept in plasma is characterized by an initial phase of increasing concentrations as the drug is absorbed from the ocular space into the systemic circulation, followed by a mono-exponential elimination phase. The longer duration of systemic exposure to free aflibercept for HD aflibercept is attributed to not only a higher administered dose and non-linear systemic target mediated elimination but also to a 34% slower ocular clearance of free aflibercept, which is statistically attributed to the HD drug product as a covariate in the expanded PopPK model.

This slower than expected ocular clearance of free aflibercept when presented as the HD aflibercept drug product is simulated to provide a 6-week longer duration of efficacy compared to 2q8, as the time to achieve the free aflibercept amount in the ocular compartment for the 2q8 regimen at the end of an 8-week dosing interval occurs 6 weeks later for the HD aflibercept drug product. Consistent with these simulations for the 8mg presented as the HD drug product, the HDq12 and HDq16 regimens demonstrated noninferiority (at a longer treatment interval) to the 2q8 regimen presented as the reference drug product in the predefined statistical analysis plan for both the PHOTON (for DME only) and PULSAR phase 3 studies.

[000848]Based on expanded population PK analysis, following single IVT doses of 2 mg aflibercept and HD aflibercept, systemic exposures of free aflibercept ($AUC_{0\text{-}28}$ and C_{max}) in the combined nAMD and DME population increase in a greater than dose-proportional manner (approximately 9.0-fold and 7.7-fold). These results demonstrate and are consistent with the known nonlinear PK for free aflibercept. Bioavailability of free aflibercept following IVT administration is estimated to be approximately 72%, and the total volume of distribution of free aflibercept after IV administration is estimated to be approximately 7 L.

[000849]Following 3 initial monthly HD aflibercept doses, the population PK simulated mean accumulation ratio of free and adjusted bound aflibercept in plasma based on AUC was 1.16 and 2.28 in the combined DME and nAMD population. After the 3 initial monthly doses of HD aflibercept (presented as the HD drug product), no further accumulation of either free or adjusted bound aflibercept in plasma occurs as the dosing interval is extended from every 4 weeks to every 12 weeks or 16 weeks resulting in a decline in systemic concentrations of both free and adjusted bound aflibercept.

[000850]Amongst the covariates evaluated in the Population PK analysis, body weight was the covariate with the greatest impact on systemic exposures to free and adjusted bound aflibercept. For participants in the lowest quintile of body weight (38.1 kg to 64.5 kg), the predicted impact on systemic exposures (C_{max} and AUC_{tau}) was modest, with 27% to 39% higher exposures to free aflibercept and 25% to 27% higher exposures to adjusted bound aflibercept when compared to the reference body weight range (73.5 to 83.5 kg). The effects of other covariates (age, albumin, disease population, and race, which included evaluation of Japanese race) on systemic exposures (C_{max}, AUC_{tau}) to free and adjusted bound aflibercept were small (<25% increase in exposure for covariate subgroups relative to the reference group), with several of these other covariate effects correlating with a consistent trend in body weight. All of these covariates were independent of the HD drug product effect on ocular clearance and

did not confound the interpretation of the HD drug product effect on the ocular clearance. No dosage adjustments of HD aflibercept are warranted based on the assessed covariates.

[000851]Mild to severe renal impairment also had a small impact on free aflibercept systemic exposures, as the increase in free aflibercept C_{max} and AUC_{tau} in these participants was less than approximately 28% compared to participants with normal renal function. Adjusted bound aflibercept systemic exposures in participants with mild to severe renal impairment ranged from 13% to 39% higher compared to participants with normal renal function. Here too, the perceived impact of renal impairment is best explained by the associated decrease in body weight with increasing renal impairment. Mild hepatic impairment had no effect on systemic exposures to free and adjusted bound aflibercept. No dosage adjustments of aflibercept are warranted for these populations.

[000852]Model-Based Exposure-Response Analysis for Proportion of Participants Requiring Dose Regimen Modification Cox proportional hazard modeling was performed to evaluate factors that may contribute to the need for a reduction in the dosing interval. Within any one specific patient population, nAMD, DME (with and without DR), ocular clearance of free aflibercept and baseline CRT were identified as significant predictors of time to DRM. Within an indication (nAMD or DME (with and without DR)), for participants with the same ocular clearance of free aflibercept, a 52.8% higher rate of DRM is modeled for participants at the 75th vs 25th percentile of baseline CRT. Similarly, for participants with the same baseline CRT, a 32.9% higher rate of DRM is modeled for participants at the 75th vs 25th percentile of ocular clearance of free aflibercept, corresponding to those participants who are predicted to have the lowest aflibercept concentration in the eye. These results are shown in Table 2-89. The outcomes of these analyses also estimate that the slower ocular clearance for HD aflibercept, attributable to a HD drug product effect, results in a 20.6% lower rate of DRM than would have been expected if the HD drug product had the same ocular clearance as 2 mg aflibercept presented as the reference drug product.

Table 2-89. Hazard Ratio Contrasts for Time to DRM Model

Effect	Hazard Ratio
Baseline CRT	1.53 (1.34 - 1.75)
Ocular Clearance (QE)	1.33 (1.18 - 1.49)
Indication AMD Participants: DME Participants	3.6 (2.56-5.06)

AMD = age-related macular degeneration, CRT = central retinal thickness, DME = diabetic macular edema, DRM = dose regimen modification, QE = ocular clearance

[000853]Dose-Response and Exposure-Response Conclusions. As the IVT dose increased from 2 mg of aflibercept to 8 mg of HD aflibercept, no further increase in PD effect (decrease in CRT) was observed 4 weeks after each initial q4w dose through 12 weeks, in either the nAMD or DME population. Despite 2 mg of aflibercept (as reference drug product) and 8 mg of HD aflibercept (as HD drug product) having similar PD effect during the initial 3 x q4w dosing period, the 8 mg HD drug product provided a longer duration of pharmacological effect in the maintenance phase compared to 2 mg aflibercept. In nAMD participants, the small fluctuations in CRT or CST during a maintenance dosing interval attenuated over time for all dosing regimens, with only minor numerical differences observed between treatment groups. For DME participants, a greater reduction in CRT was observed from weeks 16 to 20 for 2q8 compared to both HD aflibercept regimens (HDq12 and HDq16). This is attributable to a difference in the number of doses administered during this time period, with the 2q8 regimen receiving 2 additional initial q4w doses at weeks 12 and 16 compared to the HD aflibercept regimens which received their last initial q4w dose at week 8. These differences in CRT did not translate into any meaningful difference in mean BCVA response. The fluctuations in CRT response over the course of a maintenance dosing interval attenuated over time for all dosing regimens. For participants with nAMD or DME, the HDq12 and HDq16 regimens provided rapid and durable response in CRT and BCVA over 48 weeks of treatment, with the majority of participants maintaining their randomized HDq12 (79% nAMD; 91% DME) and HDq16 (77% nAMD; 89% DME) treatment regimens, without the need for DRM. Ocular clearance of free aflibercept and baseline CRT were identified as significant covariates contributing to the need for DRM. Higher ocular clearance of free aflibercept and higher baseline CRT (indicative of more severe disease) were associated with an increased rate of DRM. The slower ocular clearance for HD aflibercept, attributable to a HD drug product effect, is estimated to result in a 20.6% lower rate of DRM compared to HD aflibercept if the same ocular clearance was observed as the 2 mg aflibercept when presented as the reference drug product.

[000854]Overall Clinical Pharmacology Conclusions. Consistent with the known target-mediated kinetic properties exhibited at low plasma concentrations of aflibercept, free aflibercept exhibited nonlinear systemic PK over the 2 mg to 8 mg IVT dose range. Following the initial IVT dose, the concentration-time profile for free aflibercept in plasma is characterized by an initial absorption phase as drug moves from the ocular space into the systemic circulation. This absorption phase is followed by a mono-exponential elimination phase. The concentration time profile of adjusted bound aflibercept in plasma following the initial IVT dose is characterized

by a slower attainment of C_{max} (t_{max}) compared to free aflibercept, after which the concentrations are sustained or slightly decrease until the end of the dosing interval.

[000855]Analyses of observed PK by cross-study comparison and by Population PK analyses suggested similar systemic PK in the nAMD and DME populations. Following IVT administration, Population PK methods estimate the bioavailability of free aflibercept at 72%, a median t_{max} of 2.89 days, and mean C_{max} of 0.304 mg/L for the 8 mg dose of HD aflibercept. As the aflibercept IVT dose increased from 2 mg to 8 mg and the treatment changes from 2 mg aflibercept (presented as the reference drug product) to 8 mg HD aflibercept (presented as the HD drug product), consistent with the known target-mediated related nonlinear PK of free aflibercept mean AUC_{0-28} and C_{max} for free aflibercept increased in a greater than dose-proportional manner. After IV administration, free aflibercept has a low total volume of distribution of 7 L, indicating distribution largely in the vascular compartment. Following 3 initial monthly HD aflibercept IVT doses, the mean accumulation ratio of free and adjusted bound aflibercept in plasma based on AUC is 1.16 and 2.28. After the 3 initial monthly doses of HD drug product, no further accumulation of either free or adjusted bound aflibercept in plasma occurred as the dosing interval is extended from every 4 weeks to every 12 weeks or 16 weeks resulting in an expected decline in systemic concentrations of both free and adjusted bound aflibercept.

[000856]The longer duration of systemic exposure to free aflibercept for HD aflibercept is attributed to not only a higher administered dose and nonlinear systemic target-mediated elimination, but also to a 34% slower ocular clearance of free aflibercept. This 34% slower ocular clearance of free aflibercept for HD aflibercept is attributed to a HD drug product effect, which was identified as a statistically significant covariate in the Population PK model. Based on the extended PopPK model, the slower ocular clearance of the HD aflibercept drug product provides a 6-week longer duration of efficacy compared to 2q8 when presented as the reference drug product. Resulting from this unexpected and non-obvious slower ocular clearance, was a longer than expected ocular residence time, leading to a greater than expected proportion of patients able to be maintained on the longer dosing intervals of q12 and q16 with HD drug product. Consistent with these predictions, the HDq12 and HDq16 regimens demonstrated non-inferiority to the 2q8 regimen in the PHOTON and PULSAR studies.

[000857]Body weight was the covariate with the greatest impact on systemic exposures to free and adjusted bound aflibercept. For participants in the lowest quintile of body weight (38.1 to 64.5 kg), the predicted impact on free aflibercept C_{max} and AUC_{tau} was modest, with 27% to 39% higher exposures and 25% to 27% higher for adjusted bound aflibercept when compared the

reference body weight range (73.5 to 83.5 kg). The effects of other covariates (age, albumin, disease population. and race, which included evaluation of Japanese race) on systemic exposures (C_{max}, AUC_{tau}) to free and adjusted bound aflibercept were small (<25% increase in exposure for covariate subgroups relative to the reference group). These other covariates did not confound the assessment of the effect of HD drug product on ocular clearance. No dosage adjustments of aflibercept are warranted based on the above findings.

[000858]No formal studies were conducted in special populations (*e.g.*, participants with renal or hepatic impairment) because like most therapeutic proteins, the large molecular weight of aflibercept (approximately 115 kDa) is expected to preclude elimination via the kidney, and its metabolism is expected to be limited to proteolytic catabolism to small peptides and individual amino acids. Mild to severe renal impairment had a small impact on free aflibercept systemic exposures, as the increase in free aflibercept C_{max} and AUC_{tau} in these participants was less than approximately 28% compared to participants with normal renal function. Adjusted bound aflibercept systemic exposures in participants with mild to severe renal impairment ranged from 13% to 39% higher compared to participants with normal renal function. The perceived impact of renal impairment is explained by the associated decrease in body weight with increasing renal impairment. Mild hepatic impairment had no effect on systemic exposures to free and adjusted bound aflibercept. No dosage adjustments of aflibercept are warranted in these populations.

[000859]Dose-response analyses of CRT performed in the CANDELA, PULSAR, and PHOTON studies indicated no further increase in PD effect for 2 mg aflibercept and HD aflibercept IVT 4 weeks after each initial q4W dose through 12 weeks. Despite the 2 mg aflibercept and HD aflibercept having similar PD effect during the initial q4w dosing period, the HD aflibercept drug product provided a longer duration (up to 16 weeks) of pharmacological effect in the maintenance phase than the 2 mg dose presented as the reference drug product (up to 8 weeks).

[000860]For participants with nAMD or DME, the HDq12 and HDq16 regimens provided rapid and durable response in CRT and BCVA over 48 weeks of treatment, with the majority of participants maintaining their randomized HDq12 (79% nAMD; 91% DME) and HDq16 (77% nAMD; 89% DME) treatment regimens, without the need for DRM.

[000861]Ocular clearance of free aflibercept and baseline CRT were identified as significant covariates contributing to the need for DRM. Higher ocular clearance and higher baseline CRT (indicative of more severe disease) were associated with an increased rate of DRM. For HD aflibercept, the slower ocular clearance and longer duration of ocular exposure to free

aflibercept, attributable to the HD drug product effect, have been identified in an exposure-response analysis to result in a reduction of DRM of 20.6%.

[000862]Immunogenicity of HD aflibercept administered IVT was low across all treatment groups for both nAMD and DME participants. During the 48-week treatment with aflibercept administered IVT, the incidence of ADA in the combined 8 mg HD aflibercept treatment group was 2.7% (25/937 participants with nAMD or DME). None of the TE ADA positive samples were found to be positive in the NAb assay. Based on the lack of impact of ADA on concentrations of aflibercept in plasma, no effect on efficacy is anticipated. Positive responses in the ADA assays were not associated with significant AEs.

[000863]Overall, the clinical pharmacology data support the proposed aflibercept dosing regimens of 8 mg every 8 to 16 weeks after 3 initial monthly doses for the treatment of adults with nAMD, DME (with and without DR).

[000864]*Immunogenicity.* Samples for anti-drug antibody (ADA) examinations were taken at baseline and subsequently at Week 48 and the results are presented based on the Week 60 database. The samples were analyzed using a validated, electrochemiluminescence bridging assay to detect the presence of ADA.

[000865]Out of the 833 participants in the ADA analysis set (AAS), a total of 43 participants had positive samples in the ADA assay at any time (including baseline); 11 participants in the 2q8 group, 19 participants in the HDq12 group, and 13 participants in the HDq16 group (Table 2-90).

[000866]A total of 24 participants participating in this study exhibited a treatment-emergent ADA response; 4 participants in the 2q8 group, 11 participants in the HDq12 group, and

[000867]9 participants in the HDq16 group. The incidence of treatment-emergent immunogenicity in the 2q8, HDq12 and HDq16 groups was approximately 1.5%, 3.9%, and 3.2%, respectively. No treatment-boosted ADA was observed, and all treatment-emergent responses were low titer (< 1000). None of the samples that were positive in the ADA assay demonstrated neutralizing activity (Table 2-90).

Table 2-90. Summary of ADA status, ADA category, maximum titer category, and NAb status through Week 60

Visit	Category	**2q8** N = 273 (100%)	**HDq12** N = 283 (100%)	**HDq16** N = 277 (100%)	**All HD** N = 560 (100%)
Week 48	Total ADA subjects, n (%)	273 (100%)	283 (100%)	277 (100%)	560 (100%)
	Negative (a)	262 (96.0%)	263 (92.9%)	263 (94.9%)	526 (93.9%)
	Pre-existing immunoreactivity (b)	7 (2.6%)	8 (2.8%)	4 (1.4%)	12 (2.1%)
	Treatment-boosted (c)	0	0	0	0
	Treatment-emergent positive (d)	4 (1.5%)	11 (3.9%)	9 (3.2%)	20 (3.6%)
	Missing	0	1 (0.4%)	1 (0.4%)	2 (0.4%)

Treatment-emergent positive or Treatment-boosted				
Low (< 1000)	4	11	9	20
Moderate (1000-10000)	0	0	0	0
High (> 10000)	0	0	0	0

ADA = anti-drug antibody, NAb = neutralizing antibody
(a) ADA Negative: negative response in the ADA assay at all time points and those that exhibited a pre-existing response, as defined in (b), regardless of any missing samples.
(b) Pre-existing immunoreactivity: either a positive response in the ADA assay at baseline with all post first dose ADA results negative OR a positive response at baseline with all post first dose ADA responses less than 4-fold of baseline titer levels.
(c) Treatment-boosted ADA response: positive response post first dose that is greater than or equal to 4-fold over baseline titer level, when baseline results were positive.
(d) Treatment-emergent positive: ADA-positive response post first dose when baseline results were negative or missing.
(e) Samples that tested negative for ADA were not assayed in the NAb assay and the corresponding NAb result was imputed as negative and included as such in the NAb analysis set. Participants in the NAbAS with multiple post-dose ADA results which consisted of both imputed NAb-negative result(s) for ADA negative samples and only missing NAb results for all ADA-positive result(s), were set to NAb negative. Participants in the NAbAS that have at least one post-dose positive NAb analysis result were set to NAb positive even if other NAb results were missing.

[000868]Overall, the low level of immunogenicity was not considered clinically relevant. In participants with treatment-emergent ADA, one participant in the HDq12 group had an AE of mild iritis which was not considered to be related to study treatment by the investigator.

[000869]*Treatment Exposure.* A summary of exposure to study treatment and duration of treatment in the SAF is presented in Table 2-91.

[000870]The mean number of active injections in the SAF population through Week 60 was 8.5, 6.9 and 6.0 in the 2q8, HDq12 and HDq16 treatment groups, respectively (Table 2-91). For the 925 participants in the SAF considered as completers of 60 weeks of study treatment (*i.e.*, SAF completers), the mean number of active injections was 8.8, 7.1 and 6.2 in the 2q8, HDq12 and HDq16 treatment groups, respectively. The observed decrease in the mean and median number of active injections and the corresponding increase in the number of sham injections from the 2q8 group to the HDq12 and HDq16 group reflects the protocol-driven increase in treatment intervals across these groups.

Table 2-91. Exposure to Study Treatment: Through Week 48 and Week 60 (Safety Analysis Set)

	2q8 N = 336 (100%)	**HDq12** N = 335 (100%)	**HDq16** N = 338 (100%)	**All HD** N = 673 (100%)
Week**48**				
Total number of active injections, n	2267	1986	1703	3689
Total number of sham injections, n	1212	1515	1793	3308
Number of active injections, n (%)				

1	1 (0.3%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
2	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
3	4 (1.2%)	3 (0.9%)	9 (2.7%)	12 (1.8%)
4	6 (1.8%)	7 (2.1%)	22 (6.5%)	29 (4.3%)
5	6 (1.8%)	22 (6.6%)	263 (77.8%)	285 (42.3%)
6	29 (8.6%)	260 (77.6%)	11 (3.3%)	271 (40.3%)
7	288 (85.7%)	39 (11.6%)	29 (8.6%)	68 (10.1%)
8	1 (0.3%)	0	0	0
Number of active injections				
n	336	335	337	672
Mean (SD)	6.7 (0.8)	5.9 (0.8)	5.1 (0.8)	5.5 (0.9)
Median	7.0	6.0	5.0	6.0
Min, Max	1,8	1,7	1,7	1,7
Number of sham injections, n (%)				
1	7 (2.1%)	4 (1.2%)	3 (0.9%)	7 (1.0%)
2	15 (4.5%)	4 (1.2%)	8 (2.4%)	12 (1.8%)
3	46 (13.7%)	17 (5.1%)	5 (1.5%)	22 (3.3%)
4	258 (76.8%)	63 (18.8%)	40 (11.8%)	103 (15.3%)
5	1 (0.3%)	240 (71.6%)	45 (13.3%)	285 (42.3%)
6	0	0	229 (67.8%)	229 (34.0%)
Number of sham injections				
n	327	328	330	658
Mean (SD)	3.7 (0.7)	4.6 (0.7)	5.4 (1.0)	5.0 (1.0)
Median	4.0	5.0	6.0	5.0
Min, Max	1,5	1,5	1,6	1,6
Duration of treatment (weeks)				
n	336	335	337	672
Mean (SD)	46.28 (6.62)	46.54 (6.56)	46.18 (6.97)	46.36 (6.77)

	2q8 N = 336 (100%)	**HDq12** N = 335 (100%)	**HDq16** N = 338 (100%)	**All HD** N = 673 (100%)
Median	48.00	48.00	48.00	48.00
Min, Max	4,50.9	4,52	4,53.3	4,53.3
Week **60**				
Total number of active injections, n	2854	2324	2018	4342
Total number of sham injections, n	1502	2080	2380	4460
Number of active injections, n (%)				
1	1 (0.3%)	2 (0.6%)	2 (0.6%)	4 (0.6%)
2	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
3	4 (1.2%)	3 (0.9%)	9 (2.7%)	12 (1.8%)
4	6 (1.8%)	7 (2.1%)	10 (3.0%)	17 (2.5%)
5	5 (1.5%)	5 (1.5%)	20 (5.9%)	25 (3.7%)
6	9 (2.7%)	24 (7.2%)	255 (75.4%)	279 (41.5%)
7	6 (1.8%)	239 (71.3%)	11 (3.3%)	250 (37.1%)
8	43 (12.8%)	38 (11.3%)	21 (6.2%)	59 (8.8%)
9	260 (77.4%)	15 (4.5%)	8 (2.4%)	23 (3.4%)
10	1 (0.3%)	0	0	0
Number of active injections				
n	336	335	337	672
Mean (SD)	8.5 (1.3)	6.9 (1.1)	6.0 (1.1)	6.5 (1.2)
Median	9.0	7.0	6.0	6.0
Min, Max	1,10	1,9	1,9	1,9
Number of sham injections, n (%)				
1	5 (1.5%)	4 (1.2%)	3 (0.9%)	7 (1.0%)
2	12 (3.6%)	2 (0.6%)	8 (2.4%)	10 (1.5%)
3	15 (4.5%)	5 (1.5%)	2 (0.6%)	7 (1.0%)
4	48 (14.3%)	12 (3.6%)	5 (1.5%)	17 (2.5%)
5	246 (73.2%)	34 (10.1%)	19 (5.6%)	53 (7.9%)
6	1 (0.3%)	58 (17.3%)	31 (9.2%)	89 (13.2%)
7	0	213 (63.6%)	42 (12.4%)	255 (37.9%)
8	0	0	220 (65.1%)	220 (32.7%)

Number of sham injections				
n	327	328	330	658
Mean (SD)	4.6 (0.9)	6.3 (1.2)	7.2 (1.5)	6.8 (1.4)
Median	5.0	7.0	8.0	7.0
Min, Max	1,6	1,7	1,8	1,8
Duration of treatment (weeks)				
n	336	335	337	672
Mean (SD)	57.23 (9.56)	57.74 (9.12)	57.44 (9.80)	57.59 (9.46)
Median	60.00	60.00	60.00	60.00
Min, Max	4,64.7	4,63.3	4,63.6	4,63.6

Max = maximum, Min = minimum, SD = standard deviation
Duration (weeks) = [(date of last study treatment) – (date of first study treatment) +28]/7; 28 days were added because of the minimum 4 week dosing interval in the study. Study interventions given at Week 60 or beyond are not included in this table.

[000871]The results of the exploratory endpoints, proportions of participants with a q16 or longer treatment interval through Week 48 and Week 60 in the HDq16 group, with a q12 or longer interval through Week 48 and Week 60 in the HDq12 and HDq16 groups, and with a q12 or q16 or longer treatment interval as the last intended interval at Week 48 and Week 60 in the HDq12 and HDq16 groups, respectively, in the SAF, are presented Table 2-92. In addition, the proportions of participants with q20 treatment interval as the last intended interval at Week 60 in the HDq16 group and the proportion of participants who shortened treatment intervals in the HDq12 and HDq16 groups are presented in this table.

[000872]Overall, the target treatment intervals of either q12 or q16 were maintained in more than 3 quarters of all participants in the HD groups through Week 48 and in approximately 3 quarters of all participants in the HD groups through Week 60.

[000873]Overall, the target treatment intervals of either q12 or q16 were maintained in more than 3 quarters of all participants in the HD groups through Week 48 and in approximately 3 quarters of all participants in the HD groups through Week 60.

Table 2-92. Exposure to study treatment through Week 48 and Week 60 – Dosing intervals (safety analysis set, only participants considered as completers for Week 48)

Through Week **48 (a)**	**2q8** N = 309 (100%)	**HDq12** N = 316 (100%)	**HDq16** N = 312 (100%)	**All HD** N = 628 (100%)
Subjects with q12 or longer dosing interval (b), n (%)	/	251 (79.4%)	272 (87.2%)	523 (83.3%)
Subjects with q16 dosing interval (c), n (%)	/	/	239 (76.6%)	/
Subjects with q12 or longer dosing interval as the last intended dosing interval (d), n (%)	/	251 (79.4%)	271 (86.9%)	522 (83.1%)
Subjects with q16 dosing interval as the last intended dosing interval (d), n (%)	/	/	239 (76.6%)	/
Subjects shortened to q8 dosing interval at Week 16, n (%)	/	17 (5.4%)	10 (3.2%)	27 (4.3%)
Subjects shortened to q8 dosing interval at Week 20, n (%)	/	25 (7.9%)	21 (6.7%)	46 (7.3%)
Subjects shortened anytime, n (%)	/	65 (20.6%)	73 (23.4%)	138 (22.0%)
Subjects shortened to q8 dosing interval anytime, n	/	65 (20.6%)	40 (12.8%)	105 (16.7%)

(%)				
Subjects shortened to q12 dosing interval anytime, n (%) (without shortening to q8)	/	/	33 (10.6%)	/
Through Week **60 (e)**				
	2q8 N = 305 (100%)	**HDq12** N = 311 (100%)	**HDq16** N = 309 (100%)	**All HD** N = 620 (100%)
Subjects maintained with q12 or longer dosing interval (f), n (%)	/	242 (77.8%)	264 (85.4%)	506 (81.6%)
Subjects maintained with q16 or longer dosing interval (g), n (%)	/	/	229 (74.1%)	/
Subjects with q12 or longer dosing interval as the last intended dosing interval (h), n (%)	/	263 (84.6%)	278 (90.0%)	541 (87.3%)
Subjects with q16 or longer dosing interval as the last intended dosing interval (h), n (%)	/	134 (43.1%)	239 (77.3%)	373 (60.2%)
Subjects with q20 dosing interval as the last intended dosing interval (h), n (%)	/	/	119 (38.5%)	/
Subjects shortened to q8 dosing interval at Week 16, n (%)	/	17 (5.5%)	10 (3.2%)	27 (4.4%)
Subjects shortened to q8 dosing interval at Week 20, n (%)	/	25 (8.0%)	20 (6.5%)	45 (7.3%)
Subjects shortened anytime, n (%)	/	69 (22.2%)	80 (25.9%)	149 (24.0%)
Subjects shortened to q8 dosing interval anytime, n (%)	/	69 (22.2%)	45 (14.6%)	114 (18.4%)
Subjects shortened to q12 dosing interval anytime (without shortening to q8), n (%)	/	/	35 (11.3%)	/
Subjects never extended dosing interval, n (%) (i)	/	159 (51.1%)	174 (56.3%)	333 (53.7%)
Subjects extended dosing interval anytime, n (%) (j)	/	152 (48.9%)	135 (43.7%)	287 (46.3%)

DRM = dose regimen modification
/ indicates categories that do not apply.
a Study interventions given at Week 48 or beyond are not included in this table.
b All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 44] prior to Week 48.
c All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 44] prior to Week 48.
d Based on DRM criteria assessed at the last visit on or before Week 48.
e Study interventions given at Week 60 or beyond are not included in this table.
f All subjects on q12 or q16 interval for whom it was not planned to have their interval shortened to q8 interval [according to DRM criteria until Week 56] prior to Week 60.
g All subjects on q16 interval for whom it was not planned to have their interval shortened to q12 or q8 interval [according to DRM criteria until Week 56] prior to Week 60.
h Based on DRM criteria assessed at the last visit on or before Week 60.
i All subjects on q12 or q16 interval for whom it was not planned to have their interval extended [according to DRM criteria until Week 56] prior to Week 60.
j All subjects on q12 or q16 interval for whom it was planned to have their interval extended [according to DRM criteria until Week 56] prior to Week 60.

[000874]At Weeks 60 and 96, 91 and 89% of patients receiving aflibercept 8q16 maintained ≥Q12 dosing intervals and 78% maintained or extended to Q16 intervals. See Table 2-93. See summary of last completed dosing intervals in Table 2-94.

Table 2-93. Aflibercept 8q16: Last Assigned Dosing Interval at Week 60 and Week 96

	q8 (%)	**q12 (%)**	**q16 (%)**	**q20 (%)**	**q24 (%)**

Randomized to 8q16 at BL at Week 60 (n=309)*	10.0	12.6	38.8	38.5	0
Randomized to 8q16 at BL at Week 96 (n=292)#	11.0	10.6	25.3	22.3	30.8

*Patients completing Week 60.
#Patients completing Week 96.
Values may not add up to 100% due to rounding.

Table 2-94. Last Completed Dosing Interval at Week 96

	q8 (%)	q12 (%)	q16 (%)	q20 (%)
Randomized to 8q16 at BL (n=292)*	11	10	30	48
Randomized to 8q12 at BL (n=291)#	13	26	29	31

aDosing intervals were extended in Year 2 if patients had <5-letter loss in BCVA from Week 12 AND no fluid at the center subfield AND no new foveal hemorrhage or neovascularization. bPatients completing Week 96. cPatients were assigned to 24-week dosing intervals if they continued to meet extension criteria but did not have enough time to complete the interval within the 96-week study period. Values may not add up to 100% due to rounding.

[000875] *Polypoidal Choroidal Vascularization*. A subgroup analysis focused on patients with PCV as confirmed by indocyanine green angiography (ICGA) at a central reading center. Subgroup analyses were exploratory only.

[000876] In this trial (PULSAR), PCV was present in 139 of the 293 patients with ICGA results (2q8: n=54; 8q12: n=44; 8q16: n=41). Both aflibercept 8 mg and 2 mg markedly reduced the proportion of patients with active polyps, and total polyp area from baseline to Week 96. The mean number of injections through Week 96 was similar between the PCV subgroup and overall population, ranging from approximately 13 injections for 2q8 to 8 injections for 8q16.

[000877] Visual acuity gains from baseline were largely maintained from Week 48 to Week 96 in the aflibercept 8q12, 8q16, and 2q8 PCV subgroups, with gains of +8.4, +8.2, and +9.6 letters, respectively, from baseline to Week 96. The last observation carried forward (LOCF) mean±SD best-corrected visual acuity (BCVA) change from baseline (BL) at Week 96 was similar in the three treatment groups, with gains of 8.4±12.8, 8.2±9.0, and 9.6±12.1 letters for 8q12, 8q16, and 2q8 (BL: 56.3±13.3, 60.1±11.5, and 57.6±15.5 letters), respectively. In the overall PULSAR population, these gains were 5.5±14.9, 5.4±13.3, and 7.1±13.0 letters (BL: 59.9±13.4,

60.0±12.4, and 58.9±14.0 letters), respectively. Absolute BCVA amont the PCV subgroup over time is set forth in Table 2-95.

Table 2-95. Absolute BCVA (ETDRS letters) Through Week 96: Similar in PCV Subgroup

Week	2q8	8q12	8q16
0	57.6	56.3	60
4	62.8	59.1	63.4
8	65.2	62.4	64.9
12	66.3	62.9	65.3
16	65.4	63.3	66.3
20	66.6	63.5	66.2
24	66.1	63.8	65
28	67.1	65	66.5
32	66.8	64.8	68.7
36	67.6	64.3	68.6
40	67.1	64.9	67.3
44	67.6	65.3	67.4
48	66.8	65.8	67.5
52	68	65.7	68.4
56	68	65	67.6
60	67.9	65.7	68.9
64	67.9	65.5	69
68	68.1	65.2	68.8
72	67.4	64	68.1
76	67	64	67.6
80	66.9	64.4	68.8
84	67.7	63.8	68.7
88	68	64.7	67.9
92	67	64.6	67.9
96	67.2	64.8	68.3

FAS, LOCF (last available observed value prior to ICE was used to impute missing data; ICE were handled according to sensitivity estimand strategy for continuous endpoints). N values are number of patients with BCVA assessments at baseline.

[000878]Through Week 96, the absolute and mean change in CST from baseline were numerically similar in the three treatment arms. See Table 2-96.

Table 2-96. CST through Week 96: Similar with 8q12 and 8q16 vs 2q8

	Mean ± SD change from BL to Week 96 (LOCF)	Two-sided 95% CI
PCV Sub-group		
2q8	−207 ± 50	−195, −118
8q12	−219 ± 49	−215, −130
8q16	−232 ± 77	−190, −100
Overall Population		
2q8	−141 ± 132	−155, −126
8q12	−147 ± 128	−161, −133
8q16	−145 ± 135	−160, −131

FAS, LOCF. PCV subgroup: 2q8 n=54, 8q12 n=44, 8q16 n=41 (at baseline); overall population: 2q8 n=335, 8q12 n=333, 8q16 n=334 (at baseline).

[000879]At Week 96, 72% of patients with PCV treated with aflibercept 8q16 qualified for extended dosing interval of ≥20 weeks, suggesting extended durability of aflibercept 8 mg vs aflibercept 2 mg. In patients with PCV who completed the Week 96 visit, 77.5% in the 8q12 arm had maintained ≥12 week dosing intervals, and 77.8% in the 8q16 arm had maintained ≥16-week dosing intervals. At Week 96, in patients receiving aflibercept 8 mg, the dosing interval could be extended to ≥20 weeks and 24 weeks in 56.6% and 34.2% patients, respectively. See Table 2-97.

Table 2-97. Dosing Interval Extension in Year 2[a]:Majority of Patients with PCV Qualified (Last assigned dosing interval (PCV Subgroup))-proportion of patients (%)

Group	q8	q12	q16	q20	q24
Randomized to 8q12 at BL (n=40)[b]	18	10	30	15	28[c]

Randomized to 8q16 at BL (n=36)[b]	8	8	11	31	42[c]

[a]Dosing intervals were extended in Year 2 if patients had <5-letter loss in BCVA from Week 12 AND no fluid at the central subfield AND no new foveal hemorrhage or neovascularization.
[b]Patients completing Week 96.
[c]Patients were assigned to 24-week dosing intervals if they continued to meet extension criteria but did not have enough time to complete the interval within the 96-week study period.
Values may not add up to 100% due to rounding.

[000880]After 48 weeks of treatment, approximately half of all patients had no lesions (active or inactive) present in either treatment cohort. Through Week 96, this regression was maintained. Aflibercept 8 mg and 2 mg treatment also led to marked increases in the proportion of patients with inactive polypoidal lesions through Week 48, to 78% of patients in the All 8 mg group after a mean total of 5.6 injections, and 79% of patients in the 2q8 group after a mean total of 7.0 injections. These reductions in active polypoidal lesions were stable through Week 96. In PULSAR, compared with the aflibercept 8 mg arms, the aflibercept 2 mg arm included a disproportionately high number of patients with “questionable” polypoidal lesions that contributed toward the absent/inactive data shown for this arm. Due to the high number of cases graded as questionable in the aflibercept 2 mg arm, the regression rate seen here for this arm (68%) is much higher than that reported in the PLANET study (33%) after two years of treatment. Overall, these data indicate robust reductions in polypoidal lesions through Week 96 with aflibercept 8 mg. Once improvements were obtained by Week 48, these could be maintained with only 2 or 3 more injections in the second year of treatment with aflibercept 8

mg. The proportion of patients with "questionable" polypoidal lesions at Week 96 was 31% vs 12% for the 2q8 and All 8 mg arms

[000881]At least 49% of patients had no polypoidal lesions at week 96. See Table 2-98.

Table 2-98. Proportion (%) of Patients With or Without Polypoidal Lesions at Week 48 and Week 96#

	Week 48		Week 96	
	Any polypoidal lesion present: No	**Any polypoidal lesion present: Yes**	**Any polypoidal lesion present: No**	**Any polypoidal lesion present: Yes**
2q8	52	48	68	32
All 8 mg	51	49	49	51

Data are for patients with PCV who completed Week 96: 2q8, n=49; All 8 mg, n=76; all % calculated based on number of patients with known number of polypoidal lesions.
At Week 48, number of polypoidal lesions unknown for n=5 and n=7 patients in the 2q8 and All 8 mg groups, respectively; at Week 96, number of polypoidal lesions unknown for n=2 and n=5 patients in the 2q8 and All 8 mg groups, respectively.

[000882]At least 70% of patients maintained zero active polypoidal lesions through week 96. See Table 2-99.

Table 2-99. Proportion (%) of Patients with Inactive Polypoidal Lesions^

	Proportion of patients at Week 48 having inactive polypoidal lesions	**Proportion of patients at Week 96 having inactive polypoidal lesions**
2q8	79	90
All 8 mg	78	70

Data are for patients with PCV who completed Week 96: 2q8, n=49; All 8 mg, n=76; all % calculated based on number of patients with known number of polypoidal lesions
^Inactive polypoidal lesions defined as no polypoidal lesions present OR IRF and SRF are "absent" or "questionable"; at Week 48, number of inactive polypoidal lesions was unknown for n=2 patients in both the 2q8 and All 8 mg groups. IRF, intraretinal fluid; SRF, subretinal fluid.

[000883]Aflibercept 8 mg markedly reduced the proportion of patients with PCV with active polypoidal lesions from screening to Week 96 (97.4% vs. 30.3%). See Tables 2-100 and 2-101.

Table 2-100. Proportion of patients with number of polypoidal lesions (%)[a]

Number of polypoidal lesions	Screening	Week 48	Week 96
2q8			
0	6.122	46.939	65.306
1–3	61.224	34.694	22.449
4–6	18.367	6.122	6.122
≥7	14.286	2.041	2.041
Unknown	0.000	10.204	4.082
8q12			
0	2.500	42.500	42.500
1–3	60.000	32.500	32.500
4–6	27.500	7.500	5.000
≥7	10.000	7.500	10.000
Unknown	0.000	10.000	10.000
8q16			
0	2.778	50.000	50.000
1–3	66.667	25.000	25.000
4–6	19.444	8.333	13.889
≥7	11.111	8.333	8.333
Unknown	0.000	8.333	2.778

Data are for patients with PCV who completed Week 96. Screening (Visit 1) occurred before the baseline visit (Visit 2). a% are calculated based on number of patients at baseline (2q8, n=49; 8q12, n=40; 8q16, n=36); at Week 48, number of polypoidal lesions was unknown in 5, 4, and 3 patients in the 2q8, 8q12, and 8q16 groups, respectively, and at Week 96, number of polypoidal lesions was unknown in 2, 4, and 1 patients in the 2q8, 8q12, and 8q16 groups, respectively.

[000884]Patients across the three treatment arms exhibited comparable reductions in total polypoidal lesion area through Week 48 and Week 96.

Table 2-101. Total area of polypoidal lesions

Group	Baseline	Week 48	Week 96
2q8	0.107 (n=49)	0.045 (n=44)	0.033 (n=47)
8q12	0.134 (n=40)	0.073 (n=36)	0.054 (n=36)
8q16	0.157 (n=36)	0.068 (n=33)	0.077 (n=36)

Data are for patients with PCV who completed Week 96. Screening (Visit 1) occurred before the baseline visit (Visit 2). a% are calculated based on number of patients at baseline (2q8, n=49; 8q12, n=40; 8q16, n=36); at Week 48, number of polypoidal lesions was unknown in 5, 4, and 3 patients in the 2q8, 8q12, and 8q16 groups, respectively, and at Week 96, number of polypoidal lesions was unknown in 2, 4, and 1 patients in the 2q8, 8q12, and 8q16 groups, respectively.

[000885]The proportion of patients with active polyps was markedly reduced for aflibercept 8 mg. See Tables 2-102 and 2-103.

Table 2-102. Patients with active polypoidal lesions[a,b]

	No	Yes	Unknown
2q8 screening	6.122	93.878	0.000
8q12 screening	2.500	97.500	0.000
8q16 screening	2.778	97.222	0.000
2q8 Wk 48[c]	75.510	20.408	4.082
8q12 Wk 48[c]	80.000	20.000	0.000
8q16 Wk 48[c]	72.222	22.222	0.000
2q8 Wk 96	89.796	10.204	0.000
8q12 Wk 96	62.500	37.500	0.000
8q16 Wk 96	77.778	22.222	0.000

Data are for patients with PCV who completed Week 96. Screening (Visit 1) occurred before the baseline visit (Visit 2).
[a]% are calculated based on number of patients at baseline: 2q8, n=49; 8q12, n=40; 8q16, n=36.
[b]"No" active polypoidal lesions defined as no polypoidal lesions present OR IRF and SRF are "absent" or "questionable".
[c]At Week 48, two patients in the 2q8 group had an unknown number of polypoidal lesions.

Table 2-103. Absolute macular volume (mm^3)

	Baseline	Week 48	Week 96
2q8	8.695	7.451	7.543
8q12	8.770	7.372	7.545
8q16	8.469	7.529	7.650

[000886]The safety profile of aflibercept 8 mg and 2 mg was similar in the PCV subgroup and overall PULSAR population. Ocular TEAEs occurring in ≥5% of patients in any treatment arm in the PCV subgroup were retinal hemorrhage, conjunctival hemorrhage, reduced visual acuity, vitreous floaters, conjunctivitis, intraocular pressure increased, (worsening of) AMD, dry eye, and macular edema. Intraocular inflammation TEAEs occurring in the PCV subgroup were

chorioretinitis and eye inflammation; there were no cases of endophthalmitis or occlusive retinal vasculitis in patients with PCV. See Table 2-104.

Table 2-104. 96-Week Ocular Safety Profile of Aflibercept 8 mg: Similar to 2 mg in PCV and Overall Populations

	PCV subgroup				Overall population			
TEAE, % (study eye)	2q8	8q12	8q16	All 8 mg	2q8	8q12	8q16	All 8 mg
	n=54	n=44	n=41	n=85	n=336	n=335	n=338	n=673
Any ocular TEAE	38.9	45.5	48.8	47.1	53.9	51.0	51.5	51.3
Any intraocular inflammation TEAE	2 cases (not considered serious)[a]				2.1	1.8	0.9	1.3

Data are from the SAF. TEAEs are AEs occurring from the first injection to 30 days after the last injection (active or sham); ocular TEAEs are those occurring in the study eye.
[a]Data presented in this way to avoid unintentional patient unmasking. AE, adverse event; IOI, intraocular inflammation; TEAE, treatment-emergent adverse event; SAF, safety analysis set.

[000887]In the PCV subgroup, the proportion of patients without retinal fluid at weeks 48 and 96 was markedly larger than at baseline (Table 2-105). At week 96, 68% of patients treated with aflibercept 8 mg had no retinal fluid in the central subfield. In addition, patients across the three treatment arms in the PCV subgroup exhibited comparable reductions in total polypoidal lesion area through week 48 and week 96 (Table 2-106).

Table 2-105. Retinal Fluid through Week 96 in PCV Subgroup

	Baseline				Week 48				Week 96			
	2q8	8q12	8q16	All 8 mg	2q8	8q12	8q16	All 8 mg	2q8	8q12	8q16	All 8 mg
	n=54	n=44	n=41	n=85	n=54	n=44	n=41	n=85	n=54	n=44	n=41	n=85
proportion of patients (%) without retinal fluid	**2**	**0**	**5**	**2**	**76**	**70**	**68**	**69**	**72**	**59**	**78**	**68**

Table 2-106. Total Area of Polypoidal Lesions through Week 96 in PCV Subgroup

	Week 48				Week 96			
	2q8	8q12	8q16	All 8 mg	2q8	8q12	8q16	All 8 mg
	n=44	n=36	n=33	n=69	n=47	n=36	n=35	n=71
change in area from baseline (mm^2)	**-0.1**	**-0.1**	**-0.1**	**-0.1**	**-0.1**	**-0.1**	**-0.1**	**-0.1**

[000888]*Asian Sub-group Analysis*. Of 1009 patients treated in PULSAR, 234 patients were Asian (8q12: n=74; 8q16: n=77; 2q8: n=83; baseline BCVA (±SE): 57.7±13.9, 58.1±12.2, and 59.2±14.1 letters, respectively). At Wk 48, aflibercept 8q12 and 8q16 demonstrated comparable BCVA gains versus 2q8 in Asian patients (exploratory tests for NI at 4-letter margin; 8q12 vs 2q8: nominal p=0.0015; 8q16 vs 2q8: nominal p=0.0011), with estimated least squares (LS) mean (95%CI) differences of 2.3 (–1.8, 6.4) and 1.6 (–2.0, 5.1) letters for 8q12 vs 2q8 and 8q16 vs 2q8, respectively. LS_{mean} (±SE) change from baseline in BCVA was +9.8±1.5, +9.0±1.0, and +7.5±1.5 letters with 8q12, 8q16, and 2q8, respectively. At Wk 60, mean (95%CI) BCVA gains from baseline were 9.4 (5.8, 13.1), 8.7 (6.7, 10.7), and 8.2 (5.4, 11.0) letters, respectively, and at Wk 96 were 8.9 (5.1, 12.8), 7.2 (4.8, 9.6) and 7.5 (4.8, 10.3) letters, respectively. At Wk 96, 90% (8q12) and 84% (8q16) of Asian patients were assigned dosing intervals ≥12 and ≥16 wks, respectively; 55% of patients receiving aflibercept 8 mg had treatment intervals extended to ≥q20 and 33% to q24. Aflibercept 8 mg and 2q8 had similar safety profiles in the Asian subpopulation. In Asian patients with nAMD, similar to the overall population, aflibercept 8 mg demonstrated comparable BCVA gains at Wk 48 versus aflibercept 2 mg, which was maintained with fewer injections and no new safety signals through Wk 96.

[000889]*Baseline Analysis*. The effect of clinically relevant baseline characteristics on the efficacy of aflibercept 8 mg and 2 mg at Week 96 (W96) in patients with treatment-naïve neovascular age-related macular degeneration (nAMD) in PULSAR (NCT04423718), a double-masked, 96-week, Phase 3 trial was determined. Patients were randomly assigned 1:1:1 to receive intravitreal aflibercept 8 mg every 12 or 16 weeks (8q12, 8q16) or 2 mg every 8 weeks (2q8), each after three initial monthly injections. The effect of aflibercept on BCVA through W96 was assessed according to baseline BCVA letter score categories (≤54, 55-73, ≥74 letters), baseline central subfield retinal thickness (CRT) by quartiles (CRT ≤278 µm; 279–343 µm; 344–

420 µm; ≥423 µm), choroidal neovascularization (CNV) size and type (classic, occult and predominantly classic), and race (Asian and White), using a last observation carried forward approach. Subgroups were determined post hoc and subgroup analyses were exploratory. At W96, mean increases from baseline in BCVA were numerically larger in patients in the lower (≤54 letters) vs higher (≥74 letters) baseline BCVA categories (range: 6.5–11.7 vs 0.9–1.5 letters, respectively). Within the baseline BCVA categories, absolute BCVA letter scores at W96 were similar across the 8q12, 8q16 and 2q8 treatment groups. Similarly, mean decreases from baseline in CRT at W96 were numerically larger in patients in the higher (≥423 µm) vs lower (≤278 µm) baseline CRT quartiles, and absolute CRT values at W96 were similar across the 8q12, 8q16 and 2q8 treatment groups. Mean BCVA gains from baseline with 8q12, 8q16 and 2q8 were similar with overlapping CIs in patients across baseline CRT quartiles, CNV type

and size, and race. The proportions of patients on 8q12 and 8q16 extending dosing intervals in Year 2 will also be presented by subgroups. See Table 2-107.

Table 2-107. Mean change in BCVA letter scores and CRT according to BL BCVA and CRT

	N	Mean (95% CI) Wk 96 BCVA change from BL	Mean±SD absolute Wk 96 BCVA	Mean (95% CI) Wk 96 CRT change from BL	Mean±SD absolute Wk 96 CRT
BL BCVA: ≤54 letters					
8q12	97	+10.4 (7.0, 13.7)	52.9±17.2	–254 (–283, –224)	201±66
8q16	99	+6.5 (2.9, 10.0)	50.7±18.2	–237 (–270, –205)	220±84
2q8	105	+11.7 (8.8, 14.7)	53.0±16.9	–224 (–255, –193)	211±85
BL BCVA: 55–73 letters					
8q12	195	+4.1 (2.1, 6.1)	69.1±14.9	–109 (–121, –96)	231±65
8q16	191	+5.9 (4.4, 7.5)	70.2±11.0	–112 (–126, –97)	225±57
2q8	181	+5.9 (4.2, 7.6)	70.6±12.5	–115 (–129, –100)	230±56
BL BCVA: ≥74 letters					
8q12	42	+0.9 (–2.6, 4.3)	76.8±11.2	–76 (–101, –51)	240±59
8q16	48	+1.1 (–2.1, 4.4)	76.8±11.9	–82 (–107, –57)	238±52
2q8	49	+1.5 (–0.8, 3.9)	77.1±8.6	–58 (–75, –42)	236±41
BL CRT: ≤278 µm					
8q12	80	+3.1 (0.7, 5.4)	67.1±15.5	–49 (–58, –40)	193±37
8q16	81	+7.4 (5.3, 9.5)	72.2±11.4	–41 (–50, –33)	198±40
2q8	90	+4.8 (2.2, 7.4)	67.7±15.9	–32 (–45, –19)	207±59
BL CRT: 279–343 µm					
8q12	80	+4.2 (0.3, 8.0)	68.8±17.7	–80 (–94, –67)	228±58
8q16	91	+5.0 (2.6, 7.4)	67.3±13.5	–82 (–94, –69)	227±58
2q8	79	+6.3 (3.8, 8.8)	71.6±12.3	–79 (–91, –66)	234±55
BL CRT: 344–422 µm					
8q12	90	+5.2 (2.4, 8.1)	65.7±17.0	–143 (–157, –128)	236±70
8q16	79	+4.3 (0.9, 7.7)	65.3±17.6	–142 (–156, –128)	239±61
2q8	82	+6.9 (4.1, 9.7)	66.1±16.3	–146 (–161, –132)	230±61
BL CRT: ≥423 µm					
8q12	85	+9.3 (5.7, 12.9)	60.0±18.0	–308 (–335, –280)	234±80
8q16	85	+4.8 (1.2, 8.3)	56.8±19.7	–317 (–347, –288)	236±87
2q8	84	+10.4 (7.2, 13.6)	58.8±17.6	–310 (–335, –285)	232±80

[000890]In patients with nAMD, consistent with the full study population, comparable sustained BCVA gains and anatomic improvements were achieved at W96 with aflibercept 8 mg with extended treatment intervals compared to 2 mg every 8 weeks, in all subgroups based on baseline BCVA, CRT, CNV type and size, and race.

[000891]In the PULSAR trial, with 8q12 and 8q16 regimens, treatment intervals could be shortened (to 8 weeks minimum) in Year 1 and shortened or extended (to 24 weeks maximum) in Year 2, according to prespecified dose regimen modification criteria denoting disease activity.

This analysis describes baseline characteristics of patients according to the last assigned dosing interval at Week 96.

[000892]Patients were randomly assigned 1:1:1 to receive intravitreal aflibercept 8q12 or 8q16 or 2q8, each after three initial monthly injections. Key baseline disease characteristics (including BCVA, central retinal thickness [CRT], and total choroidal neovascularization [CNV] lesion area) were evaluated post hoc for patients in the 8q12 and 8q16 groups who completed 96 weeks of study treatment.

[000893]Overall, 583 patients randomized to 8q12 or 8q16 completed 96 weeks of study treatment. By Week 96, BCVA had increased by 5.9 letters (95%CI: 4.4, 6.5) and CRT had decreased by –150 µm (–136, –156). At Week 96, 252/291 (86.6%) patients initially assigned to 8q12 were assigned to ≥q12-week dosing and 229/292 (78.4%) patients initially assigned to 8q16 were assigned to ≥q16-week dosing. Mean±SD baseline BCVA, CRT, and CNV area, respectively, were 59.4±12.8 letters, 364±130 µm and 6.1±5.0 mm^2 in 162/583 patients assigned to q24 dosing at Week 96; 61.0±13.0 letters, 352±122 µm and 6.2±5.1 mm^2 in 141/583 patients assigned to q16 at Week 96; and 60.6±10.6 letters, 400±128 µm, and 7.1±5.9 mm^2 in 71/583 patients assigned to q8 at Week 96. See Table 2-108.

Table 2-108. Baseline Characteristics according to Last Assigned Dosing Interval at Week 96.

Baseline parameter (mean±SD)	Last assigned dosing interval at Week 96 for patients randomized to aflibercept 8 mg					
	q8 (n=71)	q12 (n=98)	q16 (n=141)	q20 (n=111)	q24 (n=162)	Total (n=583)
BCVA score (letters)	60.6±10.6	59.4±13.7	61.0±13.0	60.4±13.4	59.4±12.8	60.1±12.8
CRT (µm)	400±128	401±140	352±122	372±136	364±130[a]	373±132[b]
CNV size (mm^2)	7.1±5.9	5.8±5.7	6.2±5.1	6.6±5.0	6.1±5.0	6.3±5.3

BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; CRT, central retinal thickness.
[a]n=161;
[b]n=582.

[000894] More than 85% of patients with nAMD treated with intravitreal aflibercept 8 mg completed two years of aflibercept 8 mg treatment assigned to ≥q12 week dosing. The investigated disease characteristics at baseline were not predictive of dosing interval at Week

96. Thus, the need for dosing intervals shorter than q12 or q16 does not appear to be influenced by baseline characteristics, including lesion size, in patients with nAMD.

[000895] *Pooled Safety Analysis*. The safety of aflibercept 8 mg and 2 mg in the CANDELA, PHOTON, and PULSAR trials was compared. CANDELA was a single-masked, open-label, 44-week, phase 2 trial: treatment-naïve patients with neovascular age-related macular degeneration (nAMD) were randomized 1:1 to receive 3 monthly doses of aflibercept 8 mg or 2 mg followed by doses at Weeks 20 and 32. PHOTON was a double-masked, 96-week, non-inferiority, phase 2/3 trial: patients with diabetic macular edema were randomized 1:2:1 to receive aflibercept 2 mg every 8 weeks after 5 monthly doses or 8 mg every 12 or 16 weeks after 3 monthly doses. PULSAR was a double-masked, 96-week, non-inferiority, phase 3 trial: patients with nAMD were randomized 1:1:1 to receive aflibercept 2 mg every 8 weeks, or 8 mg every 12 or 16 weeks after 3 monthly doses. Safety data were pooled from all 3 trials up to Week 96 (CANDELA only through Week 44). Overall, 1773 patients (aflibercept 8 mg: n=1217; aflibercept 2 mg: n=556) were treated and evaluated. Ocular treatment-emergent adverse events (TEAEs) in the study eye were reported in 47.9% and 47.3% of patients who received aflibercept 8 mg and 2 mg. The most common ocular TEAEs were cataract (10.9% and 9.2%), reduced visual acuity (4.4% and 5.4%), vitreous floaters (4.0% and 4.0%), conjunctival hemorrhage (3.8% and 3.1%), and retinal hemorrhage (3.6% and 4.0%) with aflibercept 8 mg and 2 mg. Ocular hypertension was reported in 1.0% and 0.5% of patients and increased intraocular pressure (IOP) in 2.8% and 3.1% of patients with aflibercept 8 mg and 2 mg. Intraocular inflammation was reported in 1.3% and 1.6% of patients with aflibercept 8 mg and 2 mg. There were two cases of endophthalmitis, one case of ischemic optic neuropathy, and no cases of occlusive retinal vasculitis. Serious ocular TEAEs were reported in 2.3% and 1.3% of patients with aflibercept 8 mg and 2 mg. Serious ocular TEAEs occurring in >1 patient in either treatment group were cataract (8 patients), retinal detachment (7 patients), retinal hemorrhage (5 patients), increased IOP, vitreous hemorrhage (each 3 patients), and retinal tear (2 patients). Adjudicated APTC events were reported in 3.7% and 4.1% of patients with aflibercept 8 mg and 2 mg. Aflibercept 8 mg demonstrated comparable safety to 2 mg up to 96 weeks across the CANDELA, PHOTON, and PULSAR trials.

[000896] *Conclusions.* This is an ongoing Phase 3, multi-center, randomized, double-masked, active-controlled study investigating the efficacy, safety, and tolerability of IVT administration of HD aflibercept versus aflibercept 2 mg in participants with treatment-naïve nAMD. Presented herein are the results of the pre-planned Week 48 and Week 60 analyses of the data for the primary and the key secondary endpoints, and for the additional secondary efficacy, PK, and

safety endpoints. Study participants, the masked study team, central reading center, and Steering Committee members are remaining masked until the end of the masked part of the study (up to Week 96).

[000897]A total of 1011 participants recruited at 223 sites in 27 countries/regions (Europe, North America, Latin America, Australia, and Asia Pacific) were randomized in nearly equal numbers to 1 of the 3 treatment groups, of whom 1009 participants received at least one IVT injection. All of these treated participants were included in the safety analysis (SAF).

[000898]Compliance with the treatment schedule was high in all groups with a mean treatment compliance through Week 48 and through Week 60 of > 97% in all groups. The analysis of efficacy was based on the data of the FAS (n=1009), which was identical to the SAF, and the PPS (n=970 in Week 48 analysis, n=969 in Week 60 analysis), which showed group sizes of ≥ 95% in all treatment groups. The analysis of general PK assessments was based on the data of the PKS (n=934), and the analysis of the Dense PK study on the data of the DPKS (n=23).

[000899]The FAS (and SAF) consisted of 459 (45.5%) male and 550 (54.5%) female participants aged from 50 to 96 years (median: 75 years) overall. Most participants were White (75.8%) or Asian (23.2%). The mean (SD) visual acuity score BCVA at baseline was 59.6 (13.3) letters. All lesion types, *i.e.*, occult, minimally classic, and predominantly classic lesions, were represented. Overall, the 3 treatment groups were well balanced with regard to demographic and disease characteristics. Minor numerical imbalances in some comparisons were considered not to be of relevance for the evaluation of the study objectives.

[000900]The primary endpoint, change from baseline in BCVA measured by the ETDRS letter score at Week 48, and the key secondary endpoints, change from baseline in BCVA measured by the ETDRS letter score at Week 60 and proportion of participants with no IRF and no SRF in central subfield at Week 16, were assessed together using a hierarchical testing procedure as per the EP-SAP based on the FAS.

[000901]The primary analysis endpoint was met: treatment with HDq12 and HDq16 demonstrated non-inferiority to 2q8 using the margin of 4 letters, with LS_{mean} changes from baseline in BCVA from baseline to Week 48 of 6.06 letters (HDq12) and 5.89 letters (HDq16), respectively, versus 7.03 letters in the 2q8 group. Treatment differences in LS_{means} (95% CI) were -0.97 (-2.87, 0.92) letters and -1.14 (-2.97, 0.69) letters for HDq12 and HDq16, respectively, compared to 2q8. The corresponding key secondary endpoint at Week 60 was also met: treatment with HDq12 and HDq16 demonstrated non-inferiority to 2q8 using the margin of 4 letters, with LS_{mean} changes from baseline in BCVA from baseline to Week 60 of 6.37 letters (HDq12) and 6.31 letters (HDq16), respectively, versus 7.23 letters in the 2q8

group. Treatment differences in LS_{means} (95% CI) were -0.86 (-2.57, 0.84) letters and -0.92 (-2.51, 0.66) letters for HDq12 and HDq16, respectively, compared to 2q8. The robustness of these results for the primary endpoint and the corresponding key secondary endpoint was supported by supplementary analyses in the PPS as well as by sensitivity analyses in the FAS.

[000902]The non-inferiority in the mean change in BCVA at Week 48 and Week 60 were achieved in participants treated at extended intervals in the HD groups compared to the 2q8 group. Moreover, 79.4% and 77.8% of completers in the HDq12 group and 76.6% and 74.1% of completers in the HDq16 group maintained their randomized treatment interval through Week 48 and Week 60, respectively. This resulted in numerically lower mean numbers of active injections through Week 60 of 6.9 in the HDq12 group and 6.0 in the HDq16 group compared to 8.5 in the 2q8 group. Overall, 82% of participants in the pooled HD groups were able to be maintained on a dosing interval of 12 weeks or longer with HD aflibercept treatment through Week 60 and, thus, the remaining proportion of 18% of HD participants did require shortening of the dosing interval to every 8 weeks.

[000903]For the key secondary endpoint of proportion of participants with no IRF and no SRF in central subfield at Week 16, superiority in the pooled HD groups versus the comparator 2q8 was demonstrated. This analysis showed that no retinal fluid status (no IRF and no SRF) at Week 16 was reached in 63.3% of the participants in the pooled HD groups compared with 51.6% in the 2q8 group. This resulted in a difference (95% CI) between the pooled HD groups and the 2q8 group of 11.73% (5.26%, 18.20%) with an associated p-value for the one- sided test for superiority of 0.0002.

[000904]The subsequent test for superiority in the primary endpoint of HDq12 vs. 2q8 treatment was not statistically significant ($p = 0.8437$) so that the hierarchical testing strategy was stopped at this point.

[000905]Subgroup analyses for the primary and key secondary endpoints, which were performed on a descriptive level by age, sex, geographic region, ethnicity, race, baseline BCVA letters, and baseline PCV, did not show clinically meaningful differences between the subgroup population and the total population.

[000906]Descriptive analyses of the additional secondary endpoints at Week 48, change in CNV size from baseline, change in total lesion area from baseline, change from baseline in CST, and proportion of participants with no IRF and no SRF in the center subfield, provided differences across the treatment groups that were in favor of HD vs. 2q8 treatment. The exploratory descriptive analyses of the same endpoints at Week 60 suggested similar outcomes across all treatment groups through Week 60.

[000907]The estimated contrasts for change in CNV size from baseline at Week 48 suggested greater reductions of -1.22 mm^2 in the HDq12 group and of -0.48 mm^2 in the HDq16 group in comparison with 2q8 treatment. The corresponding estimated contrasts for change in total lesion area from baseline to Week 48 were -0.55 mm^2 and 0.44 mm^2, respectively. The corresponding contrasts for change from baseline in CST at Week 48 were -11.12 µm and -10.51 µm, respectively, while the mean decreases in CST over time were similar across all groups. Moreover, the proportion of participants with no IRF and no SRF in the center subfield was 11.725% higher in the HDq12 and 7.451% higher in the HDq16 groups in comparison with 2q8 treatment.

[000908]The descriptive analyses of the other additional secondary endpoints evaluated at Week 48, which were evaluated as exploratory endpoints at Week 60, proportion of participants who gained at least 15 letters in BCVA from baseline, proportion of participants achieving an ETDRS letter score of at least 69 (approximate 20/40 Snellen equivalent), and change from baseline in NEI-VFQ-25 total score, provided similar results in the HD groups and the 2q8 group at Week 48 and Week 60.

[000909]The mean number of active injections in the SAF population was 8.5, 6.9 and 6.0 in the 2q8, HDq12 and HDq16 treatment groups, respectively. For the 925 participants in the SAF considered as completers of 60 weeks of study treatment (*i.e.*, SAF completers), the mean number of active injections was 8.8, 7.1 and 6.2 in the 2q8, HDq12 and HDq16 treatment groups, respectively. The observed decrease in the mean and median number of active injections and the corresponding increase in the number of sham injections from the 2q8 group to the HDq12 and HDq16 group reflects the protocol-driven increase in treatment intervals across these groups.

[000910]The safety profile of the HD treatments was similar to that of the comparator treatment (2 mg). The overall rates of ocular and non-ocular TEAEs and SAEs reported through Week 60 were similar among the treatment groups. Most of the reported TEAEs were evaluated as mild and resolved within the observation period without permanent discontinuation of the study drug. Ocular TEAEs in the study eye that resulted in discontinuation of the study drug affected few participants: 8 (1.2%) participants in the pooled HD groups and 2 (0.6%) participants in the 2q8 group. Similarly, non-ocular TEAEs resulted in discontinuation of the study drug in 3 (0.4%) participants in the pooled HD groups and 6 (1.8%) participants in the 2q8 group.

[000911]A total of 10 deaths were reported during the study through Week 60, 5 (0.7%) in the pooled HD groups and 5 (1.5%) in the 2q8 group. None of these deaths were considered related to the study drug, to fellow-eye treatment, the injection procedure, or protocol-required

procedures and were consistent with concurrent medical conditions and the complications of these conditions associated with an older population.

[000912]No dose-response relationship in the incidence or the types of TEAEs was apparent between participants in the HD groups and the 2q8 group. The results of the subgroup analyses of the TEAEs were similar to those in the entire study population and did not suggest medically relevant differences across the treatment groups.

[000913]The analyses of laboratory data, vital signs, and ECG data (including QT interval) did not show any remarkable mean changes over time within the HD groups and the 2q8 group or differences between the groups.

[000914]No clinically meaningful trends in mean or median changes from baseline to pre-dose IOP in the study eye were observed in any treatment group through Week 60. The proportion of participants meeting pre-defined IOP criteria was generally low and similar across the treatment groups. Other technical ophthalmologic examinations (slit lamp) did also not point to any noticeable trends towards differences among the treatment groups or relevant changes within treatment groups from baseline through Week 60.

[000915]After the initial aflibercept dose of 2 mg (2q8) or 8 mg (HDq12 pooled with HDq16) aflibercept in the dense PK group, the concentration-time profiles of free aflibercept were characterized by an initial phase of increasing concentrations reflecting initial absorption from the ocular space and initial distribution into the systemic circulation from the ocular space into systemic circulation followed by a mono-exponential elimination phase. The concentration-time profiles of adjusted bound aflibercept were characterized by a slower attainment of C_{max} compared to free aflibercept. Following attainment of C_{max}, a slight decrease of the concentration-time profile was observed until approximately the end of the dosing interval (Day 29).

[000916]As the IVT dose of aflibercept increased from 2 mg to 8 mg (4-fold dose), the median C_{max} and AUC_{last} for free aflibercept increased in a slightly less than dose-proportional manner (about 3-fold) for C_{max} and a greater than dose-proportional manner for AUC_{last} (about 7-fold). This larger increase in AUC_{last} is unexpected and difficult to explain based on dose alone but it is consistent with known nonlinear target-mediated kinetics of aflibercept. Mean C_{max} and AUC_{last} for adjusted bound aflibercept increased in a less than dose-proportional manner (approximately 2- to 2.5-fold) which is also consistent with the known nonlinear kinetics of aflibercept.

[000917]There was no accumulation seen after the 2 mg dose which is consistent with historical data. Accumulation of free aflibercept for the 8-mg treatments was 1.17. For adjusted

bound aflibercept, accumulation ranged from 1.83 to 1.72 for the 2 mg and 8 mg treatments, respectively.

[000918]In general, PK in Japanese participants were in the same range as seen in non-Japanese participants. However, this should be interpreted with caution as concentrations and PK parameter were based on single participants.

[000919]In the general (sparse) PK assessment of mainly trough concentrations (except Visit 5 which was 4-8 days after the third administration), IVT administration of mean free aflibercept concentrations increased from baseline to Visit 5 (60-64 days after first administration).

[000920]Thereafter, mean concentrations of free aflibercept declined in all 3 dose groups. In the 2q8 treatment group mean concentrations of free aflibercept decline to values close to or below LLOQ in almost all participants 4 weeks after treatment, in the HD groups 8 weeks after treatment (Week 28 for HDq12, Week 48 for HDq16). Comparison of mean concentrations of free aflibercept at Visit 5 showed that concentrations increased about 6-fold as the IVT dose of aflibercept increased from 2 mg to 8 mg (4-fold dose).

[000921]Mean adjusted bound aflibercept concentrations increased from baseline to Visit 5. Following attainment of C_{max}, a slight decrease of the concentration-time profiles was observed until approximately the end of the observation period for both dose groups. Comparison of mean concentrations of adjusted bound aflibercept at Visit 5 showed that concentrations increased close to dose-proportional (3-fold) as the IVT dose of aflibercept increased from 2 mg to 8 mg (4-fold dose).

[000922]Immunogenicity was low across all treatment groups. Out of the 833 participants included in the ADA analysis set, the incidence of treatment-emergent ADA during the 48-week of treatment with aflibercept administered IVT in the 2q8, HDq12, and HDq16 treatment groups was 4/273 (1.5%), 11/283 (3.9%), and 9/277 (3.2%), respectively; all of these responses were of low maximum titer. None of the ADA-positive samples were found to be positive in the NAb assay. The immunogenicity observed in this study was consistent with that historically observed at the 2 mg dose suggesting no increase in immunogenicity at this higher dose.

[000923]*Overall conclusions.*

- Treatment with HD aflibercept at intervals of 12 or 16 weeks provided non-inferior increases in BCVA from baseline at Week 48 and at Week 60 compared to treatment with aflibercept 2 mg every 8 weeks.
- Treatment with HD aflibercept was superior to treatment with aflibercept 2 mg in that 11.7% more participants in the pooled HD groups than in the 2q8 group had no IRF and no SRF in central subfield at Week 16.

- The non-inferior visual acuity outcomes in the HDq12 and HDq16 groups compared to 2q8 were achieved with the majority of participants remaining on their randomized treatment interval through Week 48 (79% and 77%, respectively) and through Week 60 (78% and 74%, respectively). Based on the dosing schedule, the Week 60 time point represents four 12-week intervals for the HDq12 group and three 16-week intervals for the HDq16 group following the 3 initial monthly doses. This led to a clinically meaningful reduction in the number of injections over 60 weeks compared to treatment with aflibercept 2 mg every 8 weeks.
- Overall, 82% of participants in the pooled HD groups were able to be maintained on a dosing interval of 12 weeks or longer with HD aflibercept treatment through Week 60, while 18% of participants did require shortening of the dosing interval to q8.
- Overall, the efficacy results obtained at Week 60 were consistent with those from Week 48.
- Immunogenicity was low across all treatment groups. None of the ADA-positive samples were found to be positive in the NAb assay.
- Review of the safety data did not reveal any new safety signals or adverse trends in the HD aflibercept groups compared to the 2 mg group. The ocular and systemic safety profile of aflibercept HD was consistent with the established safety profile of aflibercept 2 mg.

Case Report (1)

[000924]This is a case report for a patient in the PULSAR trial with nAMD for whom treatment intervals were increased over the course of the trial. The patient's characteristic are summarized in Figure 74(A). Absolute BCVA and absolute CRT achieved by the patient up to week 96 (end of study) are summarized below in Figure 74(A). The patient was assigned to a q16w maintenance interval and later assigned to increasing intervals of q20w and q24w. Where this patient is situated with respect to the assigned intervals of the overall trial's patients is shown in Figure 74(B). At week 100, the patient's BCVA was 74 letters and the patient's CRT was 235 micrometers. These data demonstrated that after a 24 week interval between 8 mg doses of aflibercept, from week 76 to 100, the patient maintained BCVA and CRT. See Table 2-109.

Table 2-109. Retinal Thickness and Visual Acuity for Case Report 1 Patient Starting at Week 96

Measurement	Value	Timepoint
Thickness Sector C Retinal Thickness	233	VISIT 27 (EOS or ED Week 96)
Thickness Sector C Retinal Thickness	235	VISIT E02 (WEEK 100)
Thickness Sector C Retinal Thickness	232	VISIT E03 (WEEK 104)
Thickness Sector C Retinal Thickness	225	VISIT E04 (WEEK 108)
Thickness Sector C Retinal Thickness	234	VISIT E05 (WEEK 120)
Thickness Sector C Retinal Thickness	232	VISIT E05 (WEEK 124)
Thickness Sector C Retinal Thickness	237	VISIT E06 (WEEK 132)
Visual Acuity Final Score	74	VISIT 27 (EOS or ED Week 96)
Visual Acuity Final Score	74	VISIT E02 (WEEK 100)
Visual Acuity Final Score	73	VISIT E03 (WEEK 104)
Visual Acuity Final Score	75	VISIT E04 (WEEK 108)
Visual Acuity Final Score	64	VISIT E05 (WEEK 120)
Visual Acuity Final Score	58	VISIT E05 (WEEK 124)
Visual Acuity Final Score	58	VISIT E06 (WEEK 132)

Case Report (2)

[000925]This is a case report for a patient in the PULSAR trial with nAMD for whom treatment intervals were shortened over the course of the trial. The patient's characteristic are summarized in Figure 75(A). Absolute BCVA and absolute CRT achieved by the patient up to week 96 (end of study) are summarized below in Figure 75(A). The patient was assigned to a q16w maintenance interval and later assigned to shortened intervals of q12w. The interval assigned was later increased back to q16w. Where this patient is situated with respect to the assigned intervals of the overall trial's patients is shown in Figure 75(B). At week 100, the patient's BCVA was 79 letters and the patient's CRT was 332 micrometers. See Table 2-110. The patient did not extend the interval to 24 weeks.

Table 2-110. Retinal Thickness and Visual Acuity for Case Report 2 Patient Starting at Week 96

Measurement	Value	Timepoint
Thickness Sector C Retinal Thickness	285	VISIT 27 (EOS or ED Week 96)

Thickness Sector C Retinal Thickness	285	VISIT E01 (WEEK 96)
Thickness Sector C Retinal Thickness	332	VISIT E02 (WEEK 100)
Thickness Sector C Retinal Thickness	284	VISIT E03 (WEEK 104)
Thickness Sector C Retinal Thickness	281	VISIT E04 (WEEK 108)
Thickness Sector C Retinal Thickness	439	VISIT E04 (WEEK 116)
Thickness Sector C Retinal Thickness	321	VISIT E05 (WEEK 120)
Visual Acuity Final Score	80	VISIT 27 (EOS or ED Week 96)
Visual Acuity Final Score	79	VISIT E02 (WEEK 100)
Visual Acuity Final Score	79	VISIT E03 (WEEK 104)
Visual Acuity Final Score	78	VISIT E04 (WEEK 108)
Visual Acuity Final Score	78	VISIT E04 (WEEK 116)
Visual Acuity Final Score	76	VISIT E05 (WEEK 120)

Example 3: Population Pharmacokinetic Modeling and Simulation

[000926]The objectives of this analysis were to update the previously developed population PK model for free and adjusted bound aflibercept concentrations in plasma to include additional concentration data from year 1 of the pivotal PULSAR (86-5321-20968) and PHOTON (VGFTe (HD)-DME-1934) studies that were not available at the time of the prior analysis; and re-estimate metrics of aflibercept exposure in plasma and the eye in nAMD and DME participants using this updated population PK dataset.

[000927](see WO2023/177691 and WO2023/177689).

Background (Prior Population PK Analysis)

[000928]A population PK model of free and adjusted bound aflibercept in plasma was previously developed. This model was based on a dataset of the available concentration data at the time of database lock for the week 48 analysis of the PULSAR (86-5321-20968) and PHOTON (VGFTe (HD) DME-1934) and Phase 2 CANDELA studies. Briefly, this model was a

semi-mechanistic model describing the disposition of free aflibercept using a 3-compartment model with a nonlinear binding to VEGF, a linear clearance and an additional nonlinear clearance pathway hypothesized to represent the saturable uptake of aflibercept by circulating platelets. Elimination of the adjusted bound aflibercept (as a reflection of the elimination of the aflibercept:VEGF complex) was described by a linear clearance. After IVT injection, the transfer of free aflibercept from the study eye and, if treated, fellow eye to the systemic circulation was described by a linear clearance (QE) and was considered reversible. QE was estimated to be 34.4% slower after IVT injection of HD aflibercept than after that of 2 mg aflibercept, which was attributable to a HD drug product effect, and not just an increase in dose. QE was also found to decrease with increasing age. Parameters for bioavailability after IVT dosing (F_{IVT}) were utilized, to quantify the apparent loss of aflibercept prior to its transfer to the systemic circulation. If not otherwise specified, any reference to an 8 mg aflibercept dose implies the use of the HD formulation. If not otherwise specified, any reference to an 8 mg aflibercept dose implies the use of the HD formulation (see Highlights of Prescribing Information for Eylea HD (revised August 2023)).

Data Description

[000929]The key data for the current analysis were obtained in 3 clinical trials testing the safety and efficacy of IVT injections of HD aflibercept: the 1-year phase 2 CANDELA study in nAMD patients, the multi-year phase 3 PULSAR study in nAMD patients, and the multi-year phase 2/3 PHOTON study in patients with DME and DR. For the current analysis, the prior population PK dataset was updated with a small number of data points from the PULSAR and PHOTON studies following database lock at week 96. These data points were collected during the first year of study but were not available at the time of database lock for the week 48 analysis. The dataset utilized in the current analysis included data from 16 clinical studies: 8 studies in patients with nAMD (VGFT-OD-0305, VGFT-OD-0306, VGFT-OD-0502 [VGFT-OD-502 part A and VGFT-OD-0502 part C], VGFT-OD-0603, VGFT-OD-0702.PK, 311523, CANDELA [VGFTe (HD)-AMD-1905], and PULSAR [86-5321-20968]), 5 studies in patients with DME (VGFT-OD-0307, VGFT-OD-0512, VGFT-OD-0706.PK, 91745, and PHOTON [VGFTe (HD)-DME-1934]), 2 studies in healthy male subjects (PDY6655 and PDY6656), and 1 study in patients with solid tumors or lymphoma (TED6113). The current dataset included 31,326 samples records from 2,744 unique participants (76 healthy participants, 38 oncology participants, 1,662 nAMD participants, and 968 DME participants). Compared to the previous analysis dataset, the

revised data included 1 more participant (+0.04%), 172 more samples records (+0.55%), and 186 new dosing records, and changes in the time of 86 dosing records.

Methodology

[000930]The previously developed population PK model was re-estimated using the current analysis dataset, without any changes to its structural or statistical components. Because the prior model was developed sequentially and parameter estimates were fixed at various stages of analysis, only the parameters that were estimated in the final stage of the prior analysis were re-estimated in the analysis reported herein. Specifically, all fixed and random effect parameters related to aflibercept PK in the eye were re-estimated. The resulting model was evaluated using VPC, NPDE, and bootstrap procedures. A sensitivity analysis was conducted to evaluate the statistical significance of the HD effect on QE in the final model and assess the impact of shrinkage in QE on this conclusion. For this purpose, alternatives to the final population PK model were estimated, including models in which the HD drug product effect on QE and/or the IIV on QE were removed. The final PK model was then used to perform various simulation-based assessments. Free and adjusted bound aflibercept exposure metrics were predicted using the *post hoc* estimates of final population PK model parameters to assess the effects of the following intrinsic and extrinsic factor covariates in participants from the CANDELA, PULSAR, and PHOTON studies: age, body weight, albumin concentration, renal function, hepatic function, racial classification, Japanese origin, disease population (nAMD versus DME), and manufacturing process of the HD drug product effect. Exposures after 3 monthly IVT injections of aflibercept or at steady state were predicted for 3 dosing regimens: 2q8 (2 mg aflibercept Q8W in the study eye after 5 initial monthly doses), HDq12 (HD aflibercept Q12W in the study eye after 3 initial monthly doses), and HDq16 (HD aflibercept Q16W in the study eye after 3 initial monthly doses). *Post hoc*-based simulations for the nAMD participants from the CANDELA and PULSAR studies and the DME participants from the PHOTON study were performed to predict metrics of exposures describing the maximum free and adjusted bound aflibercept accumulation in plasma achieved during a typical loading period consisting of 3 monthly IVT injections. Additional post-hoc-based simulations were conducted to compare predicted aflibercept systemic exposures after various unilateral and bilateral IVT administration scenarios. Stochastic simulations were performed in a large virtual population of 5,000 nAMD and 5,000 DME participants to predict the concentrations of aflibercept in the eye as well as aflibercept systemic exposure metrics, accumulation, and time to steady state under various unilateral IVT administration scenarios.

[000931]The semi-mechanistic PK model for aflibercept was characterized by the following system of ordinary differential equations:

$$\begin{aligned}
\frac{dA_1}{dt} &= \frac{Q_E}{V_2} \times A_2 - \frac{Q_E}{V_{eye}} \times A_1 \\
\frac{dA_2}{dt} &= \frac{Q_E}{V_{eye}} \times (A_1 + A_5) + \frac{Q_{F1}}{V_3} \times A_3 + K_{62} \times A_6 + \frac{Q_{F2}}{V_8} \times A_8 \ldots \\
&\quad - \left(\frac{2 \times Q_E + Q_{F1} + Q_{F2}}{V_2} + K_{20} \right) \times A_2 - V_{max} \times V_2 \times \frac{A_2 \times V_2}{K_m + A_2 \times V_2} \ldots \\
&\quad - V_{max,p} \times V_2 \times \left(1 - \frac{A_7}{K_{m,p} + A_7} \right) \times A_2 \\
\frac{dA_3}{dt} &= \frac{Q_{F1}}{V_2} \times A_2 - \frac{Q_{F1}}{V_3} \times A_3 \\
\frac{dA_4}{dt} &= V_{max} \times V_2 \times \frac{A_2 \times V_2}{K_m + A_2 \times V_2} - K_{40} \times A_4 \\
\frac{dA_5}{dt} &= \frac{Q_E}{V_2} \times A_2 - \frac{Q_E}{V_{eye}} \times A_5 \\
\frac{dA_6}{dt} &= -K_{62} \times A_6 \\
\frac{dA_7}{dt} &= V_{max,p} \times V_2 \times \left(1 - \frac{A_7}{K_{m,p} + A_7} \right) \times A_2 - K_{70} \times A_7 \\
\frac{dA_8}{dt} &= \frac{Q_{F2}}{V_2} \times A_2 - \frac{Q_{F2}}{V_8} \times A_8
\end{aligned}$$

where A1 and A5 are the amounts of aflibercept in the study and fellow eyes, A2, A3, and A8 are the amounts of free aflibercept in the central compartment, first and second peripheral compartments, A4 is the amount of adjusted bound aflibercept in the central compartment, A6 is the amount of aflibercept in the SC depot compartment, A7 is the amount of free aflibercept in the platelet compartment, K20 is the elimination rate constant of free aflibercept from the central compartment, K40 is the elimination rate constant of adjusted bound aflibercept from the central compartment, K62 is the absorption rate constant of free aflibercept from the SC depot compartment, K70 is the elimination rate constant of free aflibercept from the platelet compartment, Km is concentration of free aflibercept at half of maximum binding capacity with

VEGF, Km,p is the concentration of free aflibercept at half of maximum binding capacity to platelets, QE is the ocular distribution clearance, QF1 and QF2 are the first and second distribution clearances for free aflibercept, V1 and V5 are the volumes of the study and fellow eyes (fixed to 4 mL), V2 is the volume of the central compartment for free aflibercept, V3 and V8 are the volumes of the first and second peripheral compartments for free aflibercept, V4 is the volume of the central compartment for adjusted bound aflibercept (assumed to be equal to V2), Vmax is the maximum binding rate of free aflibercept to VEGF, and Vmax,p is the maximum binding rate of aflibercept to platelets.

Results

[000932]Parameter estimates of the final PK model are presented in Table 3-1. Overall, the marginal changes between the prior and updated datasets had minimal influence on the estimates of the population PK model, which changed by ≤ 2.1% compared to the previous analysis and remained precisely estimated. In final PK model, QE was estimated to be 34.4% slower after IVT injection of HD aflibercept than after that of 2 mg aflibercept.

Table 3-1. Parameter Estimates of the Final Pharmacokinetic Model for Aflibercept

	Parameter	Estimate	95% CI	RSE (%)	Magnitude of Variability (%)	Shrinkage (%)
Fixed effects for free aflibercept	F_{IVT}: Bioavailability after IVT injection[a]	0.718	0.707, 0.733	1.03%	-	-
	Q_E: Ocular distribution clearance (mL/day)[b]	0.625	0.572, 0.679	4.27%	-	-
	Proportional effect of HD aflibercept on Q_E[c]	0.656	0.608, 0.717	4.52%	-	-
	Power of age effect on Q_E[c]	-1.54	-1.81, -1.27	10.3%	-	-
	V_1 & V_E: Volume of study and fellow eye (mL)	4.00	Fixed	Fixed	-	-
	K_{20}: Elimination rate constant (1/day)[b]	0.0807	0.0400, 0.126	29.5%	-	-
	Power of body weight effect on K_{20}[b]	-0.192	-1.45, 0.714	234%	-	-
	V_2: Volume of the central compartment (L)[b]	4.99	4.69, 5.22	2.79%	-	-
	Power of body weight effect on V_2[b]	0.872	0.590, 1.22	19.3%	-	-
	V_3: Volume of the first peripheral compartment (L)[b]	1.68	0.792, 1.56	17.0%	-	-
	Power effect of body weight on V_3[b]	1.68	0.257, 2.71	51.3%	-	-
	V_4: Volume of the second peripheral compartment (L)[b]	1.18	0.769, 2.07	39.8%	-	-
	Power effect of body weight on V_4[b]	1.16	-0.962, 7.40	135%	-	-
	Q_{23}: First distribution clearance (L/day)[b]	0.849	0.425, 1.26	39.2%	-	-
	Q_{24}: Second distribution clearance (L/day)[b]	0.0763	0.0442, 0.110	23.7%	-	-
	$V_{max,P}$: Maximum binding rate to platelets (mg/day/L)[b]	0.0310	0.0148, 0.0649	35.3%	-	-
	$K_{ss,P}$: Amount of free aflibercept at half $V_{max,P}$ (mg)[b]	42.7	2.16, 214	159%	-	-
	K_{PC}: Elimination rate constant from platelet (1/day)[b]	0.0265	0.00762, 0.105	99.0%	-	-
	F_{SC}: Bioavailability after SC injection[b]	0.536	0.487, 0.601	5.26%	-	-
	K_{SC}: Rate of absorption after SC injection (1/day)[b]	0.368	0.296, 0.430	10.5%	-	-
Fixed effects for adjusted bound	V_1: Volume of the central compartment (L)[b, c]	4.99	4.69, 5.22	2.70%	-	-
	Power of body weight effect on V_1[b,c]	0.872	0.590, 1.22	19.3%	-	-
	V_{max}: Maximum binding rate to VEGF (mg/day/L)[b]	0.167	0.150, 0.187	5.93%	-	-
	K_{ss}: Concentration of free aflibercept at half V_{max} (mg/L)[b]	0.411	0.272, 0.510	16.8%	-	-
	K_{20}: Elimination rate constant (1/day)[d]	0.0350	0.0339, 0.0364	1.87%	-	-
	Power of body weight effect on K_{20}[d]	-0.153	-0.251, -0.0768	27.8%	-	-
	Power of serum albumin effect on K_{20}[d]	-0.767	-0.989, -0.599	14.0%	-	-

Inter-individual variability	ω^2 in Q_D[b]	0.297	0.231, 0.362	11.0%	58.8%	31.5%
	ω^2 in K_{SC}[a,b]	0.207	0.0917, 0.622	54.1%	48.0%	54.2%
	Covariance (ω^2 in K_{SC}, ω^2 in V_2 & V_3)[b]	-0.0727	-0.144, -0.0239	38.9%	-	-
	ω^2 in V_2 and V_3[b]	0.0618	0.0251, 0.106	34.7%	25.3%	15.2%
	ω^2 in V_{max}[b]	0.305	0.0723, 0.760	65.4%	59.8%	42.0%
	ω^2 in F_{SC}[b]	0.628	0.278, 0.910	26.4%	29.2%	17.7%
	ω^2 in K_M[b]	0.852	0.261, 1.46	43.0%	11.6%	1e-10%
	ω^2 in K_{el}[c]	0.0452	0.0372, 0.0555	9.42%	21.5%	39.0%
Residual variability for free aflibercept	$\sigma_{relative}$ after IV + SC dosing when LLOQ is 0.0313 mg/L[d]	0.0250	0.00486, 0.0342	52.0%	40.3, 89.5%	-
	$\sigma_{proportional}$ after IV + SC dosing when LLOQ is 0.0313 mg/L[d]	0.463	0.364, 0.461	5.07%		-
	$\sigma_{relative}$ after IV + SC dosing when LLOQ is 0.0156 mg/L[d]	0.00788	0.00591, 0.00913	11.8%	35.7, 61.8%	-
	$\sigma_{proportional}$ after IV + SC dosing when LLOQ is 0.0156 mg/L[d]	0.357	0.324, 0.384	4.18%		-
	$\sigma_{relative}$ after IVT dosing when LLOQ is 0.0156 mg/L[d]	0.00777	0.00582, 0.00931	11.5%	43.2, 65.9%	-
	$\sigma_{proportional}$ after IVT dosing when LLOQ is 0.0156 mg/L[d]	0.432	0.400, 0.464	3.21%		-
Residual variability for adjusted bound	$\sigma_{relative}$ after IV + SC dosing when LLOQ is 0.0313 mg/L[d]	0.0206	0.0162, 0.0241	10.9%	16.7, 67.5%	-
	$\sigma_{proportional}$ after IV + SC dosing when LLOQ is 0.0313 mg/L[d]	0.167	0.152, 0.186	5.07%		-
	$\sigma_{relative}$ after IVT dosing when LLOQ is 0.0313 mg/L[d]	0.0216	0.0162, 0.0258	12.4%	16.1, 70.4%	-
	$\sigma_{proportional}$ after IVT dosing when LLOQ is 0.0313 mg/L[d]	0.159	0.120, 0.204	12.3%		-
	$\sigma_{relative}$ after IVT dosing when LLOQ is 0.0224 mg/L[d]	0.0285	0.0141, 0.0378	28.7%	21.5, 129%	-
	$\sigma_{proportional}$ after IVT dosing when LLOQ is 0.0224 mg/L[d]	0.215	0.195, 0.244	5.56%		-

a estimates obtained from run811
b estimates obtained from run431
c set to the same values as V2-related estimates
d estimates obtained from run463
σ = Standard deviation; ω2 = Variance; CI = Confidence intervals; HD = High dose (8 mg intravitreal cohorts); IV =
Intravenous; IVT = Intravitreal; LLOQ = Lower limit of quantitation; RSE = Relative standard error; SC = Subcutaneous;
VEGF = Vascular endothelial growth factor
Note: Estimates of fixed-effect parameters are presented in the natural scale; interindividual variability terms are reported as variances around the log of the parameters or the logit of FSC. Magnitudes of residual variability are provided as ranges calculated at the maximum observed concentration of either free aflibercept or adjusted bound aflibercept and their respective LLOQ values based on route of administration. RSE are presented in the logit scale for F_{IVT} and FSC and in the natural scale for all other parameters.

The typical values of the model parameters can be calculated as follows:

$$Q_2 = 0.625 \times 0.656^{HD} \times \left(\frac{age}{71}\right)^{-1.54} \qquad V_2 = V_4 = 4.99 \times \left(\frac{weight}{76}\right)^{0.872}$$

$$V_3 = 1.08 \times \left(\frac{weight}{76}\right)^{1.08} \qquad V_8 = 1.18 \times \left(\frac{weight}{76}\right)^{1.16}$$

$$K_{20} = 0.0807 \times \left(\frac{weight}{76}\right)^{-1.92} \qquad K_{40} = 0.035 \times \left(\frac{weight}{76}\right)^{-0.163} \times \left(\frac{ALB}{4.3}\right)^{-0.767}$$

[000933]The sensitivity analysis showed that the magnitude of the effect of HD drug product on QE (34.4% in the final PK model) and the statistical significance of this effect were not influenced by the variance and shrinkage on QE. In the final population PK model, the magnitude of shrinkage in QE was 24.4% in the subset of participants who received HD aflibercept and 31.5% in the overall data, just above the level of no concern and substantially below the threshold categorized as medium shrinkage level (45-65%).

[000934]The effects of age, body weight, albumin concentration, renal function, hepatic function, racial group, Japanese origin, and disease population on free and adjusted aflibercept exposures were evaluated for 3 prototypical dosing regimens (2q8, HDq12, and HDq16) in the 1,687 participants from the CANDELA, PULSAR, and PHOTON studies based on the final population PK model and individual *post hoc* PK parameter estimates. The results for the covariates evaluated are shown for a prototypical HDq12 regimen in Figure 77; results for the other 2 prototypical dosing regimens were similar to those for the HDq12 regimen. Overall, age, serum albumin, and hepatic function were predicted to have limited impact on aflibercept PK in plasma. Body weight was the predictor of aflibercept PK variability associated with the largest impact among the participants to the CANDELA, PHOTON, and PULSAR studies. However, the magnitude of change in the geometric mean of any exposure metric in plasma did not deviate by more than 38% across the different body weight groups defined by quintile compared to the reference quintile group (73.5 to 83.5 kg). Results of the analysis suggested that, after accounting for differences in body weight, there were no relevant differences in the PK of free or adjusted bound aflibercept related to renal impairment, Asian versus non-Asian, Japanese versus non-Japanese, or nAMD versus DME populations. The marginal effect of the manufacturing process of HD aflibercept in 1,163 participants who received it in the CANDELA, PULSAR, and PHOTON studies is illustrated in Figure 79.

[000935]The predictions of free and adjusted aflibercept exposure in plasma under various dosing regimens repeated in this analysis were generally consistent with the results of the

previous analysis. In particular, the metrics used for determination of the non-clinical multiple of exposures remained unchanged with mean (SD) values of AUCweek8- 12 and Cmax,week8-12 after 3 monthly IVT injections of 2.03 (0.998) mg×day/L and 0.154 (0.0882) mg/L (based upon predictions from *post hoc* PK estimates). The stochastic simulations also confirmed the lack of accumulation of free aflibercept in plasma at steady state following unilateral HDq12 or HDq16 dosing, and only small accumulation of adjusted bound aflibercept in plasma at steady state following unilateral HDq12 (1.16) or HDq16 dosing (1.06).

[000936]The 34.4% slower release of aflibercept from the eye after injection of HD drug product led to a more-than-dose proportional increase in exposures of free aflibercept in the eye compared to those predicted after 2 mg aflibercept injection. Figure 78 overlays the median and 90% PI of model-predicted concentrations of free aflibercept in the study eye after 2q8 or HDq12 dosing up to week 56 and different reference concentrations, including the concentration reached in the eye 8 weeks after 2 mg IVT injection, the LLOQ for measurement of free aflibercept in plasma, and 1×, 9×, and 99× the free aflibercept *in vitro* binding constant for VEGF-A (K_D =0.497 pM) assumed to represent 50%, 90%, and 99% of ocular VEGF inhibition in an in vitro setting, respectively. Median model-estimated concentrations of free aflibercept in the eye 8 weeks after 2 mg aflibercept injection are predicted to be reached approximately 14 weeks after HD injection (Table 3-2). The final population PK model predicted that, 12 weeks after the last IVT injection at week 56, the percentage of DME or nAMD patients achieving concentrations in the eye > 9 × K_D was 79.7% for HD aflibercept versus 49.2% for 2 mg aflibercept (Table 3-3). By week 16 after the last injection, these percentages decreased to 63.6% and 30.5%, respectively. This indicated that HD aflibercept is expected to provide extended VEGF inhibition in the eye compared to 2 mg aflibercept.

Table 3-2. Median and 90% Prediction Interval of Model-Predicted Time to Reach Discrete Reference Concentrations in the Eye Following the Week 56 Intravitreal Injection in 5,000 Virtual Participants With Neovascular Age-Related Macular Degeneration and 5,000 Virtual Participants with Diabetic Macular Edema, Stratified by Repeated Dosing Regimen

Regimen	Time Above 1 × K_D (week)	Time Above 9 × K_D (week)	Time Above 99 × K_D (week)	Time Above Plasma LLOQ (week)	Time Above Week 64 Concentration for 2 mg IVT (week)
2 mg Q8W	14.0 (7.07, 37.1)	11.9 (4.79, 32.0)	9.79 (3.64, 26.5)	8.93 (3.29, 24.1)	8.00 (2.93, 21.7)
8 mg Q12W	22.8 (11.4, 61.4)	19.9 (8.14, 53.7)	16.7 (6.21, 45.2)	15.4 (5.64, 41.6)	14.0 (5.14, 38.0)

IVT = Intravitreal; K_D = Dissociation constant; LLOQ = Lower limit of quantitation; QxW = Every x weeks; VEGF-A = Vascular endothelial growth factor A

Note: 1×, 9×, and 99× K_D represent the free aflibercept concentrations required to inhibit VEGF-A by 50%, 90%, or 99% in an *in vitro* setting.

Table 3-3. Proportion of Participants with Model-predicted Concentrations in the Eye Above Discrete Reference Concentrations at Various Time Following the Week 56 Intravitreal Injection in 5,000 Virtual Participants With Neovascular Age-Related Macular Degeneration and 5,000 Virtual Participants With Diabetic Macular Edema, Stratified by Repeated Dosing Regimen

Reference	IVT dose	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88
Time since last dose (weeks)		0	4	8	12	16	20	24	26	32
Above 1 × K_D	2 mg Q8W	100 %	99.8 %	90.1 %	61.4 %	40.6 %	26.5 %	17.5 %	11.6 %	7.96 %
	8 mg Q12W	100 %	100 %	99.6 %	92.6 %	74.2 %	58.6 %	46.4 %	36.7 %	28.3 %
Above 9 × K_D	2 mg Q8W	100 %	97.5 %	74.3 %	49.2 %	30.5 %	19.0 %	11.8 %	7.57 %	5.00 %
	8 mg Q12W	100 %	99.9 %	95.2 %	79.7 %	63.6 %	49.5 %	37.8 %	28.2 %	21.2 %
Above 99 × K_D	2 mg Q8W	100 %	92.9 %	62.6 %	36.9 %	20.6 %	11.5 %	6.80 %	4.01 %	2.51 %
	8 mg Q12W	100 %	99.1 %	88.7 %	70.1 %	52.6 %	38.4 %	27.2 %	19.5 %	13.9 %
Above plasma LLOQ	2 mg Q8W	100 %	90.6 %	56.8 %	30.8 %	16.3 %	8.85 %	5.08 %	2.88 %	1.55 %
	8 mg Q12W	100 %	98.6 %	85.4 %	65.3 %	47.4 %	33.0 %	22.8 %	15.8 %	11.1 %
Above concentration at Week 64 for 2 mg IVT	2 mg Q8W	100 %	86.9 %	50.0 %	24.9 %	12.4 %	6.53 %	3.43 %	1.81 %	0.860 %
	8 mg Q12W	100 %	98.0 %	81.6 %	59.7 %	41.4 %	27.5 %	18.4 %	12.4 %	8.44 %

IVT = Intravitreal; K_D = Dissociation constant; LLOQ = Lower limit of quantitation; QxW = Every x weeks; VEGF-A = Vascular endothelial growth factor-A

Note: 1×, 9×, and 99× K_D represent the free aflibercept concentrations required to inhibit VEGF-A by 50%, 90%, or 99% in an *in vitro* setting.

Conclusions

[000937]The refinement of the population model for aflibercept PK and the subsequent model-based predictions of aflibercept exposures in plasma and in the eye were generally consistent with the previous results. Body weight was the predictor of aflibercept PK variability associated with the largest impact on free and adjusted bound exposures in plasma, with up to 38% higher and up to 31% lower exposures in the lowest (38.1 - 64.5 kg) and the highest (97.5 - 167 kg) quintile of body weight respectively, compared to the reference quintile (73.5 – 83.5 kg). The body weight differences across renal insufficiency categories and ethnic groups also accounted for exposure differences across those categories. There were no relevant differences found in the exposure metrics of aflibercept between age categories, albumin categories, hepatic function categories.

[000938]QE decreased following the administration of HD versus 2 mg aflibercept and also with increasing age. After IVT injection of HD aflibercept, QE was 34.4% slower than that for 2 mg aflibercept, resulting in a 1.52-times longer half-life of elimination. The slower ocular clearance for HD aflibercept is due to a HD drug product effect, and not just an increase in dose. These results were further confirmed by a sensitivity analysis conducted in the population PK analysis.

[000939]After accounting for an age effect on QE, no significant difference in the model-predicted exposures in plasma was found between nAMD and DME populations.

[000940]At steady state, the model predicted that 79.7% of patients receiving Q12W injection of HD aflibercept maintain concentrations of free aflibercept in the eye above 9 × K_D (that is, 90% inhibition of VEGF in an *in vitro* setting) for 12 weeks after the last dose at week 56, versus 49.2% of patients receiving Q8W injections of 2 mg aflibercept. These percentages respectively decreased to 63.6% and 30.5% by week 16 after the last injection. Thus, a considerably higher percentage of patients is expected to inhibit ocular VEGF for an extended duration of time for HD aflibercept compared to 2 mg aflibercept.

[000941] For HD aflibercept, the 34.4% slower ocular clearance and higher administered dose are estimated to result in a longer duration of ocular exposure to free aflibercept compared to 2 mg aflibercept. Population PK model-estimated median concentrations of free aflibercept in the eye 8 weeks after 2 mg aflibercept injection are predicted to be reached 14.1 weeks after HD injection, that is a typical, approximate 6-week difference. Consistent with this estimated approximately 6-week longer time to reach the 2q8 ocular trough concentration, HD aflibercept administered at intervals 4 (HDq12) to 8 weeks (HDq16) longer than those for the 2q8 regimen demonstrated non-inferior efficacy in BCVA mean change from baseline at both week 48

(primary endpoint) and week 96 (pre-specified exploratory endpoint) compared to 2q8 in the PULSAR and PHOTON studies.

[000942]In the PULSAR and PHOTON studies, by week 96, between 75% and 88% of participants randomized to HDq12 remained on a ≥ Q12W dosing interval, between 70% and 84% of participants randomized to HDq16 remained on a ≥ Q16W dosing interval, and approximately 43% of the pooled group participants who received HD aflibercept were extended to a ≥ Q20W dosing interval.

Example 4: Pharmacometric Evaluation of Patients with Age-Related Macular Degeneration and Diabetic Macular Edema who Completed 24-week Dosing Intervals of High Dose Aflibercept

[000943]The efficacy and safety of high dose (HD) aflibercept have been evaluated in 1 phase 2 study in patients with neovascular age-related macular degeneration (nAMD) (CANDELA; VGFTe-HDAMD- 1905) and 2 phase 3 studies in patients with nAMD (PULSAR; 86-5321-20968) and patients with diabetic macular edema (DME) and diabetic retinopathy (DR) (PHOTON; VGFTe- HD-DME-1934). The present analysis focused on the patients who received HD aflibercept and were extended to and completed a 24-week dosing interval without shortening. Because HD aflibercept dosing interval was set to 12 weeks and could not be extended in patients enrolled in the CANDELA study, data from the CANDELA study were not included in this analysis.

[000944]Following 3 initial monthly injections, patients randomized to HD aflibercept in the PULSAR and PHOTON studies received intravitreal (IVT) injections either every 12 weeks (HDq12) or every 16 weeks (HDq16). Over the course of these 2 studies (including the optional, on-going, extension period beyond week 96), dosing intervals could be modified by the investigators based upon the assessment of best corrected visual acuity (BCVA), central retinal thickness (CRT), and other anatomical and pathophysiological characteristics of the patient's eyes. After the 3 initial monthly injections, patients who met protocol-specified criteria underwent dosing interval shortening (by 4-week increments during the first 2 years study). Starting at the second year of the PULSAR and PHOTON studies, patients who met protocol-specified criteria were eligible to undergo dosing interval extension by 4-week increments. Patients were eligible for additional extensions if they continued maintaining vision and anatomical benefits.

[000945]Based upon the data collected in the PULSAR and PHOTON studies, an exposure-response (ER) analysis was previously conducted to characterize the predictors of the last

assigned dosing interval (LDOSINT) prior to week 96, using a multivariable ordered logistic model. Notably, this analysis determined that, along with the disease population and randomized dosing regimen, the slower *post hoc* estimates of ocular distribution clearance (QE) obtained by population pharmacokinetic (PK) analysis and lower baseline CRT were associated with longer assigned dosing intervals.

[000946]Of the participants assigned to a 24-week interval as their last assigned dosing interval prior to week 96 in the PULSAR and PHOTON studies, a subset entered into the extension phase and successfully completed the 24-week interval between weeks 96 and 108 without the need for shortening based on dose regimen modification (DRM) criteria.

[000947]It should be noted that the tables and figures shown below include, among others, statistics for a patient group labeled as "Q24W*" and a patient group labeled as "Q24W". The Q24W* comprises the subgroup of patients who completed a 24-week interval without shortening. The Q24W group includes all patients who were assigned to every 24 weeks (Q24W) including those who completed a 24-week interval without shortening.

[000948]Among the 165 patients with nAMD and 107 patients with DME who were assigned to Q24W dosing interval, 51 patients with nAMD and 18 patients with DME completed a 24-week interval without shortening (Table 4-1 and Table 4-2 below).

Table 4-1. Summary of Characteristics of Patients With Neovascular Age-Related Macular Degeneration in the PULSAR Study, Stratified by Assigned Dosing Interval at the Last Study Eye Dose of High Dose Aflibercept Through Week 96

Variable	Group or Statistic	Q8W (N=80)	Q12W (N=112)	Q16W (N=160)	Q20W (N=119)	Q24W (N=165)	Q24W* (N=51)
Q_E (mL/day)	Mean (SD)	0.452 (0.171)	0.421 (0.173)	0.387 (0.156)	0.408 (0.337)	0.359 (0.123)	0.336 (0.106)
	Median	0.443	0.367	0.359	0.356	0.338	0.323
	Min, Max	0.157, 1.11	0.124, 1.24	0.143, 1.53	0.0384, 3.30	0.121, 0.872	0.128, 0.661
	Missing	4	5	9	11	9	1
Q_E percentile, N (%)	0-<33 %	19 (23.8%)	30 (26.8%)	55 (34.4%)	42 (35.3%)	66 (40.0%)	25 (49.0%)
	33-<66 %	17 (21.2%)	34 (30.4%)	53 (33.1%)	39 (32.8%)	59 (35.8%)	18 (35.3%)
	66-100 %	40 (50.0%)	43 (38.4%)	43 (26.9%)	27 (22.7%)	31 (18.8%)	7 (13.7%)
	Missing	4 (5.00%)	5 (4.46%)	9 (5.62%)	11 (9.24%)	9 (5.45%)	1 (1.96%)
Baseline CRT (μm)	Mean (SD)	462 (133)	448 (148)	397 (134)	397 (123)	404 (135)	413 (115)
	Median	431	434	370	359	375	384

	Min, Max	203, 872	197, 1005	194, 943	176, 826	109, 896	241, 766
Baseline CRT percentile, N (%)	0-<33 %	15 (18.8%)	27 (24.1%)	55 (34.4%)	48 (40.3%)	64 (38.8%)	16 (31.4%)
	33-<66 %	29 (36.2%)	32 (28.6%)	67 (41.9%)	37 (31.1%)	49 (29.7%)	21 (41.2%)
	66-100 %	36 (45.0%)	53 (47.3%)	38 (23.8%)	34 (28.6%)	52 (31.5%)	14 (27.5%)
Randomized dosing regimen, N (%)	HDq12	44 (55.0%)	80 (71.4%)	76 (47.5%)	49 (41.2%)	72 (43.6%)	0 (0%)
	HDq16	36 (45.0%)	32 (28.6%)	84 (52.5%)	70 (58.8%)	93 (56.4%)	51 (100%)
Baseline age (years)	Mean (SD)	74.4 (8.07)	74.8 (7.64)	74.1 (8.43)	75.2 (8.41)	74.3 (8.44)	74.4 (9.59)
	Median	76.0	75.0	74.0	75.0	74.0	74.0
	Min, Max	55.0, 93.0	52.0, 90.0	54.0, 92.0	57.0, 93.0	56.0, 95.0	56.0, 95.0
Sex, N (%)	Male	45 (56.2%)	49 (43.8%)	69 (43.1%)	54 (45.4%)	73 (44.2%)	19 (37.3%)
	Female	35 (43.8%)	63 (56.2%)	91 (56.9%)	65 (54.6%)	92 (55.8%)	32 (62.7%)
Racial classification, N (%)	White	69 (86.2%)	93 (83.0%)	123 (76.9%)	89 (74.8%)	117 (70.9%)	38 (74.5%)
	Asian	11 (13.8%)	19 (17.0%)	36 (22.5%)	29 (24.4%)	44 (26.7%)	13 (25.5%)
	Black	0 (0%)	0 (0%)	1 (0.625%)	0 (0%)	1 (0.606%)	0 (0%)
	Not reported	0 (0%)	0 (0%)	0 (0%)	1 (0.840%)	3 (1.82%)	0 (0%)
Japanese origin, N (%)	No	76 (95.0%)	106 (94.6%)	144 (90.0%)	107 (89.9%)	143 (86.7%)	44 (86.3%)
	Yes	4 (5.00%)	6 (5.36%)	16 (10.0%)	12 (10.1%)	22 (13.3%)	7 (13.7%)
Baseline BCVA (letters)	Mean (SD)	60.2 (10.9)	58.9 (14.1)	61.1 (12.9)	60.3 (13.4)	59.4 (12.8)	60.8 (11.5)
	Median	60.5	62.0	64.0	63.0	61.0	61.0
	Min, Max	25.0, 77.0	26.0, 78.0	24.0, 78.0	24.0, 78.0	25.0, 78.0	32.0, 78.0
Baseline HbA1c (%)	Mean (SD)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
	Median	-	-	-	-	-	-
	Min, Max	NA, NA	NA, NA	NA, NA	NA, NA	NA, NA	NA, NA
	Missing	80.0	112	160	119	165	51.0
Duration of diabetes	Mean (SD)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)	NA (NA)
	Median	-	-	-	-	-	-
	Min, Max	NA, NA	NA, NA	NA, NA	NA, NA	NA, NA	NA, NA
	Missing	80.0	112	160	119	165	51.0
Cataract surgery, N (%)	No Surgery	58 (72.5%)	79 (70.5%)	130 (81.2%)	90 (75.6%)	121 (73.3%)	36 (70.6%)
	Surgery on study	1	0 (0%)	2 (1.25%)	4	5 (3.03%)	0 (0%)

	eye	(1.25%)			(3.36%)		
	Surgery on fellow eye	1 (1.25%)	4 (3.57%)	1 (0.625%)	4 (3.36%)	0 (0%)	0 (0%)
	Surgery on both eyes	20 (25.0%)	29 (25.9%)	27 (16.9%)	21 (17.6%)	39 (23.6%)	15 (29.4%)

BCVA = Best corrected visual acuity; CRT = Central retina thickness; HbA1c = Hemoglobin A1c; HDqX = High dose aflibercept every X weeks following initial 3 monthly injections; Max = Maximum; Min = Minimum; N = Number of participants; NA = Not Applicable; QxW = Every X weeks; SD = Standard deviation

Note: Q24W* is a subset of the Q24W group and includes patients who were extended to and completed a 24-week interval without shortening.

Table 4-2. Summary of Characteristics of Patients With Diabetic Macular Edema in the PHOTON Study, Stratified by Assigned Dosing Interval at the Last Study Eye Dose of High Dose Aflibercept Through Week 96

Variable	Group or Statistic	Q8W (N=29)	Q12W (N=108)	Q16W (N=127)	Q20W (N=84)	Q24W (N=107)	Q24W* (N=18)
Q_E (mL/day)	Mean (SD)	0.569 (0.163)	0.651 (0.617)	0.534 (0.329)	0.589 (0.289)	0.790 (1.61)	1.07 (2.30)
	Median	0.593	0.519	0.469	0.579	0.487	0.525
	Min, Max	0.288, 0.940	0.248, 5.90	0.152, 3.59	0.120, 1.88	0.167, 12.4	0.188, 10.3
Q_E percentile, N (%)	0-<33 %	6 (20.7%)	36 (33.3%)	47 (37.0%)	26 (31.0%)	37 (34.6%)	5 (27.8%)
	33-<66 %	11 (37.9%)	33 (30.6%)	46 (36.2%)	23 (27.4%)	38 (35.5%)	7 (38.9%)
	66-100 %	12 (41.4%)	39 (36.1%)	34 (26.8%)	35 (41.7%)	32 (29.9%)	6 (33.3%)
Baseline CRT (μm)	Mean (SD)	511 (102)	481 (124)	462 (123)	430 (119)	418 (131)	440 (125)
	Median	509	469	443	400	393	406
	Min, Max	347, 726	290, 926	229, 849	281, 965	255, 1309	255, 734
	Missing	0	1	0	0	0	0
Baseline CRT percentile, N (%)	0-<33 %	4 (13.8%)	25 (23.1%)	38 (29.9%)	36 (42.9%)	49 (45.8%)	7 (38.9%)
	33-<66 %	8 (27.6%)	37 (34.3%)	44 (34.6%)	23 (27.4%)	38 (35.5%)	6 (33.3%)
	66-100 %	17 (58.6%)	45 (41.7%)	45 (35.4%)	25 (29.8%)	20 (18.7%)	5 (27.8%)
	Missing	0 (0%)	1 (0.926%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Randomized dosing regimen, N (%)	HDq12	21 (72.4%)	97 (89.8%)	62 (48.8%)	57 (67.9%)	62 (57.9%)	0 (0%)
	HDq16	8 (27.6%)	11 (10.2%)	65 (51.2%)	27 (32.1%)	45 (42.1%)	18 (100%)

Baseline age (years)	Mean (SD)	61.8 (9.42)	60.5 (11.5)	62.5 (9.95)	61.4 (11.4)	62.6 (10.5)	62.3 (10.9)
	Median	62.0	62.0	63.0	61.0	63.0	62.0
	Min, Max	44.0, 83.0	24.0, 84.0	28.0, 83.0	31.0, 87.0	36.0, 81.0	45.0, 81.0
Sex, N (%)	Male	20 (69.0%)	79 (73.1%)	75 (59.1%)	50 (59.5%)	62 (57.9%)	13 (72.2%)
	Female	9 (31.0%)	29 (26.9%)	52 (40.9%)	34 (40.5%)	45 (42.1%)	5 (27.8%)
Racial classification, N (%)	White	22 (75.9%)	75 (69.4%)	102 (80.3%)	61 (72.6%)	72 (67.3%)	14 (77.8%)
	Asian	4 (13.8%)	22 (20.4%)	15 (11.8%)	10 (11.9%)	18 (16.8%)	3 (16.7%)
	Black	3 (10.3%)	6 (5.56%)	6 (4.72%)	9 (10.7%)	15 (14.0%)	1 (5.56%)
	AIAN	0 (0%)	1 (0.926%)	0 (0%)	1 (1.19%)	0 (0%)	0 (0%)
	NHOPI	0 (0%)	1 (0.926%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Not reported	0 (0%)	3 (2.78%)	4 (3.15%)	3 (3.57%)	2 (1.87%)	0 (0%)
Japanese origin, N (%)	No	25 (86.2%)	91 (84.3%)	116 (91.3%)	79 (94.0%)	92 (86.0%)	16 (88.9%)
	Yes	4 (13.8%)	17 (15.7%)	11 (8.66%)	5 (5.95%)	15 (14.0%)	2 (11.1%)
Baseline BCVA (letters)	Mean (SD)	57.2 (12.6)	63.2 (10.2)	62.3 (11.0)	64.1 (10.2)	64.4 (10.4)	58.3 (15.3)
	Median	57.0	64.0	65.0	67.0	67.0	58.0
	Min, Max	33.0, 75.0	33.0, 78.0	29.0, 78.0	27.0, 78.0	30.0, 79.0	30.0, 77.0
Baseline HbA1c (%)	Mean (SD)	7.77 (1.66)	7.94 (1.49)	8.01 (1.55)	7.80 (1.41)	7.83 (1.51)	7.96 (1.79)
	Median	7.30	7.60	7.80	7.60	7.60	7.90
	Min, Max	5.80, 11.8	5.60, 11.5	5.30, 11.8	5.60, 12.0	4.50, 11.7	4.50, 11.6
	Missing	0	1.00	1.00	1.00	1.00	0
Duration of diabetes	Mean (SD)	9.73 (8.23)	14.0 (8.99)	16.4 (9.58)	15.8 (10.8)	16.4 (11.5)	13.8 (10.7)
	Median	7.18	12.7	15.9	14.4	15.2	12.7
	Min, Max	0.0575, 32.3	0.0958, 36.1	0.372, 42.0	0.424, 51.3	0.110, 53.9	0.482, 35.2
	Missing	1.00	0	0	0	1.00	0
Cataract surgery, N (%)	No Surgery	23 (79.3%)	97 (89.8%)	106 (83.5%)	71 (84.5%)	88 (82.2%)	16 (88.9%)
	Surgery on study eye	0 (0%)	0 (0%)	2 (1.57%)	3 (3.57%)	2 (1.87%)	0 (0%)
	Surgery on fellow eye	0 (0%)	1 (0.926%)	5 (3.94%)	3 (3.57%)	2 (1.87%)	0 (0%)
	Surgery on both eyes	6 (20.7%)	10 (9.26%)	14 (11.0%)	7 (8.33%)	15 (14.0%)	2 (11.1%)

AIAN = American Indian or Alaska Native; BCVA = Best corrected visual acuity; CRT = Central retina thickness; HbA1c = Hemoglobin A1c; HDqX = High dose aflibercept every X weeks

following initial 3 monthly injections; Max = Maximum; Min = Minimum; N = Number of participants; NHOPI = Native Hawaiian or Other Pacific Islander; QxW = Every X weeks; SD = Standard deviation

Note: Q24W* is a subset of the Q24W group and includes patients who were extended to and completed a 24-week interval without shortening.

[000949]For the remaining patients, either the expected completion of the 24-week interval was either beyond week 108 or their dosing interval was shortened. All 69 patients who completed a 24-week interval without shortening had been randomized to HDq16, as expected from the dosing interval at randomization and the rules of interval extension (patients randomized to HDq12 could only be assigned to Q24W at week 88 and could not have completed a 24-week interval before week 112).

[000950]The *post hoc* estimate of QE was missing in 1 patient among the subset of 69 patients who completed a 24-week interval without shortening (Table 4-1). This patient did not contribute any measurable aflibercept concentration in plasma and was not included in the population PK analysis. Increasing LDOSINT values were associated with a decrease in median estimates of QE in patients with nAMD (Figure 80); however, no trend was observed between QE and LDOSINT in patients with DME (Figure 81). It was also previously reported that, in both subpopulations of patients with nAMD and patients with DME, increasing LDOSINT values were associated with a decrease in median estimates of baseline CRT (Figure 82 and Figure 83).

[000951]The comparison of the characteristics of patients who completed a 24-week interval without shortening versus the complete analysis population revealed that:

1. The distribution of QE in patients who completed a 24-week interval and remained assigned to Q24W dosing interval was similar to that observed in both subpopulations of patients with nAMD and patients with DME assigned to Q24W dosing intervals (Figure 80, Figure 81, and Table 4-3).
2. Among the patients with nAMD who completed a 24-week interval without shortening, 25 (49%) patients had *post hoc* estimate of QE within the lowest tertile, 18 (35%) within the middle tertile, and 7 (14%) within the highest tertile (Figure 84), evidencing that the distribution of QE in patients with nAMD who completed a 24-week interval without shortening was shifted towards the lower side of the distribution of QE in the complete analysis population (Figure 80).
3. Among the patients with DME who completed a 24-week interval without shortening, 5 (28%) patients had *post hoc* estimate of QE within the lowest tertile, 7 (39%) within the

middle tertile, and 6 (33%) within the highest tertile (Figure 84), evidencing that the distribution of QE in patients with DME who completed a 24-week interval without shortening was comparable to the distribution of QE in the complete analysis population (Figure 81).

4. The distribution of baseline CRT in patients who completed a 24-week interval without shortening was similar to that observed in both subpopulations of patients with nAMD and patients with DME assigned to Q24W dosing intervals (Figure 82, Figure 83, and Table 4-4).

5. Among the patients who completed a 24-week interval without shortening, 23 (33%) patients had a baseline CRT within the lowest tertile, 27 (39%) within the middle tertile, and 18 (27.5%) within the highest tertile (Table 4-1 and Table 4-2), indicating that the distribution of baseline CRT in patients who completed a 24-week interval without shortening was shifted towards the lower side of the distribution of baseline CRT in the complete analysis population (Figure 82 and Figure 83).

[000952]These findings are consistent with the model-based predictions of mean dosing interval assigned at the last dose broken down by tertiles of QE and baseline CRT that have been reported previously, as illustrated in Figure 84.

[000953]This analysis focused on the patients in PULSAR and PHOTON who received HD aflibercept and were extended to and completed a 24-week dosing interval without shortening by week 108. In these trials, dosing intervals could be extended if vision and anatomical benefits were maintained.

[000954]The results of this analysis indicated that patients with nAMD or DME with low baseline CRT had a higher chance of dosing interval extension to and completion of Q24W than patients with high baseline CRT. In addition, these results also indicated that patients with nAMD with low QE had a higher chance of dosing interval extension to and completion of Q24W than patients with nAMD and high QE. These results aligned with the previous ER analysis. In contrast, no relation was observed between QE and the extension to and completion of Q24W dosing intervals in patients with DME. This result also aligns with the previous ER analysis.

Table 4-3. Distribution of Ocular Distribution Clearance (mL/day), Stratified by Disease Population, Assigned Dose Interval at the Last Study Eye Dose of High Dose Aflibercept Through Week 96 in the PULSAR and PHOTON Studies

Disease Population	Statistic	Q8W	Q12W	Q16W	Q20W	Q24W	Q24W*

nAMD	Mean (SD)	0.452 (0.171)	0.421 (0.173)	0.387 (0.156)	0.408 (0.337)	0.359 (0.123)	0.336 (0.106)
	Median	0.443	0.367	0.359	0.356	0.338	0.323
	Min, Max	0.157, 1.11	0.124, 1.24	0.143, 1.53	0.0384, 3.30	0.121, 0.872	0.128, 0.661
	N	80	112	160	119	165	51
	Missing	4	5	9	11	9	1
DME	Mean (SD)	0.569 (0.163)	0.651 (0.617)	0.534 (0.329)	0.589 (0.289)	0.790 (1.61)	1.07 (2.30)
	Median	0.593	0.519	0.469	0.579	0.487	0.525
	Min, Max	0.288, 0.940	0.248, 5.90	0.152, 3.59	0.120, 1.88	0.167, 12.4	0.188, 10.3
	N	29	108	127	84	107	18
	Missing	0	0	0	0	0	0

DME = Diabetic macular edema; Max = Maximum; Min = Minimum; N = Number of participants; nAMD = Neovascular age-related macular degeneration; QxW = Every X weeks; SD = Standard deviation

Note: Q24W* is a subset of the Q24W group and includes patients who were extended to and completed a 24-week interval without shortening.

Table 4-4. Distribution of Baseline Central Retinal Thickness (µm), Stratified by Disease Population and Assigned Dose Interval at the Last Study Eye Dose of High Dose Aflibercept Through Week 96 in the PULSAR and PHOTON Studies

Disease Population	Statistic	Q8W	Q12W	Q16W	Q20W	Q24W	Q24W*
nAMD	Mean (SD)	462 (133)	448 (148)	397 (134)	397 (123)	404 (135)	413 (115)
	Median	431	434	370	359	375	384
	Min, max	203, 872	197, 1005	194, 943	176, 826	109, 896	241, 766
	N	80	112	160	119	165	51
	Missing	0	0	0	0	0	0
DME	Mean (SD)	511 (102)	481 (124)	462 (123)	430 (119)	418 (131)	440 (125)
	Median	509	469	443	400	393	406
	Min, max	347, 726	290, 926	229, 849	281, 965	255, 1309	255, 734
	N	29	108	127	84	107	18
	Missing	0	1	0	0	0	0

DME = Diabetic macular edema; Max = Maximum; Min = Minimum; N = Number of participants; nAMD = Neovascular age-related macular degeneration; QxW = Every X weeks; SD = Standard deviation

Note: Q24W* is a subset of the Q24W group and includes patients who were extended to and completed a 24-week interval without shortening.

Example 5: Population Exposure-Response Analysis of High Dose Aflibercept in Patients With Age-Related Macular Degeneration and Patients With Diabetic Macular Edema

[000955]The objectives of these analyses were to: 1) update the previously developed exposure-response (ER) model characterizing the time to first dose regimen modification (DRM) after intravitreal (IVT) injections of high dose (HD) aflibercept using a dataset revised by adding DRM data collected during the second year of the PULSAR and PHOTON studies; 2) develop an ER model characterizing the time to first dose regimen extension (DRE) during the second year of the PULSAR and PHOTON studies; 3) develop a multivariable ordered logistic model characterizing the assigned dosing interval at the last dose event in the second year of the PULSAR and PHOTON studies; and 4) for each of these models, determine if post hoc estimates of ocular distribution clearance (Q_E) (or directly related metrics) and/or other intrinsic or extrinsic factors were predictive of the time to first DRM, time to first DRE, and assigned dosing interval at the last dose.

Background and Information

[000956]An ER analysis was previously conducted to characterize the time to first DRM during the first year of the CANDELA (VGFTe-HD-AMD-1905), PULSAR (86-5321-20968), and PHOTON (VGFTe-HD-DME-1934) studies. CANDELA was a phase 2 study assessing the efficacy and safety of repeated IVT injections of HD aflibercept in patients with neovascular age-related macular degeneration (nAMD) over 1 year. PULSAR and PHOTON are on-going pivotal phase 3 studies assessing the efficacy and safety of repeated IVT injections of HD aflibercept in patients with nAMD (in PULSAR only) and in patients with diabetic macular edema (DME) (who also had diabetic retinopathy (DR); in PHOTON only) over multiple years. Following 3 initial monthly injections, patients who received HD aflibercept were randomized to IVT injections every 12 weeks (HDq12) or every 16 weeks (HDq16; in PULSAR and PHOTON only) dosing intervals. Over the course of the studies, intervals between consecutive doses could be modified by the investigators based upon the assessment of best corrected visual acuity (BCVA), central retinal thickness (CRT), and other anatomical and pathophysiological characteristics of the patient's eyes. After the 3 initial monthly injections, patients who met protocol-specified criteria underwent dosing interval shortening in the PULSAR and PHOTON studies or received *pro re nata* ("as needed") (PRN) injections, both considered as DRM events

in the present analysis. Starting at the second year of the PULSAR and PHOTON studies, patients who met protocol-specified criteria were eligible to undergo dosing interval extension, documented as DRE events. Patients were eligible for additional extensions if they continued maintaining vision and anatomical benefits.

Data

[000957]The analysis dataset used for ER analyses was constructed using longitudinal data collected in patients who received at least 1 IVT dose of HD aflibercept in the CANDELA, PULSAR, and PHOTON. It expanded on the dataset used in the prior ER analysis by including data collected during the second year of the PULSAR and PHOTON studies following database lock at week 96. The *post hoc* estimates of Q_E obtained for each CANDELA, PHOTON, and PULSAR participant in a population pharmacokinetic (PK) model that was developed [using a dataset that included data from 16 clinical studies: 8 studies in patients with nAMD (VGFT-OD-0305, VGFT-OD-0306, VGFT-OD-0502 [VGFT-OD-502 part A and VGFT-OD-502 part C], VGFT-OD-603, VGFT-OD-0702.PK, 311523, CANDELA [VGFTe (HD)-AMD-1905], and PULSAR [86-5321-20968]), 5 studies in patients with DME (VGFT-OD-0307, VGFT-OD-512, VGFT-OD-0706.PK, 91745, and PHOTON [VGFTe (HD)-DME-1934]), 2 studies in healthy male subjects (PDY6655 and PDY6656), and 1 study in patients with solid tumors or lymphoma (TED6113). The dataset included 31,326 samples records from 2,744 unique participants (76 healthy participants, 38 oncology participants, 1,662 nAMD participants, and 968 DME participants)] were combined with response variables and relevant patient characteristics.

[000958]The data subset used for the analysis of time to first DRM comprised 53 patients with nAMD from CANDELA, 673 patients with nAMD from PULSAR, and 491 patients with DME from PHOTON. It included 268 patients who had a DRM and 949 patients who did not. The data subset used for the analysis of time to first DRE comprised 621 patients with nAMD from PULSAR and 443 patients with DME from PHOTON who contributed data within the second year of study. It included 618 patients who had a DRE and 446 patients who did not. The data subset used for the analysis of assigned dosing interval at the last study eye dose (LDOSINT) included 636 patients with nAMD from PULSAR and 455 patients with DME from PHOTON who contributed data beyond the initial 3 monthly IVT injections.

[000959]Data collected in CANDELA were not used to model the time to first DRE because dosing interval extension were not allowed in this study. In addition, the last dose typically occurred at different time frames in the CANDELA study (30 to 45 weeks) compared to the

PULSAR and PHOTON studies (70 to 96 weeks), these limitations further necessitated the need to exclude data from the CANDELA study to assess LDOSINT.

Methodology

[000960]Separate ER models were developed for 3 different endpoints:

- Time to first DRM, defined as the time at which the investigator documented the first reduction of the dosing interval below the frequency assigned at randomization in participants of the PULSAR and PHOTON studies or the time at which a PRN dose was documented in CANDELA participants
- Time to first DRE, defined as the time at which the investigator documented the first extension of the dosing interval above the frequency assigned at randomization, in participants of the PULSAR and PHOTON studies
- LDOSINT, defined as the dosing interval assigned by the investigator at the time of the last study eye dose in participants of the PULSAR and PHOTON studies

[000961]In the PULSAR and PHOTON studies, the possible assigned dosing frequencies for HD aflibercept were every 8 weeks (Q8W), every 12 weeks (Q12W), every 16 weeks (Q16W), every 20 weeks (Q20W), or every 24 weeks (Q24W). In the CANDELA study, the only possible assigned dosing frequency for HD aflibercept was Q12W.

[000962]For each analysis, the data was explored by summarizing the distribution of the endpoints and the relationships between these endpoints and the participant characteristics of interest. The longitudinal DRM and DRE information was visualized with Kaplan-Meier plots stratified by participant characteristic of interest.

[000963]Time to first DRM and time to first DRE were described using Cox proportional hazard (CoxPH) models. LDOSINT data were described using multivariate ordered logistic models. For the CoxPH models, univariate models were first run to identify statistically significant predictors ($\alpha = 0.05$) for inclusion in the full multivariate models. For the model of LDOSINT, the full multivariate model included all covariates of interest. For all endpoints, the covariates of interest were: age, sex, racial classification, Japanese origin, disease population, randomized dosing regimen, baseline CRT, baseline BCVA score, baseline hemoglobin A1c (HbA1c), diabetes duration, cataract surgery, study (for DRM only), and/or Q_E or area under the curve in the eye between 2 injections (AUC_{eye}) (defined as 8 mg/Q_E). A first round of stepwise backward covariate elimination based upon Akaike information criterion (AIC) was then performed to identify preliminary reduced models. Interactions between the remaining effects were evaluated before a second round of stepwise backward covariate elimination was performed based upon

likelihood ratio test (LRT). The reduced models were further refined for parsimony and utility to arrive at the final models. The final CoxPH models were visualized with plots of the predicted survival curves at various contrasts (*i.e.*, selected sets of predictor values) and plots of the hazard ratio across continuous variables with strata for discrete variables. Hazard ratio contrasts were tabulated across relevant continuous and discrete covariate values. The final ordered logistic model of LDOSINT was evaluated by visual predict check and also illustrated with plots of probability of assignment to given dosing intervals, typical model-predicted LDOSINT, and mean model-predicted dosing interval as a function of the continuous predictors and stratified by the selected predictors.

Results

[000964]*Analysis of time to first DRM.* A Kaplan-Meier plot stratified by disease population (Figure 85) showed a statistically significant ($p<0.0001$) difference in time to first DRM between patients with nAMD and patients with DME, per the log-rank test. Additional Kaplan-Meier plots showed statistically significant ($p<0.05$) decreases in DRM rates with rank-ordered AUC_{eye} tertiles (Figure 86) and statistically significant ($p<0.001$) increases in DRM rates with rank-ordered baseline CRT tertiles, in both disease populations.

[000965]The analysis of time to first DRM by CoxPH modeling confirmed the findings of the Kaplan-Meier analyses and identified 3 significant predictors of time to first DRM: AUC_{eye}, disease population, and baseline CRT. The parameter estimates of the final CoxPH model are provided in Table 5-1 and represent the hazard ratios over a unit change of AUC_{eye} and baseline CRT and the hazard ratio between disease population. This model predicted a 38.7% lower rate for DRM for patients at the 75th versus 25th percentiles of AUC_{eye} (and the same median baseline CRT) and a 46.8% higher rate for DRM for patients at the 75th versus 25th percentiles of baseline CRT (and the same median baseline AUC_{eye}) within either disease population.

[000966]Figure 87 illustrates the change in hazard ratios as a function of Q_E in patients with nAMD and patients with DME with the same median baseline CRT using a patient with DME with median Q_E as reference. For median Q_E and baseline CRT values, the rate of DRM was predicted to increase by 254% in patients with nAMD compared to patients with DME.

[000967]The population PK analysis had concluded that Q_E was typically 34.4% lower after IVT injection of HD versus 2 mg aflibercept, attributable to a “HD drug product” effect. The CoxPH model indicated that the estimated rate of DRM with HD aflibercept was 27.7% lower than the

predicted rate of DRM in absence of the "HD product effect" on Q_E. See Figure 85 and Figure 86.

Table 5-1. Parameter Estimates of the Final Cox Proportional Hazard Model for Time to First Dose Regimen Modification of High Dose Aflibercept

Effect	log(Hazard Ratio)	Hazard Ratio	Standard Error	z	Pr(>|z|)
AUC_{eye}	-4.94e-05	1.00	9.09e-06	-5.43	5.63e-08
nAMD versus DME	1.26	3.54	0.155	8.14	3.90e-16
CRTBL	0.00225	1.00	3.62e-04	6.20	5.70e-10

AUCeye = Area under the curve of concentrations in the eye; CRTBL = Baseline central retinal Thickness; DME = Diabetic macular degeneration; nAMD = Neovascular age-related macular degeneration; Pr = Probability

[000968]*Analysis of time to first DRE*. No visible difference was observed in the Kaplan-Meier plot of time to first DRE stratified by disease population. In contrast, a Kaplan-Meier analysis showed a statistically significant ($p<0.01$) difference in time to first DRE between patients assigned to HDq16 versus HDq12 at randomization (Figure 88). Additional Kaplan-Meier plots showed statistically significant ($p<0.0001$) increases in DRE rates with rank-ordered AUCeye tertiles (Figure 89) in patients with nAMD, but not in patients with DME. Statistically significant ($p<0.01$) decreases in DRE rates with rank-ordered baseline CRT tertiles were also found in both disease populations.

[000969]The analysis of time to first DRE by CoxPH modeling generally confirmed the findings of the Kaplan-Meier analyses and identified 3 significant predictors of time to first DRE: AUCeye, randomized dosing regimen, and baseline CRT. The parameter estimates of the final CoxPH model are provided in Table 5-2 and represent the hazard ratio over a unit change of AUCeye and baseline CRT and the hazard ratio between randomized dosing regimens. This model predicted a 16.6% higher rate for DRE for patients at the 75th versus 25th percentiles of AUCeye (and the same median baseline CRT) and a 24.9% lower rate for DRE for patients at the 75th versus 25th percentiles of baseline CRT (and the same median baseline AUCeye) within either disease population.

[000970]Figure 90 illustrates the change in hazard ratios as a function of QE in patients assigned to HDq16 versus HDq12 with the same median baseline CRT using a patient with median QE and assigned to HDq12 as reference. For median QE and baseline CRT values,

the rate of DRE was predicted to decrease by 29.2% in patients assigned to HDq16 versus HDq12.

[000971]The CoxPH model indicated that the estimated rate of DRE with HD aflibercept was 11% higher than the predicted rate of DRE in the absence of the "HD product effect" on QE.

[000972]See Figure 88 and Figure 89.

Table 5-2. Parameter Estimates of the Final Cox Proportional Hazard Model for Time to First Dose Regimen Extension of High Dose Aflibercept

Effect	log(Hazard Ratio)	Hazard Ratio	Standard Error	z	Pr(>|z|)
HDq16 versus HDq12	-0.346	0.708	0.0833	-4.15	3.35e-05
AUC_{eye}	1.59e-05	1.00	4.36e-06	3.65	2.62e-04
CRTBL	-0.00171	0.998	3.35e-04	-5.09	3.54e-07

AUCeye = Area under the curve of concentrations in the eye; CRTBL = Baseline central retinal thickness; HDqX = 8 mg aflibercept every X weeks following 3 initial monthly injections; Pr = Probability

[000973] See Figure 90.

[000974]*Analysis of assigned dosing interval at the last dose (LDOSINT).* As illustrated in Figure 91, the decrease in QE appeared to correlate with the increase in LDOSINT for participants with nAMD (PULSAR study) but not in participants with DME (PHOTON study).

[000975]The analysis of LDOSINT identified the following variables as significant predictors: the effects of the randomized dosing regimen at randomization, log(QE) for participants with nAMD, disease population and baseline CRT (Table 5-3).

[000976]See Figure 91.

Table 5-3. Parameter Estimates of the Final Model for Assigned Dosing Interval at Last Dose of High Dose Aflibercept

Effect	Estimate	Standard Error	t value	Pr(>|t|)
HDq16 versus HDq12	0.570	0.111	5.12	3.07e-07
$\log(Q_E)$ in nAMD	-0.777	0.199	-3.91	9.39e-05
DME versus nAMD	0.947	0.226	4.20	2.72e-05

CRTBL	-0.00247	4.29e-04	-5.76	8.39e-09
Logit P(LDOSINT ≤ Q8W)	-2.27	0.289	-7.85	4.07e-15
Logit P(LDOSINT ≤ Q12W)	-0.845	0.278	-3.03	0.00241
Logit P(LDOSINT ≤ Q16W)	0.324	0.277	1.17	0.241
Logit P(LDOSINT ≤ Q20W)	1.20	0.279	4.29	1.75e-05

CRTBL = Baseline central retinal thickness; DME = Diabetic macular edema; HDqX = 8 mg aflibercept every X weeks following 3 initial monthly injections; LDOSINT = Last dosing interval; nAMD = Neovascular age-related macular degeneration; QE = Ocular distribution clearance; QxW = Every X weeks; Pr = Probability

[000977]The logit of the cumulative probabilities of assignment to dosing intervals shorter or equal to 8, 12, 16, or 20 weeks can be calculated as follows for the final model:

$$\begin{aligned}
\text{logit P(LDOSINT} \leq \text{Q8W)} = \; & -2.27 - 0.570 \times \text{Regimen} + 0.777 \times log(Q_E) \times \text{nAMD} - \\
& 0.947 \times (1 - \text{Disease}) + 0.00247 \times \text{CRTBL} \\
\text{logit P(LDOSINT} \leq \text{Q12W)} = \; & -0.845 - 0.570 \times \text{Regimen} + 0.777 \times log(Q_E) \times \text{nAMD} - \\
& 0.947 \times (1 - \text{Disease}) + 0.00247 \times \text{CRTBL} \\
\text{logit P(LDOSINT} \leq \text{Q16W)} = \; & 0.324 - 0.570 \times \text{Regimen} + 0.777 \times log(Q_E) \times \text{nAMD} - \\
& 0.947 \times (1 - \text{Disease}) + 0.00247 \times \text{CRTBL} \\
\text{logit P(LDOSINT} \leq \text{Q20W)} = \; & 1.20 - 0.570 \times \text{Regimen} + 0.777 \times log(Q_E) \times \text{nAMD} - \\
& 0.947 \times (1 - \text{Disease}) + 0.00247 \times \text{CRTBL}
\end{aligned}$$

where Regimen is 1 for patients assigned to HDq16 at randomization and 0 otherwise; Disease is set to 1 for patients with nAMD and 0 for patients with DME.

[000978]The model predicted that increases in Q_E (in participants with nAMD) and baseline CRT (in both disease populations) resulted in a higher probability of assignment to short dosing intervals and a lower probability of assignment to long dosing intervals in patients with nAMD (Figure 92) but had no effect in patients with DME (Figure 93). For instance, in patients with nAMD in the lowest tertiles of Q_E and baseline CRT, the median predicted probabilities of assignment to Q8W and Q24W were 0.0469 and 0.359, respectively; in patients with nAMD in the highest tertiles of Q_E and baseline CRT, the median predicted probabilities of assignment to Q8W and Q24W were 0.190 and 0.127, respectively (Figure 92). In patients with DME in the lowest tertile of baseline CRT, the median predicted probabilities of assignment to Q8W and Q24W were approximately 0.07 and 0.30, respectively, across all tertiles of Q_E; in patients with DME in the highest tertile of baseline CRT, the median predicted probabilities of assignment to Q8W and Q24W were approximately 0.14 and 0.18, respectively, across all tertiles of Q_E.

[000979]These effects resulted in higher mean dosing interval in patients in the lower tertiles of Q_E (in participants with nAMD) and baseline CRT (in both disease populations) compared to the patients in the upper tertiles. In patients with nAMD in the lowest versus the highest tertiles of Q_E, the mean dosing interval at the last dose was approximately 19 weeks versus 17 weeks in the lower tertile of baseline CRT and approximately 18 weeks versus 14 weeks in the highest tertile of baseline CRT. In patients with DME in the lowest versus the highest tertiles of baseline baseline central retinal thickness (CRTBL), the mean assigned dosing interval at the last dose was approximately 18-19 weeks versus 15-16 weeks across all tertiles of Q_E.
[000980]See Figure 92 and Figure 93.

Discussion
[000981]Across the ER analyses of time to first DRM, time to first DRE, and LDOSINT, 2 variables were consistently identified as highly significant predictors of the modeled endpoints: Q_E (either as $\log(Q_E)$ or as reflected by AUC_{eye}) and baseline CRT. Randomized dosing regimen and disease population were also identified as predictors of time to first DRE and time to first DRM, respectively. Baseline BCVA, age (which is a predictor of Q_E), sex, racial classification, Japanese origin, baseline HbA1c, duration of diabetes disease, or history of cataract surgery were not found to be statistically significant predictors of any of the 3 modeled endpoints.
[000982]These analyses indicated that slower Q_E values and, thus, higher aflibercept exposure in the eye, were associated with decreased chance of DRM and increased chance of DRE. Increased baseline CRT, which reflects more severe forms of the nAMD and DME diseases, was predictive of higher rates of DRM, lower rate of DRE, and lower LDOSINT. The effect of disease population on the time to first DRM was partially, if not largely, due to different criteria applied to trigger a DRM across studies. The lower rates of DRE in patients assigned to HDq16 versus HDq12 may be attributed to the fact that, given equal dose amount and Q_E values across randomized dosing regimen, average concentrations in the eye are 25% lower in the HDq16 group than in the HDq12 group.
[000983]Multivariate assessments showed that patients in the highest tertile of Q_E (particularly in patients with nAMD) and highest tertile of baseline CRT had the highest observed and model-predicted rates of DRM, the lowest rate of DRE, and lowest mean assigned dosing interval at the last dose events. On the contrary, patients in the lowest tertile of Q_E (particularly in patients with nAMD) and lowest tertile of baseline CRT had the highest mean assigned dosing interval, suggesting more sustained vision benefits.

[000984]Overall, the results of the analyses reported herein were consistent with the prior analysis performed at the end of year 1 of the CANDELA, PULSAR, and PHOTON studies. While there may be other factors affecting effect of HD aflibercept, such as disease progression, comorbidities, and variability in response, these analyses showed a correlation between an independently determined PK parameter (Q_E) that describes the rate of release of aflibercept from the eye and the shortening (DRM) and extension (DRE) of the dosing interval.

Conclusion

[000985]CoxPH modeling was performed to identify predictors of a reduction (DRM) or an extension (DRE) in the dosing interval in patients with nAMD and patients with DME and DR within 2 years of treatment initiation with HD aflibercept. Additionally, a multivariate ordered logistic analysis was performed to identify the predictors of the assigned dosing interval at the last dose (LDOSINT).

[000986]The results of the time to first DRM analysis estimated a 254% higher rate for DRM for patients with nAMD compared to patients with DME and DR, most likely explained by the study-specific definition of DRM. Within either disease population, a 38.7% lower rate for DRM was estimated for patients at the 75th versus 25th percentiles of AUC_{eye} (that is, patients at approximately the 25th versus 75th percentiles of Q_E) and the same median baseline CRT. Within a disease population, a 46.8% higher rate for DRM was estimated for patients at the 75th versus 25th percentiles of baseline CRT and the same median baseline AUC_{eye}.

[000987]The CoxPH model indicated that the estimated rate of DRM with HD aflibercept was 27.7% lower than the predicted rate of DRM in absence of the “HD product effect” on Q_E.

[000988]The results of the time to first DRE analysis estimated a 29.2% lower rate for patients assigned to HDq16 versus HDq12. For a given randomized dosing regimen and same median baseline CRT, a 16.6% higher rate for DRE was estimated for patients at the 75th versus 25th percentiles of AUC_{eye} (that is patients at approximately the 25th versus 75th percentiles of Q_E). For a given randomized dosing regimen and the same median baseline AUC_{eye}, a 24.9% lower rate for DRE was estimated for patients at the 75th versus 25th percentiles of baseline CRT.

[000989]The CoxPH model indicated that the estimated rate of DRE with HD aflibercept was 11% higher than the predicted rate of DRE in absence of the “HD product effect” on Q_E.

[000990]The model predicted that increases in Q_E (in participants with nAMD) and baseline CRT (in both disease populations) resulted in a higher probability of assignment to short dosing intervals and a lower probability of assignment to long dosing intervals in patients with nAMD but had no effect in patients with DME. The model also estimated that, within the lowest tertile

of baseline CRT, the mean assigned dosing interval at the last dose was approximately 2 weeks higher in patients with nAMD in the lowest tertile of Q_E than those in the highest tertile of Q_E. In the highest tertile of baseline CRT, the mean assigned dosing interval at the last dose was approximately 4 weeks higher in patients with nAMD in the lowest tertile of Q_E than those in the highest tertile of Q_E. In patients with DME, regardless of Q_E, the mean assigned dosing interval at the last dose was approximately 2-3 weeks higher in the lowest tertile of baseline CRTBL than the highest tertile of baseline CRTBL.

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[000991]All references cited herein are incorporated by reference to the same extent as if each individual publication, database entry (*e.g.*, Genbank sequences or GeneID entries), patent application, or patent, was specifically and individually indicated to be incorporated by reference. This statement of incorporation by reference is intended by Applicants to relate to each and every individual publication, database entry (*e.g.*, Genbank sequences or GeneID entries), patent application, or patent, each of which is clearly identified in even if such citation is not immediately adjacent to a dedicated statement of incorporation by reference. The inclusion of dedicated statements of incorporation by reference, if any, within the specification does not in any way weaken this general statement of incorporation by reference. Citation of the references herein is not intended as an admission that the reference is pertinent prior art, nor does it constitute any admission as to the contents or date of these publications or documents.

We claim:

1. A method
- for treating or preventing an angiogenic eye disorder, neovascular age related macular degeneration (nAMD), diabetic retinopathy (DR) and/or diabetic macular edema (DME), in a subject in need thereof,
- for improving best corrected visual acuity in a subject in need thereof with nAMD, DR and/or DME; or
- for promoting retinal drying in a subject with an angiogenic eye disorder, nAMD, DR and/or DME in need thereof;
comprising administering to an eye of the subject, one or more doses of about 8 mg (±0.8 mg) or more of VEGF receptor fusion protein about once every 8-24, 12-24, 16-24, 20-24, 21-24, 21, 22, 23 or 24 weeks.

2. The method of claim 1 for treating or preventing an angiogenic eye disorder, neovascular age related macular degeneration (nAMD), diabetic retinopathy (DR) and/or diabetic macular edema (DME), in a subject in need thereof, comprising administering to an eye of the subject,
a single initial dose of about 8 mg (±0.8 mg) or more of a VEGF receptor fusion protein, followed by
one or more secondary doses of about 8 mg or more of the VEGF receptor fusion protein, followed by
one or more tertiary doses of about 8 mg or more of the VEGF receptor fusion protein;
wherein each secondary dose is administered about 2, 3, 4 or 2-4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered about 8-24, 12-24, 16-24, 20-24, 21-24, 21, 22, 23 or 24 weeks after the immediately preceding dose.

3. The method of any one of claims 1-2 for treating or preventing an angiogenic eye disorder, neovascular age related macular degeneration (nAMD), diabetic retinopathy (DR) and/or diabetic macular edema (DME), in a subject in need thereof, comprising administering to an eye of the subject,
a single initial dose of about 8 mg (±0.8 mg) or more of a VEGF receptor fusion protein, followed by

two secondary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein, followed by
one or more tertiary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein;
wherein each secondary dose is administered about 4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered about 8-24, 12-24, 16-24, 20-24, 21-24, 21, 22, 23 or 24 weeks after the immediately preceding dose.

4. A method for treating or preventing an angiogenic eye disorder, neovascular age related macular degeneration (nAMD), diabetic retinopathy and/or diabetic macular edema, in a subject in need thereof, comprising administering to an eye of the subject, about 3 doses of about 8 mg (±0.8 mg) VEGF receptor fusion protein in a formulation that comprises about 114.3 mg/ml VEGF receptor fusion protein at an interval of about once every 4 weeks; wherein after said 3 doses, administering one or more doses of the VEGF receptor fusion protein at an interval which is lengthened up to about 24 weeks.

5. A method for slowing the clearance of free aflibercept from the ocular compartment after an intravitreal injection relative to the rate of clearance of aflibercept from the ocular compartment after an intravitreal injection of 2 mg or ≤4 mg aflibercept comprising
intravitreally injecting into an eye of a subject in need thereof,
a single initial dose of about 8 mg (±0.8 mg)or more of aflibercept, followed by
one or more secondary doses of about 8 mg (±0.8 mg) or more of the aflibercept, followed by
one or more tertiary doses of about 8 mg (±0.8 mg) or more of the aflibercept;
wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered about 8-24, 12-24, 16-24, 20-24, 21-24, 21, 22, 23 or 24 weeks after the immediately preceding dose.

6. The method of any one of claims 1-5 wherein the clearance of free aflibercept from the ocular compartment is about 34% slower than that from the ocular compartment after an intravitreal injection of 2 or ≤4 mg aflibercept.

7. The method of any one of claims 1-6 wherein the clearance of free aflibercept from the ocular compartment is about 0.37-0.46 mL/day or 0.41 mL/day after an intravitreal injection of ≥8 mg (±0.8 mg) aflibercept.

8. A method for increasing the duration of efficacy and/or the time for the amount of free aflibercept to reach the lower limit of quantitation (LLOQ) in the ocular compartment of a subject after an intravitreal injection of aflibercept, relative to the time to reach LLOQ of the amount of free aflibercept in the ocular compartment of a subject after an intravitreal injection of about 2 mg or ≤4 mg aflibercept, comprising intravitreally injecting into an eye of a subject in need thereof,
a single initial dose of about 8 mg (±0.8 mg) or more of aflibercept, followed by
one or more secondary doses of about 8 mg (±0.8 mg) or more of the aflibercept, followed by
one or more tertiary doses of about 8 mg (±0.8 mg) or more of the aflibercept;
wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered about 8-24, 12-24, 16-24, 20-24, 21-24, 21, 22, 23 or 24 weeks after the immediately preceding dose.

9. The method of any one of claims 1-8 wherein the duration of efficacy and/or the time for the amount of free aflibercept to reach the lower limit of quantitation (LLOQ) in the ocular compartment of a subject after said intravitreal injection of aflibercept is increased by about 5 or 6 weeks, relative to the time to reach LLOQ of the amount of free aflibercept in the ocular compartment of a subject after an intravitreal injection of about 2 or ≤4 mg aflibercept.

10. The method of any one of claims 1-9 wherein the time for the amount of free aflibercept to reach the lower limit of quantitation (LLOQ) in the ocular compartment of a subject after said intravitreal injection of aflibercept is increased by more than about 1, 2, 1.2 or 1.3 weeks relative to the time to reach LLOQ of free aflibercept in the ocular compartment of a subject after an intravitreal injection of about 2 or ≤4 mg aflibercept.

11 The method of any one of claims 1-10 wherein the time for the amount for free aflibercept to reach the lower limit of quantitation (LLOQ) in the ocular compartment of a subject after said intravitreal injection of ≥8 mg (±0.8 mg) aflibercept is about 15 weeks.

12. The method of any one of claims 1-11 wherein the time for the amount of free aflibercept to reach the lower limit of quantitation (LLOQ) in the ocular compartment of a subject after said intravitreal injection of ≥8 mg (±0.8 mg) aflibercept is greater than about 8, 8.7, 8.71, 9, 9.2, 9.21 or 10 weeks.

13. A method for increasing the time for free aflibercept to reach the lower limit of quantitation (LLOQ) in the plasma of a subject after an intravitreal injection of aflibercept relative to the time to reach LLOQ of free aflibercept in the plasma of a subject after an intravitreal injection of about 2 or ≤4 mg aflibercept, comprising intravitreally injecting into an eye of a subject in need thereof,
a single initial dose of about 8 mg (±0.8 mg) or more of aflibercept, followed by
one or more secondary doses of about 8 mg (±0.8 mg) or more of the aflibercept, followed by
one or more tertiary doses of about 8 mg (±0.8 mg) or more of the aflibercept;
wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered about 8-24, 12-24, 16-24, 20-24, 21-24, 21, 22, 23 or 24 weeks after the immediately preceding dose.

14. The method of claim 13 wherein said LLOQ of free aflibercept measured in plasma is about 0.0156 mg/L.

15. The method of any one of claims 1-14 wherein the time for free aflibercept to reach the lower limit of quantitation (LLOQ) in the plasma of a subject after said intravitreal injection of aflibercept is increased by about 2 weeks relative to the time to reach LLOQ of free aflibercept in the plasma of a subject after an intravitreal injection of about 2 mg aflibercept.

16. The method of any one of claims 1-15 wherein the time for free aflibercept to reach the lower limit of quantitation (LLOQ) in the plasma of a subject after said intravitreal injection of ≥8 mg (±0.8 mg) aflibercept is about 3, 3.5, 3.8 or 4 weeks.

17. The method of any one of claims 1-16 wherein the time for free aflibercept to reach the lower limit of quantitation (LLOQ) in the plasma of a subject after said intravitreal injection of ≥8 mg (±0.8 mg) aflibercept is greater than about 1.5 or 1.6 weeks.

18. The method of any one of claims 5-17 wherein ≤4mg is about 2 mg or 2-4 mg.

19. The method of any one of claims 13-18 wherein the subject suffers from an angiogenic eye disorder, neovascular age related macular degeneration, diabetic retinopathy and/or diabetic macular edema.

20. The method of any one of claims 1-19 wherein the ≥8 mg (±0.8 mg) aflibercept is in an aqueous pharmaceutical formulation comprising histidine-based buffer.

21. The method of any one of claims 1-20 wherein the ≥8 mg (±0.8 mg) aflibercept is in an aqueous pharmaceutical formulation comprising arginine.

22.The method of any one of claims 1-21 wherein the ≥8 mg (±0.8 mg) aflibercept is in an aqueous pharmaceutical formulation having a pH of about 5.8.

23.The method of any one of claims 1-22 wherein the ≥8 mg (±0.8 mg) aflibercept is in an aqueous pharmaceutical formulation comprising a sugar or polyol.

24.The method of any one of claims 1-23 wherein the ≥8 mg (±0.8 mg) aflibercept is in an aqueous pharmaceutical formulation comprising a sucrose.

25.The method of any one of claims 1-24 wherein the ≥8 mg (±0.8 mg) aflibercept is in an aqueous pharmaceutical formulation wherein the aflibercept has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8°C.

26. The method of any one of claims 1-25 wherein the ≥8 mg (±0.8 mg) aflibercept is in an aqueous pharmaceutical formulation comprising an aqueous pharmaceutical formulation comprising: at least about 100 mg/ml of a VEGF receptor fusion protein comprising two polypeptides that each comprises an immunoglobin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2, and a multimerizing component; about 10-100 mM L-arginine; sucrose; a histidine-based buffer; and a surfactant; wherein the formulation has a pH of about 5.0 to about 6.8; wherein the VEGF receptor fusion protein has less than about 3.5% high molecular weight

species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8°C.

27. A method
- for treating or preventing an angiogenic eye disorder, neovascular age related macular degeneration (nAMD), diabetic retinopathy (DR) and/or diabetic macular edema (DME), in a subject in need thereof,
- for improving best corrected visual acuity in a subject in need thereof with nAMD, DR and/or DME; or
- for promoting retinal drying in a subject with an angiogenic eye disorder, nAMD, DR and/or DME in need thereof;
comprising administering to an eye of the subject,
a single initial dose of about 8 mg (±0.8 mg) or more of a VEGF receptor fusion protein, followed by
one or more secondary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein, followed by
one or more tertiary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein;
wherein each secondary dose is administered about 2, 3, 4 or 2-4 weeks after the immediately preceding dose; and
each tertiary dose is administered about 8-23, 20, 21, 22, or 23 weeks after the immediately preceding dose, wherein if the subject exhibits:
1. <5 letter loss in BCVA;
2. CRT <300 µm or <320 µm;
3. No fluid at the central subfield on OCT; and/or
4. No new onset foveal hemorrhage or foveal neovascularization;
lengthening the interval between tertiary doses by one or more weeks.

28. The method of claim 27 wherein the interval between tertiary doses was lengthened one or more times prior.

29. The method of claim 27-28 wherein the interval between tertiary doses was lengthened one or more times prior,
to 24 weeks;

or, from:
8 weeks to 12, 16 or 20 weeks;
12 weeks to 16 or 20; and/or
16 weeks to 20 weeks.

30. The method of any one of claims 27-29 wherein lengthening the interval between tertiary doses by one or more weeks is lengthening the interval between tertiary doses by one or more 4 week increments.

31. The method of any one of claims 27-30 wherein said 8-23 weeks is 8, 12, 16 or 20 weeks.

32. The method of claim 31 wherein said 8-23 weeks is 20 weeks.

33. The method of any one of claims 27-32 wherein said interval between tertiary doses is lengthened if the subject exhibits
1. <5 letter loss in BCVA; and
2. CRT <300 μm or <320 μm.

34. The method of claim 33 wherein the subject has DR and/or DME.

35. The method of any one of claims 27-32 wherein said interval between tertiary doses is lengthened if the subject exhibits
1. BCVA loss <5 letters; and
2. No fluid at the central subfield; and
3. No new onset foveal hemorrhage or foveal neovascularization.

36. The method of claim 35 wherein the subject has nAMD.

37. The method of any one of claims 27-36 wherein said:
- <5 letter loss in BCVA is <5 letter loss in BCVA from week 12 from treatment initiation;
- CRT <300 μm or <320 μm is from SD-OCT;
- CRT <300 μm is from Cirrus SD-OCT;
- CRT <320 μm is from Spectralis SD-OCT; and/or
- No fluid at the central subfield is on OCT.

38. A method
- for treating or preventing an angiogenic eye disorder, neovascular age related macular degeneration (nAMD), diabetic retinopathy (DR) and/or diabetic macular edema (DME), in a subject in need thereof,
- for improving best corrected visual acuity in a subject in need thereof with nAMD, DR and/or DME; or
- for promoting retinal drying in a subject with an angiogenic eye disorder, nAMD, DR and/or DME in need thereof;
comprising administering to an eye of the subject,
a single initial dose of about 8 mg (±0.8 mg) or more of a VEGF receptor fusion protein, followed by
one or more secondary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein, followed by
one or more tertiary doses of about 8 mg (±0.8 mg) or more of the VEGF receptor fusion protein;
wherein each secondary dose is administered about 2 to 4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered about 8-24, 12-24, 16-24, 20-24, 21-24, 21, 22, 23 or 24 weeks after the immediately preceding dose wherein if the subject exhibits

1. BCVA loss >5 or >10 letters;
2. >25 μm or >50 μm increase in central retinal thickness (CRT);
3. new foveal hemorrhage;
4. new foveal neovascularization; and/or
5. persistent or worsening DME

shortening the interval between tertiary doses by one or more weeks.

39. The method of claim 38 wherein shortening the interval between tertiary doses by one or more weeks is shortening the interval between tertiary doses by one or more 4 week increments.

40. The method of any one of claims 38-39 wherein said interval between tertiary doses is shortened if the subject exhibits
1. >10 letter loss in BCVA in association with persistent or worsening DME; and
2. >50 μm increase in CRT.

41. The method of claim 40 wherein the subject has DR and/or DME.

42. The method of any one of claims 38-39 wherein said interval between tertiary doses is lengthened if the subject exhibits
1. BCVA loss >5 letters, and
2. >25 µm increase in central retinal thickness (CRT) or new foveal hemorrhage or new foveal neovascularization.

43. The method of claim 42 wherein the subject has nAMD.

44. The method of any one of claims 38-43 wherein said:

- >10 letter loss in BCVA, in association with persistent or worsening DME is >10 letter loss in BCVA from week 12 from treatment initiation or 4 weeks after the last secondary dose, in association with persistent or worsening DME;
- >50 µm increase in CRT is from week 12 from treatment initiation
- BCVA loss >5 letters is from week 12 from treatment initiation, and
- >25 µm increase in central retinal thickness (CRT) or new foveal hemorrhage or new foveal neovascularization is >25 µm increase in central retinal thickness (CRT) from week 12 from treatment initiation or new foveal hemorrhage or new foveal neovascularization.

45. The method of any one or claims 1-44 wherein by week 96 from treatment initiation, the subject exhibits one or more of:

- A BCVA improvement of about 6, 7, 8 or 9 letters;
- A BCVA improvement of 39, 40, 41, 42, 43, 44, 45, 46 or 47 letters;
- Does not lose 5 or more, 10 or more or 15 or more letters BCVA;
- A BCVA of about 65, 66, 67, 68, 69, 70, 71, 72 or 73 letters;
- gains 5 or more, 10 or more or 15 or more letters BCVA;
- 2 or more step improvement in DRSS;
- A decrease in CRT of about 149, 152, 155; 156; 157; 158; 159; 160; 161; 162; 163; 164; 165; 166; 167; 168; 169; 170; 171; 172; 173; 174; 175; 176; 177; 178; 179; 180; 181; 182; 183; 184; 185, 194 micrometers;

- Between week 48 and week 96 of treatment, further improvement or maintenance of BCVA improvement from baseline ± 1 or 2 letters;
- Between week 48 and week 96 of treatment, maintenance of BCVA or about 66 ± 2 letters;
- Between week 48 and week 96 of treatment, maintenance of a fluid-free retinal center subfield;
- A CRT of about 267; 268; 269; 270; 271; 272; 273; 274; 275; 276; 277; 278; 279; 280; 281; 282; 283; 284; 285; 286; 287; 288; 289; 290; 291; 292; 293; 294; 295; 296; 297; 298; 299; 300; 301; 302; 303; or 304 micrometers;
- Between week 48 and week 96 of treatment further reduction or maintenance of central subfield thickness or central retinal thickness reduction from baseline ± 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12; micrometers;
- No IRF;
- No SRF;
- No IRF and no SRF;
- No significant change in intraocular pressure;
- No significant change in systolic blood pressure; and/or
- No significant change in diastolic blood pressure.

46. The method of claim 45 wherein the subject has DR and/or DME.

47. The method of any one or claims 1-46 wherein by week 96 from treatment initiation, the subject exhibits one or more of:

- A BCVA improvement of about 5, 6 or 7 letters;
- A BCVA improvement of 43, 44, 45, 46, 47 or 48 letters;
- A BCVA of 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93 or 94 letters;
- Does not lose 5 or more, 10 or more or 15 or more letters BCVA;
- gains 5 or more, 10 or more or 15 or more letters BCVA;
- 2 or more step improvement in DRSS;
- A decrease in CRT of about 12; 13; 14; 15; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30; 31; 32; 33; 34; 35; 36; 37; 38; 39; 40; 41; 42; 43; 44; 45; 46; 47; 48; 49; 50; 51; 52; 53; 54; 55; 56; 57; 58; 59; 60; 61; 62; 63; 64; 65; 66; 67; 68; 69; 70; 71; 72; 73; 74; 75; 76; 77; 78; 79; 80; 81; 82; 83; 84; 85; 86; 87; 88; 89; 90; 91; 92; 93; 94; 95; 96;

97; 98; 99; 100; 101; 102; 103; 104; 105; 106; 107; 108; 109; 110; 111; 112; 113; 114; 115; 116; 117; 118; 119; 120; 121; 122; 123; 124; 125; 126; 127; 128; 129; 130; 131; 132; 133; 134; 135; 136; 137; 138; 139; 140; 141; 142; 143; 144; 145; 146; 147; 148; 149; 150; 151; 152; 153; 154; 155; 156; 157; 158; 159; 160; 161; 162; 163; 164; 165; 166; 167; 168; 169; 170; 171; 172; 173; 174; 175; 176; 177; 178; 179; 180; 181; 182; 183; 184; 185; 186; 187; 188; 189; 190; 191; 192; 193; 194; 195; 196; 197; 198; 199; 200; 201; 202; 203; 204; 205; 206; 207; 208; 209; 210; 211; 212; 213; 214; 215; 216; 217; 218; 219; 220; 221; 222; 223; 224; 225; 226; 227; 228; 229; 230; 231; 232; 233; 234; 235; 236; 237; 238; 239; 240; 241; 242; 243; 244; 245; 246; 247; 248; 249; 250; 251; 252; 253; 254; 255; 256; 257; 258; 259; 260; 261; 262; 263; 264; 265; 266; 267; 268; 269; 270; 271; 272; 273; 274; 275; 276; 277; 278; 279; 280; 281; 282; 283; 284; 285; 286; 287; 288; 289; 290; 291; 292; 293; or 294 micrometers;

- A CRT of about 156; 157; 158; 159; 160; 161; 162; 163; 164; 165; 166; 167; 168; 169; 170; 171; 172; 173; 174; 175; 176; 177; 178; 179; 180; 181; 182; 183; 184; 185; 186; 187; 188; 189; 190; 191; 192; 193; 194; 195; 196; 197; 198; 199; 200; 201; 202; 203; 204; 205; 206; 207; 208; 209; 210; 211; 212; 213; 214; 215; 216; 217; 218; 219; 220; 221; 222; 223; 224; 225; 226; 227; 228; 229; 230; 231; 232; 233; 234; 235; 236; 237; 238; 239; 240; 241; 242; 243; 244; 245; 246; 247; 248; 249; 250; 251; 252; 253; 254; 255; 256; 257; 258; 259; 260; 261; 262; 263; 264; 265; 266; 267; 268; 269; 270; 271; 272; 273; 274; 275; 276; 277; 278; 279; 280; 281; 282; 283; 284; 285; or 286 micrometers;
- A choroidal neovascularization size decrease of about 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 mm^2;
- A choroidal neovascularization size of about 0, 1, 2 or 3 mm^2;
- No leakage observed on fluorescein angiography;
- Total lesion size of about 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mm^2;
- Decrease in total lesion size of about 0, 0.1, 0.2 or 0.3 mm^2;
- A NEI-VFQ-25 total score of about 80;
- A NEI-VFQ-25 total score change from baseline of about 2 or 3;
- No IRF;
- No SRF;
- No IRF and no SRF;
- No significant change in pre-dose intraocular pressure;
- No significant change in systolic blood pressure; and/or

- No significant change in diastolic blood pressure.

48. The method of claim 47 wherein the subject has nAMD.

49. The method of any one of claims 1-48 wherein a subject having any one or more of
ocular or periocular infection;
active intraocular inflammation; and/or
hypersensitivity;
is excluded from administration of VEGF receptor fusion protein to the eye.

50. The method of claim 49 further comprising a step of
evaluating the subject for:
ocular or periocular infection;
active intraocular inflammation; and/or
hypersensitivity;
and excluding the subject from said administration if any one or more if found in the subject.

51. The method of any one of claims 49-50 further comprising monitoring the subject during said treatment or prevention for conjunctival hemorrhage, cataract, vitreous detachment, vitreous floaters, corneal epithelium defect and/or increased intraocular pressure.

52. The method of any one of claims 1-51 comprising, prior to each administration, providing
- one single-dose glass vial having a protective plastic cap and a stopper containing an aqueous formulation comprising 8 mg (±0.8 mg) VEGF receptor fusion protein in about 70 microliters;
- one 18-gauge x 1½-inch, 5-micron, filter needle that includes a tip and a bevel;
- one 30-gauge x ½-inch injection needle; and
- one 1-mL Luer lock syringe having a graduation line marking for 70 microliters of volume;

packaged together; then
(1) visually inspecting the aqueous formulation in the vial and, if particulates, cloudiness, or discoloration are visible, then using another vial of aqueous formulation containing the VEGF receptor fusion protein;
(2) removing the protective plastic cap from the vial; and

(3) cleaning the top of the vial with an alcohol wipe; then
using aseptic technique:
(4) removing the 18-gauge x 1½-inch, 5-micron, filter needle and the 1 mL syringe from their packaging;
(5) attaching the filter needle to the syringe by twisting it onto the Luer lock syringe tip;
(6) pushing the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or a bottom edge of the vial;
(7) withdrawing all of the VEGF receptor fusion protein vial contents into the syringe, keeping the vial in an upright position, slightly inclined, while ensuring the bevel of the filter needle is submerged into the liquid;
(8) continuing to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the formulation;
(9) drawing the plunger rod sufficiently back when emptying the vial in order to completely empty the filter needle;
(10) removing the filter needle from the syringe and disposing of the filter needle;
(11) removing the 30-gauge x ½-inch injection needle from its packaging and attaching the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip;
(12) holding the syringe with the needle pointing up, and checking the syringe for bubbles, wherein if there are bubbles, gently tapping the syringe with a finger until the bubbles rise to the top; and
(13) slowly depressing the plunger so that the plunger tip aligns with the graduation line that marks 70 microliters on the syringe.

53. The method of any one of claims 1-52 wherein injection of VEGF receptor fusion protein is performed under controlled aseptic conditions, which comprise surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) and anesthesia and a topical broad–spectrum microbicide are administered prior to the injection.

54. The method of any one of claims 1-53, wherein the VEGF receptor fusion protein comprises amino acids 27-457 of the amino acid sequence set forth in SEQ ID NO: 2.

55. The method of any one of claims 1-53, wherein the VEGF receptor fusion protein is selected from the group consisting of: aflibercept and conbercept.

56. The method of any one of claims 1-53, wherein the VEGF receptor fusion protein:
(i) comprises two polypeptides that comprise (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO: 2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO: 2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO: 2;
(ii) comprises two polypeptides that comprise an immunoglobin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component;
(iii) comprises two polypeptides that comprise an immunoglobin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of VEGFR2, an Ig domain 4 of VEGFR2 and a multimerizing component; or
(iv) comprises two VEGFR1R2-FcΔC1(a) polypeptides encoded by the nucleic acid sequence of SEQ ID NO: 1.

57. The method of claim 1-53, wherein the VEGF receptor fusion protein comprises two polypeptides that comprise an immunoglobin-like (Ig) domain 2 of VEGFR1, an Ig domain 3 of a VEGFR2, and a multimerizing component.

58. The method of any one of claims 1-57, wherein the VEGF receptor fusion protein is in an aqueous pharmaceutical formulation selected from the group consisting of A-KKKK.

59. The method of any one of claims 1-58 wherein said VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising about 114.3 mg/ml VEGF receptor fusion protein.

60. The method of any one of claims 1-59 comprising administering the VEGF receptor fusion protein to both eyes of the subject.

61. The method of any one of claims 1-60, wherein the VEGF receptor fusion protein is administered from a syringe or pre-filled syringe.

62. The method of claim 61, wherein the syringe or pre-filled syringe is glass or plastic, and/or sterile.

63. The method of any one of claims 1-62 wherein the VEGF receptor fusion protein is intravitreally injected with a 30 gauge × ½-inch sterile injection needle.

64. The method of any one of claims 1-63 wherein the subject has previously received one or more doses of 2 mg VEGF receptor fusion protein.

65. The method of any one of claims 1-64 wherein one or more further doses of VEGF receptor fusion protein are administered.

66. The method of any one of claims 5-26, 64 or 65 wherein 2 mg VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising 40 mg/ml VEGF receptor fusion protein.

67. The method of claim 5-26 or 64-66 wherein 2 mg of VEGF receptor fusion protein is in a pharmaceutical formulation comprising:
40 mg/ml VEGF receptor fusion protein, 10 mM sodium phosphate, 40 mM NaCl, 0.03% polysorbate 20 and 5% sucrose, with a pH of 6.2.

68 The method of any one of claims 1-67 wherein ≥8 mg (±0.8 mg) of VEGF receptor fusion protein is in an aqueous pharmaceutical formulation that comprises a sugar or polyol.

69. The method of any one of claims 1-68 wherein ≥8 mg (±0.8 mg) VEGF receptor fusion protein in an aqueous pharmaceutical formulation that comprises sucrose.

70. The method of any one of claims 1-69 wherein ≥8 mg (±0.8 mg) of a VEGF receptor fusion protein is in an aqueous pharmaceutical formulation that has a pH of about 5.8.

71. The method of any one of claims 1-70 wherein ≥8 mg (±0.8 mg) of a VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising about 103-126 mg/ml VEGF receptor fusion protein, histidine-based buffer and arginine.

72. The method of any one of claims 1-71 wherein ≥8 mg (±0.8 mg) of a VEGF receptor fusion protein is an aqueous pharmaceutical formulation comprising about 114.3 mg/ml VEGF receptor fusion protein, histidine-based buffer and arginine.

73. The method of any one of claims 1-72 wherein the ≥8 mg (±0.8 mg) aflibercept is in an aqueous pharmaceutical formulation wherein the aflibercept has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8° C.

74. The method of any one of claims 1-73 wherein the ≥8 mg VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising:
at least about 100 mg/ml of a VEGF receptor fusion protein;
about 10-100 mM L-arginine;
sucrose;
a histidine-based buffer; and
a surfactant;
wherein the formulation has a pH of about 5.0 to about 6.8; wherein the VEGF receptor fusion protein has less than about 3.5% high molecular weight species immediately after manufacture and purification and/or less than or equal to about 6% high molecular weight species after storage for about 24 months at about 2-8°C.

75. The method of claim 1-74 wherein ≥ about 8 mg (±0.8 mg) of VEGF receptor fusion protein is in an aqueous pharmaceutical formulation comprising

- ≥100 mg/ml VEGF receptor fusion protein, histidine-based buffer and L-arginine;
- 140 mg/ml aflibercept; 20 mM histidine-based buffer; 5 % sucrose; 0.03 % polysorbate 20; 10 mM L-arginine; pH 5.8;
- 150 ± 15 mg/ml aflibercept, 10 mM phosphate-based buffer, 8 ± 0.8% (w/v) sucrose, 0.02-0.04% (w/v) polysorbate 20 and 50 mM L-arginine, pH 5.9-6.5;
- 103-126 mg/ml aflibercept, 10 ± 1 mM histidine-based buffer, 5 ± 0.5% (w/v) sucrose, 0.02-0.04% (w/v) polysorbate 20, and 50 ± 5 mM L-arginine, pH 5.5-6.1;
- 140 mg/ml aflibercept, 10 mM histidine-based buffer, 2.5 % (w/v) sucrose, 2.0 % (w/v) proline, 0.03 % (w/v) polysorbate 20 and 50 mM L-arginine, pH 5.8;
- 114.3 mg/ml aflibercept, 10 mM histidine-based buffer, 5% (w/v) sucrose, 0.03% (w/v) polysorbate 20 and 50 mM L-arginine, pH 5.8;
- ≥100 mg/ml aflibercept, histidine-based buffer and L-arginine;

- ≥100 mg/ml aflibercept at about pH 5.8, wherein the formulation forms <3% HMW aggregates after incubation at 5°C for 2 months;
- About 114.3 mg/mL aflibercept; 10 mM – 50 mM histidine-based buffer, sugar, non-ionic surfactant, L-Arginine, pH 5.8; or
- About 114.3 mg/mL aflibercept; 10 mM His/His-HCl-based buffer, 5% sucrose, 0.03% polysorbate-20, 50 mM L-Arginine, pH 5.8.

76. The method of any one of claims 1-75 wherein the ≥8 mg (±0.8 mg) of VEGF receptor fusion protein is administered in a volume of about 100 μl or less, about 75 μl or less; about 70 μl or less; or about 50 μl; 51 μl; 52 μl; 53 μl; 54 μl; 55 μl; 56 μl; 57 μl; 58 μl; 59 μl; 60 μl; 61 μl; 62 μl; 63 μl; 64 μl; 65 μl; 66 μl; 67 μl; 68 μl; 69 μl; 70 μl; 71 μl; 72 μl; 73 μl; 74 μl; 75 μl; 76 μl; 77 μl; 78 μl; 79 μl; 80 μl; 81 μl; 82 μl; 83 μl; 84 μl; 85 μl; 86 μl; 87 μl; 88 μl; 89 μl; 90 μl; 91 μl; 92 μl; 93 μl; 94 μl; 95 μl; 96 μl; 97 μl; 98 μl; 99 μl; or 100 μl.

77. The method of claim 76 wherein said VEGF receptor fusion protein is administered in a volume of about 70 ± 4 or 5 microliters.

78. The method of any one of claims 1-77 wherein the interval between doses are adjusted (increased/maintained/reduced) based on visual and/or anatomic outcomes.

79. The method of any one of claims 1-78 further including one or more periods of *pro re nata* (PRN), capped PRN or treat and extend (T&E) dosing.

80. The method of any one of claims 1-79 wherein the VEGF receptor fusion protein is aflibercept.

81. The method of any one of claims 1-80 wherein the subject is treated for at least 96 weeks.

82. The method of any one of claims 1-81 wherein the VEGF receptor fusion protein is administered by intraocular or intravitreal injection.