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Aflibercept and Associated Biosimilar(s)

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Related Policies (if applicable)
OTH903.015: Photodynamic Therapy for Choroidal Neovascularization
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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Eylea®

Continuation Therapy

Continuation of aflibercept (Eylea®) therapy **may be considered medically necessary** for all members (including new members):

- Who are currently receiving the requested medication; AND
- Who are experiencing benefit from therapy as evidenced by disease stability or disease improvement; AND
- When dosing is in accordance with an authoritative source.

Initial Therapy

Intravitreal injection of aflibercept (Eylea®) **may be considered medically necessary** contingent on the following coverage criteria:

- Individual has tried and failed, or has a clinical reason to avoid, or there is a documented drug shortage or recalls from a wholesaler, manufacturer, the ASHP (American Hospital of Health-System Pharmacist) Drug Shortage web page or the US Food and Drug Administration of intravitreal injection(s) of bevacizumab (Avastin™) as an anti-VEGF (vascular endothelial growth factor) therapy for the following conditions:
    - Diabetic macular edema, or macular edema following retinal vein occlusion (RVO) (central retinal vein occlusion [CRVO] and branch retinal vein occlusion [BRVO]);
    - Diabetic retinopathy (DR)
    - Treatment of neovascular (wet) age-related macular degeneration (AMD);
    - Retinopathy of prematurity (ROP)
    - Treatment of choroidal neovascularization (CNV; includes myopic CNV or mCNV) due to:
        - Angioid streaks,
        - Central serous chorioretinopathy,
        - Choroidal retinal neovascularization, secondary to pathologic myopia,
        - Choroidal retinal neovascularization, degenerative progressive high myopia,
        - Choroidal rupture or trauma,
        - Idiopathic choroidal neovascularization,
        - Multifocal choroiditis,
        - Pathologic myopia,
        - Presumed ocular histoplasmosis syndrome, or
        - Uveitis.

Eylea® HD

Continuation Therapy

Continuation therapy of aflibercept (Eylea® HD) **may be considered medically necessary** for all members (including new members):

- Who are currently receiving the requested medication; AND
- Who are experiencing benefit from therapy as evidenced by disease stability or disease improvement; AND
- When dosing is in accordance with an authoritative source.

Initial Therapy

Intravitreal injection of aflibercept (Eylea® HD) **may be considered medically necessary** contingent on the following coverage criteria:

- Individual has tried and failed, or has a clinical reason to avoid, or there is a documented drug shortage or recalls from a wholesaler, manufacturer, the ASHP (American Hospital of Health-System Pharmacist) Drug Shortage web page or the US Food and Drug Administration of intravitreal injection(s) of bevacizumab (Avastin™) as an anti-VEGF (vascular endothelial growth factor) therapy for the following conditions:
    - Neovascular (Wet) Age-Related Macular Degeneration (nAMD);
    - Diabetic Macular Edema (DME);
    - Diabetic Retinopathy (DR).

Pavblu™

Continuation Therapy

Continuation therapy of aflibercept-ayyh (Pavblu™) **may be considered medically necessary** for all members (including new members):

- Who are currently receiving the requested medication; AND
- Who are experiencing benefit from therapy as evidenced by disease stability or disease improvement; AND
- When dosing is in accordance with an authoritative source.

Initial Therapy

Intravitreal injection of aflibercept-ayyh (Pavblu™) **may be considered medically necessary** contingent on the following coverage criteria:

- Individual has tried and failed, or has a clinical reason to avoid, or there is a documented drug shortage or recalls from a wholesaler, manufacturer, the ASHP (American Hospital of Health-System Pharmacist) Drug Shortage web page or the US Food and Drug Administration of intravitreal injection(s) of bevacizumab (Avastin™) as an anti-VEGF (vascular endothelial growth factor) therapy for the following conditions:
    - Neovascular (Wet) Age-Related Macular Degeneration (nAMD);
    - Macular edema following retinal vein occlusion;
    - Diabetic Macular Edema (DME);
    - Diabetic Retinopathy (DR).

Intravitreal injection of aflibercept (Eylea®, Eylea® HD) or aflibercept-ayyh (Pavblu™) **is considered experimental, investigational and/or unproven** for the treatment of all other ophthalmological indications.

Policy Guidelines

None.

Description

NOTE 1: Several different anti-VEGF (vascular endothelial growth factor) agents are mentioned throughout the policy. However, the focus of this policy is specific to the use of aflibercept (Eylea® or Eylea® HD) rather than the other agents that may be mentioned. Please refer to other policies for information on those agents as listed in the Related Policies (if applicable) section above.

Angiogenesis inhibitors (e.g., ranibizumab, bevacizumab, pegaptanib, aflibercept, brolucizumab-dbll) are being evaluated for the treatment of disorders of choroidal circulation. Ophthalmic disorders affecting the choroidal circulation include age-related macular degeneration (ARMD), central serous chorioretinopathy (CSC), pathologic myopia, presumed ocular histoplasmosis syndrome, angioid streaks, idiopathic choroidal neovascularization (CNV), uveitis, choroidal rupture or trauma, retinopathy of prematurity (ROP), and chorioretinal scars.

Background
Vascular endothelial growth factor (VEGF) has been implicated in the pathogenesis of a variety of ocular vascular conditions characterized by CNV and macular edema. The macula, with the fovea at its center, has the highest photoreceptor concentration and is where visual detail is discerned. VEGF has been implicated in the pathogenesis of a variety of ocular vascular conditions characterized by neovascularization (including CNV) and macular edema. Anti-VEGF agents are also being evaluated for the treatment of disorders of retinal circulation (e.g., diabetic retinopathy, retinal vein occlusion, and retinopathy of prematurity). Other therapeutic options may include photodynamic therapy (PDT), antioxidants, and thermal laser photocoagulation. The safety and efficacy of each treatment depends on the form and location of the neovascularization. Angiostatic agents block some stage in the pathway leading to new blood vessel formation (angiogenesis). In contrast to palliative treatments for CNV (e.g., thermal photocoagulation and PDT), they are potentially disease modifying by inhibiting the development of newly formed vessels.

For the treatment of ocular disorders, these agents are given by intravitreal injection every 1 to 2 months. The distinct pharmacologic properties of available VEGF inhibitors suggest that safety and efficacy data from one agent cannot be extrapolated to another. These agents may vary by penetration, potency, half-life, localization to the retina, and initiation of the immune system.

Bevacizumab is a full-length anti-VEGF antibody derived from the same murine monoclonal antibody precursor as ranibizumab and inhibits all isoforms of VEGF-A.

Age-Related Macular Degeneration (AMD or ARMD)

Neovascular AMD is characterized by CNV, which is the growth of abnormal choroidal blood vessels beneath the macula, which causes severe loss of vision and is responsible for most of the loss of vision caused by AMD. In its earliest stages, AMD is characterized by minimal visual impairment and the presence of large drusen and other pigmentary abnormalities on ophthalmoscopic examination. As AMD progresses, 2 distinctively different forms of degeneration may be observed. The first, called the atrophic or areolar or dry form, evolves slowly. Atrophic AMD is the most common form of degeneration and is often a precursor of the second form, the more devastating exudative neovascular form, also referred to as disciform or wet degeneration. The wet form is distinguished from the atrophic form by serous or hemorrhagic detachment of the retinal pigment epithelium and the development of CNV, sometimes called neovascular membranes. Risk of developing severe irreversible loss of vision is greatly increased by the presence of CNV. The pattern of CNV, as revealed by fluorescein or indocyanine angiography, is further categorized as classic or occult. For example, classic CNV appears as an initial lacy pattern of hyperfluorescence followed by more irregular patterns as the dye leaks into the subretinal space. Occult CNV lacks the characteristic angiographic pattern, either due to the opacity of coexisting subretinal hemorrhage or, especially in CNV associated with AMD, by a tendency for epithelial cells to proliferate and partially or completely surround the new vessels. Interestingly, lesions consisting only of classic CNV carry a worse visual prognosis than those made up of only occult CNV, suggesting that the proliferative response that obscures new vessels may also favorably alter the clinical course of AMD.

Intravitreal triamcinolone acetonide is one of the first pharmacologic compounds evaluated for the treatment of CNV secondary to AMD. The most important effects of this treatment consist of the stabilization of the blood-retinal barrier and the down-regulation of inflammation. Triamcinolone acetonide also has antiangiogenic and anti-fibrotic properties and remains active for months after intravitreal injection. However, cataracts are a common adverse effect, and steroid-related pressure elevation occurs in approximately one third of patients, with some requiring filtration surgery.

Photodynamic therapy (PDT) is a treatment modality designed to selectively occlude ocular choroidal neovascular tissue. The therapy is a 2-step process, consisting initially of an injection of the photosensitizer verteporfin, followed 15 minutes later by laser treatment to the targeted sites of neovascularization in the retina. The laser treatment selectively damages the vascular endothelium. Patients may be retreated if leakage from CNV persists. Combination therapy with PDT and VEGF antagonists is being investigated. Refer to OTH903.015, Photodynamic Therapy (PDT) for Choroidal Neovascularization (CNV), for coverage information.

Before the availability of angiostatic agents and PDT, CNV was treated with photocoagulation using either argon, green, or infrared lasers. This conventional photocoagulation was limited to extrafoveal lesions due to the risk of retinal burns. Introduction of a scotoma or enlargement of

a pre-existing scotoma, with or without visual acuity loss, is an immediate and permanent effect of photocoagulation surgery. Because of the loss of vision associated with laser photocoagulation, photocoagulation is no longer recommended as the initial treatment of sub-foveal neovascularization.

Polypoidal Choroidal Vasculopathy (PCV)

PCV is characterized by the presence of a branching vascular network with terminal, polyp-like aneurismal dilations. Some investigators consider PCV to be a subtype of AMD, while others suggest that the lesions, when sub-macular, can be mistaken for AMD. PCV is more common in Asian compared with white populations. Both PDT and ranibizumab have been used to treat PCV; although the optimal treatment for PCV may differ from that for AMD.

Central Serous Chorioretinopathy (CSC)

CSC is the fourth most common retinopathy after AMD, diabetic retinopathy, and branch retinal vein occlusion. CSC refers to an idiopathic disease in which there is a serious detachment of the macula due to leakage of fluid from the choriocapillaris through the retinal pigment epithelium. CSC can be divided into acute, recurrent, and chronic conditions. Usually, serous retinal detachments have spontaneous resolution with recovery of visual function; however, a subset of patients may experience permanent deterioration of visual function attributable to chronic CSC or multiple recurrences of CSC. The pathogenesis of CSC is believed to be ischemia and inflammation, which lead to abnormal permeability of the inner choroid and elevation of the retinal pigment epithelium, causing serous epithelial detachments. The separated retinal pigment epithelium can then undergo tiny rips (blowouts) with a break in continuity. The change in permeability of the retinal pigment epithelium results in focal leakage and retinal detachment. Neovascularization can occur as a secondary complication. In about 90% of cases, CSC resolves spontaneously with detachment resolution within 3 months. The traditional management of acute CSC is observation. Recurring or chronic CSC can be treated with focal laser photocoagulation if the leaks are extrafoveal. Although laser may shorten the duration of symptoms, it does not have any impact on the final vision or the recurrence rate of CSC. In addition, laser photocoagulation causes collateral damage creating symptomatic scotomas and a risk of triggering secondary CNV. PDT is not a standard treatment for CSC due to complications that may include CNV, although low-fluence PDT is being evaluated.

Other Causes of CNV

Other causes of CNV include pathologic myopia, presumed ocular histoplasmosis syndrome, angioid streaks, idiopathic CNV, uveitis, choroidal rupture or trauma, and chorioretinal scars. Treatments that have been evaluated for CNV not related to AMD include sub-macular surgery, laser photocoagulation, and PDT. Efficacy of these treatment modalities is limited.

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)

Diabetic retinopathy (DR) is a common microvascular complication of diabetes and a leading cause of blindness in adults. The 2 most serious complications for vision in patients with diabetes are DME and DR. At its earliest stage, microaneurysms occur. With disruption of the blood-retinal barrier, macular retinal vessels become permeable, leading to exudation of serous

fluid and lipids into the macula (macular edema). As the disease progresses, blood vessels that provide nourishment to the retina are blocked, triggering the growth of new and fragile blood vessels (proliferative retinopathy). Severe vision loss with proliferative retinopathy arises from vitreous hemorrhage. Moderate vision loss can also arise from macular edema (fluid accumulating in the center of the macula) during the proliferative or non-proliferative stages of the disease. Although proliferative disease is the main blinding complication of DR, macular edema is more frequent and is the leading cause of moderate vision loss in people with diabetes.

Tight glycemic and blood pressure control is the first line of treatment to control DME and DR, followed by laser photocoagulation for patients whose retinopathy is approaching the high-risk stage. Although laser photocoagulation is effective at slowing the progression of retinopathy and reducing vision loss, it results in collateral damage to the retina and does not restore lost vision. Focal macular edema (characterized by leakage from discrete microaneurysms on fluorescein angiography) may be treated with focal laser photocoagulation, while diffuse macular edema (characterized by generalized macular edema on fluorescein angiography) may be treated with grid laser photocoagulation. Corticosteroids may reduce vascular permeability and inhibit VEGF production but are associated with serious adverse effects including cataracts and glaucoma with damage to the optic nerve. Corticosteroids can also worsen diabetes control. VEGF inhibitors (e.g., ranibizumab, bevacizumab, aflibercept, pegaptanib), which reduce permeability and block the pathway leading to new blood vessel formation (angiogenesis) are being evaluated for the treatment of DME and proliferative DR. For DME, outcomes of interest include macular thickness and visual acuity. For proliferative and non-proliferative DR, outcomes of interest are operative and perioperative outcomes and visual acuity.

Central (CRVO) and Branch Retinal Vein Occlusions (BRVO)

Retinal vein occlusions are classified by whether there is a CRVO or BRVO. CRVO is also categorized as ischemic or nonischemic. Ischemic CRVO is associated with a poor visual prognosis, with macular edema and permanent macular dysfunction occurring in virtually all patients. Nonischemic CRVO has a better visual prognosis, but many patients will have macular edema, and it may convert to the ischemic type within 3 years. Most of the vision loss associated with CRVO results from the main complications, macular edema and intraocular neovascularization. BRVO is a common retinal vascular disorder in adults between 60 and 70 years of age and occurs approximately 3 times more commonly than CRVOs. Macular edema is the most significant cause of central vision loss in BRVO. Patients with ischemic CRVO may go on to develop neovascular glaucoma due to neovascularization of the iris and/or the anterior chamber angle.

Retinal vein occlusions are associated with increased venous and capillary pressure and diminished blood flow in the affected area, with a reduced supply of oxygen and nutrients. The increased pressure causes water flux into the tissue while the hypoxia stimulates the production of inflammatory mediators such as VEGF, which increases vessel permeability and induces new vessel growth. Intravitreal corticosteroid injections or implants have been used to

treat the macular edema associated with retinal vein occlusions, with a modest beneficial effect on visual acuity. However, cataracts are a common adverse effect, and steroid-related pressure elevation occurs in about one-third of patients, with some requiring filtration surgery. Macular grid photocoagulation has also been used to improve vision in BRVO but is not recommended for CRVO. The serious adverse effects of available treatments have stimulated the evaluation of new treatments, including intravitreal injection of VEGF inhibitors. Outcomes of interest for retinal vein occlusions are macular thickness and visual acuity.

Retinopathy of Prematurity (ROP) (1)

ROP is a neovascular retinal disorder that primarily affects premature infants of low birth weight. It is one of the most common causes of childhood blindness in the United States. Typically, retinal vascularization begins at the optic nerve when the eye begins to develop (16 weeks of gestation) and reaches the edge of the retina at 40 weeks of gestation. If an infant is born prematurely, normal vessel growth may stop, followed by neovascularization at the interface between the vascular and avascular retinal areas. Stages of ROP are defined by vessel appearance and the level of retinal detachment, ranging from mild (stage I) to severe (stage V). Stage I or stage II ROP may resolve on its own. The optimal time for treatment is stage III when a ridge with neovascularization extends into the vitreous gel. The neovascularization may progress and form fibrous scar tissue that causes partial (stage IV) or total retinal detachment (stage V), accompanied by loss of vision. Both cryotherapy and laser therapy have been used to slow or reverse the abnormal growth of blood vessels in the peripheral areas of the retina. While successful in about 50% of cases, these treatments can cause myopia and permanent loss of the peripheral field of vision. Vitrectomy may be needed when cryotherapy or laser therapy fails to induce regression.

In the day(s) following Eylea administration, patients may experience temporary visual disturbances, endophthalmitis and/or retinal detachment. (1) If the eye becomes red, sensitive to light, painful, or develops a change in vision, the patient and/or caregiver should seek immediate care from an ophthalmologist. In infants with ROP, treatment with Eylea will necessitate extended periods of ROP monitoring.

Other Retinal Vascular Conditions

Other retinal vascular conditions that are being evaluated for treatment with VEGF inhibitors are cystoid macular edema resulting from vasculitis, Coats disease, Eales disease, idiopathic macular telangiectasia type II, neovascularization of the iris/neovascularization of the angle/neovascular glaucoma, pseudoxanthoma elasticum, radiation retinopathy, retinal neovascularization, rubeosis, von Hippel-Lindau, and vitreous hemorrhage secondary to retinal neovascularization.

Regulatory Status

Eylea®

In 2011, Eylea® (Regeneron) was originally approved by the FDA for the treatment of wet (neovascular) AMD and is administered by intravitreal injections every 4 or 8 weeks. Additional FDA indications were granted as follows:

- Diabetic macular edema (2014);
- Macular edema following retinal vein occlusion (2014);
- Diabetic retinopathy in patients with diabetic macular edema (2015);
- Diabetic retinopathy (2019); and
- Retinopathy of prematurity (2023). (5)

Eylea® HD

In 2023, Eylea® HD was originally approved by the FDA for the treatment of individuals with neovascular (wet) age-related macular degeneration (nAMD); diabetic macular edema (DME); and diabetic retinopathy (DR). (6)

Pavblu™

In 2024, Pavblu™ (aflibercept-ayyh) was approved by the FDA for the treatment of individuals with:

- Neovascular (Wet) Age-Related Macular Degeneration (nAMD);
- Macular edema following retinal vein occlusion;
- Diabetic Macular Edema (DME);
- Diabetic Retinopathy (DR). (7)

Rationale

This policy was developed in 2014 and is based on the clinical studies provided to the U.S. Food and Drug Administration (FDA) for consideration of approval. (1, 6-7)

Eylea® and Pavblu™

Neovascular (Wet) Age-Related Macular Degeneration (AMD) (1, 7**)**

The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, active-controlled studies in patients with wet AMD. A total of 2412 patients were treated and evaluable for efficacy (1817 with aflibercept) in the two studies (VIEW1 and VIEW2). In each study, up to week 52, patients were randomly assigned in a 1:1:1:1 ratio to 1 of 4 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 3 initial monthly doses (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); 3) aflibercept 0.5 mg administered every 4 weeks (aflibercept 0.5Q4); and 4) ranibizumab administered 0.5 mg every 4 weeks (ranibizumab 0.5 mg Q4). Protocol-specified visits occurred every 28±3 days. Patient ages ranged from 49 to 99 years with a mean of 76 years.

In both studies, the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at week 52 compared to baseline. Both aflibercept 2Q8 and aflibercept 2Q4 groups were shown to have efficacy that was clinically equivalent to the ranibizumab 0.5 mg Q4 group in year 1.

Detailed results from the analysis of the VIEW1 and VIEW2 studies are shown in Table 1 below.

Table 1. Efficacy Outcomes at Week 52 (Full Analysis Set with LOCF) in VIEW1 and VIEW2 Studies

	VIEW1			VIEW2		
	Aflibercept 2 mg Q8 weeks[a]	**Aflibercept 2 mg Q4 weeks**	**Ranibizumab 0.5 mg Q4 weeks**	**Aflibercept 2 mg Q8 weeks[a]**	**Aflibercept 2 mg Q4 weeks**	**Ranibuzumab 0.5 mg Q4 weeks**
Full Analysis Set	N=301	N=304	N=304	N=306	N=309	N=291
Efficacy Outcomes						
Proportion of patients who maintained visual acuity (%) (<15 letters of BCVA loss)	94%	95%	94%	95%	95%	95%
Difference [b] (%) (95.1% CI)	0.6 (-3.2, 4.4)	1.3 (-2.4, 5.0)		0.6 (-2.9, 4.0)	-0.3 (-4.0, 3.3)	
Mean change in BCVA as measured by ETDRS letter score from Baseline	7.9	10.9	8.1	8.9	7.6	9.4
Difference [b] in LS mean (95.1% CI)	0.3 (-2.0, 2.5)	3.2 (0.9, 5.4)		-0.9 (-3.1, 1.3)	-2.0 (-4.1, 0.2)	
Number of patients who gained at least 15 letters of vision from	92 (31%)	114 (38%)	94 (31%)	96 (31%)	91 (29%)	99 (34%)

Baseline (%)						
Difference [b] (%) (95.1% CI)	-0.4 (-7.7, 7.0)	6.6 (-1.0, 14.1)		-2.6 (-10.2, 4.9)	-4.6 (-12.1, 2.9)	

BCVA: Best Corrected Visual Acuity; CI: Confidence Interval; ETDRS: Early Treatment Diabetic Retinopathy Study; LOCF: Last Observation Carried Forward (baseline values are not carried forward); 95.1% confidence intervals were presented to adjust for safety assessment conducted during the study.
[a] After treatment initiation with 3 monthly doses.
[b] Eylea group minus the ranibizumab group.

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline visual acuity) in each study were in general consistent with the results in the overall populations.

VIEW1 and VIEW2 studies were both 96 weeks in duration. However, after 52 weeks patients no longer followed a fixed dosing schedule. Between week 52 and week 96, patients continued to receive the drug and dosage strength to which they were initially randomized on a modified 12-week dosing schedule (doses at least every 12 weeks and additional doses as needed). Therefore, during the second year of these studies there was no active control comparison arm.

Macular Edema Following Central Retinal Vein Occlusion (CRVO) (1,7)

The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, sham-controlled studies in patients with macular edema following CRVO. A total of 358 patients were treated and evaluable for efficacy (217 with aflibercept) in the two studies (COPERNICUS and GALILEO). In both studies, patients were randomly assigned in a 3:2 ratio to either 2 mg aflibercept administered every 4 weeks (2Q4), or sham injections (control group) administered every 4 weeks for a total of 6 injections. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 22 to 89 years with a mean of 64 years.

In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA compared to baseline. At week 24, the aflibercept 2 mg Q4 group was superior to the control group for the primary endpoint.

Results from the analysis of the COPERNICUS and GALILEO studies are shown in Table 2 below.

Table 2. Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in COPERNICUS and GALILEO Studies

	COPERNICUS		**GALILEO**	
	Control	**Aflibercept 2 mg Q4 weeks**	**Control**	**Aflibercept 2 mg Q4 weeks**
	N=73	N=114	N=68	N=103
Efficacy Outcomes				
Proportion of patients who	12%	56%	22%	60%

gained at least 15 letters in BCVA from Baseline (%)				
Weighted Difference[a,b] (%) (95.1% CI)		44.8%[c] (32.9, 56.6)		38.3%[c] (24.4, 52.1)
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	-4.0 (18.0)	17.3 (12.8)	3.3 (14.1)	18.0 (12.2)
Difference in LS mean[a,d] (95.1% CI)		21.7[c] (17.3, 26.1)		14.7[c] (10.7, 18.7)

BCVA: Best Corrected Visual Acuity; CI: Confidence Interval; ETDRS: Early Treatment Diabetic Retinopathy Study; LOCF: Last Observation Carried Forward (baseline values are not carried forward); LS: least square; SD: standard deviation.

[a] Difference is EYLEA 2 mg Q4 weeks minus Control.

[b] Difference and CI are calculated using Cochran-Mantel-Haenszel (CMH) test adjusted for baseline factors; 95.1%confidence intervals were presented to adjust for the multiple assessments conducted during the study.

[c] $p<0.01$ compared with Control.

[d] LS mean and CI based on an ANCOVA model.

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline visual acuity, retinal perfusion status, and CRVO duration) in each study and in the combined analysis were in general consistent with the results in the overall populations.

Macular Edema Following Branch Retinal Vein Occlusion (BRVO) (1,7)

The safety and efficacy of aflibercept were assessed in a 24-week, randomized, multi-center, double-masked, controlled study in patients with macular edema following BRVO. A total of 181 patients were treated and evaluable for efficacy (91 with aflibercept) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg aflibercept administered every 4 weeks (2Q4) or laser photocoagulation administered at baseline and subsequently as needed (control group). Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 42 to 94 years with a mean of 65 years.

In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline. At week 24, the aflibercept 2 mg Q4 group was superior to the control group for the primary endpoint.

Detailed results from the analysis of the VIBRANT study are shown in Table 3 below.

Table 3. Efficacy Outcomes at Week 24 (Full Analysis Set with LOCF) in VIBRANT Study

	VIBRANT (3)	
	Control	**Aflibercept 2 mg Q4 weeks**
	N=90	N=91
Efficacy Outcomes		
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	26.7%	52.7%
Weighted Differences [a,b] (%) (95% CI)		26.6%[c] (13.0, 40.1)
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	6.9 (12.9)	17.0 (11.9)
Difference in LS mean[a,d] (95% CI)		10.5[c] (7.1, 14.0)

BCVA: Best Corrected Visual Acuity; CI: Confidence Interval; ETDRS: Early Treatment Diabetic Retinopathy Study; LOCF: Last Observation Carried Forward (baseline values are not carried forward); LS: least square; SD: Standard Deviation.

[a] Difference is EYLEA 2 mg Q4 weeks minus Control.

[b] Difference and CI are calculated using Mantel-Haenszel weighting scheme adjusted for region (North America vs. Japan) and baseline BCVA category (> 20/200 and ≤ 20/200).

[c] $p<0.01$ compared with Control.

[d] LS mean and CI based on an ANCOVA model.

Treatment effects in evaluable subgroups (e.g., age, gender, and baseline retinal perfusion status) in the study were in general consistent with the results in the overall populations.

Diabetic Macular Edema (DME) (1,7)

The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years.

Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA [2]). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8); 2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of vision loss were eligible to receive additional treatment: patients in the aflibercept groups could receive laser and patients in the laser group could receive aflibercept.

In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score. Efficacy of both aflibercept 2Q8 and aflibercept 2Q4 groups was statistically superior to the control group. This statistically superior improvement in BCVA was maintained at week 100 in both studies.

Results from the analysis of the VIVID and VISTA studies (2) are shown in Table 4 and Figure 16 below.

Table 4. Efficacy Outcomes at Weeks 52 and 100 (Full Analysis Set with LOCF) in VIVID and VISTA Studies

	VIVID			VISTA		
	Aflibercept 2 mg Q8 weeks[a]	**Aflibercept 2 mg Q4 weeks**	**Control**	**Aflibercept 2 mg Q8 weeks[a]**	**Aflibercept 2 mg Q4 weeks**	**Control**
Full Analysis Set	N=135	N=136	N=132	N=151	N=154	N=154
Efficacy Outcomes at Week 52						
Mean change in BCVA as measured by ETDRS letter score from Baseline (SD)	10.7 (9.3)	10.5 (9.6)	1.2 (10.6)	10.7 (8.2)	12.5 (9.5)	0.2 (12.5)
Difference[b,c] in LS mean (97.5% CI)	9.1[d] (6.3, 11.8)	9.3[d] (6.5, 12.0)		10.5[d] (7.7, 13.2)	12.2[d] (9.4, 15.0)	
Proportion of patients who gained at least 15 letters in BCVA from Baseline (%)	33.3%	32.4%	9.1%	31.1%	41.6%	7.8%
Adjusted Difference[c,e] (%) (97.5% CI)	24.2%[d] (13.5, 34.9)	23.3%[d] (12.6, 33.9)		23.3%[d] (13.5, 33.1)	34.2%[d] (24.1, 44.4)	
Efficacy Outcomes at Week 100						
Mean change in BCVA as measured by	9.4 (10.5)	11.4 (11.2)	0.7 (11.8)	11.1 (10.7)	11.5 (13.8)	0.9 (13.9)

ETDRS letter score from Baseline (SD)						
Difference[b,c] in LS mean (97.5% CI)	8.2[d] (5.2, 11.3)	10.7[d] (7.6, 13.8)		10.1[d] (7.0, 13.3)	10.6[d] (7.1, 14.2)	
Proportion of people who gained at least 15 letters in BCVA from Baseline (%)	31.1%	38.2%	12.1%	33.1%	38.3%	13.0%
Adjusted Difference[c,e] (%) (97.5% CI)	19.0%[d] (8.0, 29.9)	26.1%[d] (14.8, 37.5)		20.1%[d] (9.6, 30.6)	25.8%[d] (15.1, 36.6)	

BCVA: Best Corrected Visual Acuity; CI: Confidence Interval; ETDRS: Early Treatment Diabetic Retinopathy Study; LOCF: Last Observation Carried Forward (baseline values are not carried forward); LS: least square; SD: Standard Deviation.

[a] After treatment initiation with 5 monthly injections.

[b] LS mean and CI based on an ANCOVA model with baseline BCVA measurement as a covariate and a factor for treatment group. Additionally, protocol specified stratification factors were included in the model.

[c] Difference is EYLEA group minus Control group.

[d] $p<0.01$ compared with Control.

[e] Difference with confidence interval (CI) and statistical test is calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors.

Treatment effects in the subgroup of patients who had previously been treated with a VEGF inhibitor prior to study participation were similar to those seen in patients who were VEGF inhibitor naïve prior to study participation.

Treatment effects in evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity, prior anti-VEGF therapy) in each study were in general consistent with the results in the overall populations.

<u>Diabetic Retinopathy (DR) (1,7)</u>

Efficacy and safety data of aflibercept in diabetic retinopathy (DR) are derived from the VIVID, VISTA, and PANORAMA studies.

VIVID AND VISTA (2)

In the VIVID and VISTA studies, an efficacy outcome was the change in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (ETDRS-DRSS). The

ETDRS-DRSS score was assessed at baseline and approximately every 6 months thereafter for the duration of the studies.

All enrolled patients had DR and DME at baseline. The majority of patients enrolled in these studies (77%) had moderate-to-severe nonproliferative diabetic retinopathy (NPDR) based on the ETDRS-DRSS. At week 100, the proportion of patients improving by at least 2 steps on the ETDRS-DRSS was significantly greater in both Eylea treatment groups (2Q4 and 2Q8) when compared to the control group.

Results from the analysis of ETDRS-DRSS at week 100 in the VIVID and VISTA studies are shown in Table 5 below.

Table 5. Proportion of Patients Who Achieved a ≥2-Step Improvement from Baseline in the ETDRS-DRSS Score at Week 100 in VIVID and VISTA Studies

	VIVID			**VISTA**		
	Aflibercept 2 mg Q8 weeks[a]	**Aflibercept 2 mg Q4 weeks**	**Control**	**Aflibercept 2 mg Q8 weeks[a]**	**Aflibercept 2 mg Q4 weeks**	**Control**
Evaluable Patients[b]	N=101	N=97	N=99	N=148	N=153	N=150
Number of patients with a ≥2-step improvement on ETDRS-DRSS from Baseline (%)	31 (32%)	27 (28%)	7 (7%)	56 (38%)	58 (38%)	24 (16%)
Difference[c,d] (%) (97.5% CI)	24%[e] (12, 36)	21%[e] (9, 33)		22%[e] (11, 33)	22%[e] (11, 33)	

ETDRS-DRSS: Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale; CI: confidence interval.

Non-gradable post-baseline ETDRS-DRSS values were treated as missing and were imputed using the last gradable ETDRS-DRSS values (including baseline values if all post-baseline values were missing or non-gradable).

[a] After treatment initiation with 5 monthly injections.

[b] The number of evaluable patients included all patients who had valid ETDRS-DRSS data at baseline.

[c] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by protocol specified stratification factors.

[d] Difference is EYLEA minus Control group.

[e] $p<0.01$ compared with Control.

Results of the evaluable subgroups (e.g., age, gender, race, baseline HbA1c, baseline visual acuity) on the proportion of patients who achieved a ≥2-step improvement on the ETDRS-DRSS from baseline to week 100 were, in general, consistent with those in the overall population.

PANORAMA
The PANORAMA study assessed the safety and efficacy of aflibercept in a randomized, multi-center, double-masked, controlled study in patients with moderately severe to severe nonproliferative diabetic retinopathy (NPDR) (ETDRS-DRSS of 47 or 53), without central-involved DME (CI-DME). A total of 402 randomized patients were evaluable for efficacy. Protocol-specified visits occurred every 28±7 days for the first 5 visits, then every 8 weeks (56±7 days). Patient ages ranged from 25 to 85 years with a mean of 55.7 years.

Patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: 1) 3 initial monthly aflibercept 2 mg injections followed by one injection after 8 weeks and then one injection every 16 weeks (aflibercept 2Q16); 2) 5 monthly aflibercept 2 mg injections followed by one injection every 8 weeks (aflibercept 2Q8); and 3) sham treatment.

The primary efficacy endpoint was the proportion of patients who improved by ≥ 2 steps on the DRSS from baseline to week 24 in the combined aflibercept groups and at week 52 in the 2Q16 and 2Q8 groups individually versus sham. A key secondary endpoint was the proportion of patients developing the composite endpoint of proliferative diabetic retinopathy or anterior segment neovascularization through week 52.

At week 52, efficacy in the 2Q16 and 2Q8 groups was superior to the sham group (see Table 6 and Table 7).

Table 6: Proportion of Patients Who Achieved a ≥ 2-Step Improvement from Baseline in the ETDRS-DRSS Score at Weeks 24 and 52 in PANORAMA

	PANORAMA				
	Week 24		**Week 52**		
	Aflibercept Combined	**Control (sham)**	**Aflibercept 2Q16**	**Aflibercept 2Q8**	**Control (sham)**
Full Analysis Set	N=269	N=133	N=135	N=134	N=133
Proportion of patients with a ≥ 2-step improvement on ETDRS-SRSS from Baseline (%)	58%	6%	65%	80%	15%

Adjusted Difference[a] (%) (95% CI)[b]	53%[c] (45, 60)		50%[c] (40, 60)	65%[c] (56, 74)	

ETDRS-DRSS: Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale; CI: confidence interval.

Non-gradable post-baseline ETDRS-DRSS values were treated as missing and were imputed using the last gradable ETDRS-DRSS values (including baseline values if all post-baseline values were missing or non-gradable)

[a] Difference is Eylea group minus sham.

[b] Difference with CI was calculated using the Mantel-Haenszel weighting scheme adjusted by baseline DRSS stratification variable

[c] p<0.01 compared with Control. p-value was calculated using a 2-sided Cochran-Mantel-Haenszel test adjusted by baseline DRSS stratification variable.

Table 7. Effect of Eylea on Worsening of Diabetic Retinopathy in PANORAMA through Week 52

	Aflibercept 2Q16	**Aflibercept 2Q8**	**Control (Sham)**
Full Analysis Set	N=135	N=134	N=133
Composite Endpoint of Developing PDR or ASNV[a]			
Event Rate[b]	4.0%[d]	2.4%[d]	20.1%
Hazard Ratio	0.15	0.12	
Development of Proliferative Diabetic Retinopathy[c]			
Event Rate[b]	1.6%[d]	0.0%[d]	11.9%
Hazard Ratio	0.11	0.00	

PDR = Proliferative Diabetic Retinopathy; ASNV = Anterior Segment Neovascularization

[a] As diagnosed by either the Reading Center or Investigator through week 52

[b] Estimated using Kaplan-Meier method

[c] Defined as ≥ 2-step worsening on the ETDRS-DRSS score through week 52

[d] p<0.01 compared with Control

Retinopathy of Prematurity (ROP) (1)

Efficacy and safety data of Eylea in ROP are derived from two studies (BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT). BUTTERFLEYE was a 52-week study. FIREFLEYE included 24 weeks of treatment and follow-up. FIREFLEYE NEXT was an observational follow-up of FIREFLEYE through week 52.

Both BUTTERFLEYE and FIREFLEYE studies assessed the efficacy, safety and tolerability of Eylea in randomized, 2-arm, open-label, parallel-group studies. The studies were conducted in pre-term infants with ROP providing a comparison between Eylea treatment and laser photocoagulation therapy (laser). Each eligible eye received the assigned study treatment at baseline. Re-treatment and/or rescue treatment was administered if needed based on pre-specified criteria. Rescue treatment could potentially include the alternative treatment (Eylea or laser). Re-treatment with aflibercept, if required, was administered up to 2 times in a particular eye, with at least 28 days between consecutive injections.

Eligible patients had a maximum gestational age at birth of 32 weeks or a maximum birth weight of 1500 g, had to weigh >800 g on the day of treatment and had treatment-naïve ROP classified according to the International Classification for Retinopathy of Prematurity (IC-ROP 2005) in a least one eye with one of the following retinal findings:

- ROP Zone 1 Stage 1+, 2+, 3 or 3+, or
- ROP Zone 11 Stage 2+ or 3+, or
- AP-ROP (aggressive posterior ROP)

The primary efficacy endpoint of each study was the proportion of patients with absence of active ROP and unfavorable structural outcomes (retinal detachment, macular dragging, macular fold, retrolental opacity) at week 52 of chronological age.

In BUTTERFLEYE, patients were randomized in a 3:1 ratio to receive 1 of 2 treatment regimens: 1) Eylea 0.4 mg at baseline and if required, up to 2 additional injections and 2) laser photocoagulation in each eye at baseline and if required, retreatment. In FIREFLEYE, patients were randomized to the same two treatments, but in a 2:1 ratio. Rescue treatment was administered if required, per pre-specified criteria. In both studies, greater than 92% of all treated patients in the aflibercept group received bilateral injections during the study.

Results from week 52 of chronological age in the BUTTERFLEYE and FIREFLEYE/ FIREFLEYE NEXT studies are shown in Table 8 below.

The proportion of patients without clinically significant reactivations of ROP who also did not develop unfavorable structural outcomes was higher in each arm of each study than would have been expected in infants who had not received treatment. Neither trial demonstrated superiority of one are compared to the other arm. Neither trial demonstrated inferiority of one arm compared to the other arm.

Table 8: Efficacy Outcomes at Week 52 Chronological Age in BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT Studies

	BUTTERFLEYE[a]		**FIREFLEYE/FIREFLEYE NEXT[a]**	
	Eylea 0.4 mg	**Laser**	**Eylea 0.4mg**	**Laser**
Full Analysis Set[b]				
	N=93	N=27	N=75	N=38
Efficacy Outcomes				
Proportion of patients with absence of active ROP and unfavorable structural outcomes (%)	79.6%	77.8%	78.7%	81.6%

Adjusted Difference[c] (%) (95.1% CI)	1.18% (-15.7, 19.3)	-1.88% (-17.0, 13.2)

[a] In case of bilateral treatment, success was achieved only if both eyes met the primary endpoint. Treatment interval between 2 doses injected into the same eye had to be at least 28 days apart.
[b] Included patients who were both randomized and treated from the BUTTERFLEYE and FIREFLEYE NEXT studies. This was the primary analysis population as defined in the Statistical Analysis Plans.
[c] Difference with confidence internal (CI) was calculated using Mantel-Haenszel weighting scheme adjusted by baseline ROP status. Success criterion: Lower limit of 95.1% CI above -5%.

Treatment interval between 2 doses injected into the same eye had to be at least 28 days. Included patients who were both randomized and treated from the BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT studies. This was the primary analysis population as defined in the Statistical Analysis Plans.

Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighing scheme adjusted by baseline ROP status. Success criterion: Lower limit of 95.1% CI above -5%.

The proportion of patients without clinically significant reactions of ROP who also did not develop unfavorable structural outcomes was higher in each arm of each study than would have been expected in infants who had not received treatment. Neither trial demonstrated superiority of one arm compared to the other arm. Neither trial demonstrated inferiority of one arm compared to the other.

Eylea® HD

Neovascular (Wet) Age-Related Macular Degeneration (nAMD) (6)

The safety and efficacy of Eylea HD were assessed in a randomized, multi-center, double-masked, active controlled study (PULSAR) in treatment-naïve patients with nAMD. A total of 1009 patients were treated and analyzed for efficacy (673 with Eylea HD). Patients were randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups: 1) Eylea HD administered every 12 weeks following 3 initial monthly doses (HDq12); 2) Eylea HD administered every 16 weeks following 3 initial monthly doses (HDq16); 3) Eylea 2 mg administered every 8 weeks (2q8) following 3 initial monthly doses. In the Eylea HD groups, patients could be treated as frequently as every 8 weeks based on protocol-defined visual and anatomic criteria, starting at week 16. Patients ranged from 50 to 96 years of age with a mean of 74.5 years. At baseline, mean visual acuity was approximately 60 letters (range: 24 to 78 letters).

The primary efficacy endpoint was the change from baseline in BCVA at week 48 as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

Both HDq12 and HDq16 treatments were shown to be non-inferior and clinically equivalent to 2q8 treatment with respect to the change in BCVA score at week 48 using the pre-specified non-inferiority margin of 4 letters. In patients completing week 48, the mean number of injections administered were 5.2 in the HDq16 group (n=312), 6.1 in the HDq12 group (n=316)

and 6.9 in the Eylea q8 group (n=309). Detailed results from the analysis of the PULSAR study are shown in Table 9.

Efficacy results in all subgroups (e.g., age, gender, geographic region, ethnicity, race, baseline BCVA and lesion type) were consistent with those in the overall population.

Table 9. Efficacy Outcomes (Full Analysis Set) in PULSAR Study

Efficacy Outcomes	Eylea HDq12	Eylea HDq16	Eylea 2q8
Full Analysis Set[a]	N=335	N=338	N=336
Mean change in BCVA as measured by ETDRS letter score from baseline (SD) at week 48[b]	6.7 (12.6)	6.2 (11.7)	7.6 (12.2)
LS mean (SE) change from baseline[c]	6.1 (0.8)	5.9 (0.7)	7.0 (0.7)
Difference in LS mean (95% CI)[c]	-1.0 (-2.9, 0.9)	-1.1 (-3.0, 0.7)	

BCVA: Best Corrected Visual Acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; SD: Standard Deviation; LS: Least Square; SE: Standard Error; CI: Confidence Interval.

[a.] Full Analysis Set (FAS) includes all randomized patients who received at least 1 dose of study medication.

[b.] Observed values at week 48: n=299 for HDq12; n=289 for HDq16; n=285 for 2q8.

[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.

Diabetic Macular Edema (DME)

The safety and efficacy of Eylea HD was assessed in a randomized, multi-center, double-masked, active-controlled study (PHOTON) in patients with DME involving the center of the macula. A total of 658 patients were treated and analyzed for efficacy (491 with Eylea HD). Patients were randomly assigned in a 2:1:1 ratio to 1 of 3 treatment groups: 1) Eylea HD administered every 12 weeks following 3 initial monthly doses (HDq12); 2) Eylea HD administered every 16 weeks following 3 initial monthly doses (HDq16); 3) Eylea 2 mg administered every 8 weeks (2q8) following 5 initial monthly doses. In the Eylea HD groups, patients could be treated as frequently as every 8 weeks based on protocol-defined visual and anatomic criteria, starting at week 16. Patient ages ranged from 24 to 90 years with a mean of 62.3 years. A total of 44% of patients were previously treated for DME. At baseline, the overall mean visual acuity was 63 letters (range: 24 to 79 letters).

The primary efficacy endpoint was the change from baseline in BCVA at week 48 as measured by the ETDRS letter score. Both HDq12 and HDq16 treatments were shown to be non-inferior and clinically equivalent to 2q8 treatment with respect to the change in BCVA score at week 48 using the pre-specified non-inferiority margin of 4 letters. In patients completing week 48, the mean number of injections administered were 5.0 in the HDq16 group (n=155), 6.0 in the

HDq12 group (n=298) and 7.9 in the EYLEA q8 group (n=156). Detailed results from the analysis of the PHOTON study are shown in Table 10.

Table 10. Efficacy Outcomes (Full Analysis Set) in PHOTON Study

Efficacy Outcomes	Eylea HDq12	Eylea HDq16	Eylea 2q8
Full Analysis Set[a]	N=328	N=163	N=167
Mean change in BCVA as measured by ETDRS letter score from baseline (SD) at week 48[b]	8.8 (9.0)	7.9 (8.4)	9.2 (9.0)
LS mean (SE) change from baseline[c]	8.1 (0.6)	7.2 (0.7)	8.7 (0.7)
Difference in LS mean (95% CI)[c]	-0.6 (-2.3, 1.1)	-1.4 (-3.3, 0.4)	

BCVA: Best Corrected Visual Acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; SD: Standard Deviation; LS: Least Square; SE: Standard Error; CI: Confidence Interval.

[a.] Full Analysis Set (FAS) includes all randomized patients who received at least 1 dose of study medication.

[b.] Observed values at week 48: n=277 for HDq12; n=149 for HDq16; n=150 for 2q8.

[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.

Efficacy results in all subgroups (e.g., age, gender, geographic region, ethnicity, race, baseline, BCVA, baseline CRT and prior DME treatment) were consistent with those in the overall population.

Diabetic Retinopathy (DR)

Efficacy and safety data of Eylea HD in diabetic retinopathy (DR) are derived from the PHOTON study.

In the PHOTON study, a key efficacy outcome was the change in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (ETDRS-DRSS). Each Eylea HD group was compared to the 2q8 group using a NI margin of 10%.

The ETDRS-DRSS score was assessed at baseline and approximately every 3 months thereafter for the duration of the study. Baseline ETDRS-DRSS scores were generally balanced across treatment groups. Results from the analysis of ETDRS-DRSS scores at week 48 in the PHOTON study are shown in Table 11.

Table 11. Proportion of Patients Who Achieved a ≥2-Step Improvement from Baseline in the ETDRS-DRSS Score at Week 48 (Full Analysis Set) in PHOTON

Efficacy Outcomes	Eylea HDq12	Eylea HDq16	Eylea 2q28
Full Analysis Set[a]	N=328	N=163	N=167

Proportion of patients with a ≥2-step improvement in ETDRS-DRSS from baseline (%)[b]	29%	20%	27%
Difference[c] (%) (95% CI)	2% (-6.6, 10.6)	-8% (-16.9, 1.8)	

CI: confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale.

Missing or non-gradable post-baseline ETDRS-DRSS values were imputed using the last gradable ETDRS-DRSS values. 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.] Full Analysis Set (FAS) includes all randomized patients who received at least 1 dose of study medication.

[b.] Last observation carried forward.

[c.] Difference with confidence interval (CI) was calculated using Mantel-Haenszel weighting scheme.

The Eylea HDq16 did not meet the non-inferiority criteria for the proportion of patients with a ≥2-step improvement on ETDRS-DRSS and is not considered clinically equivalent to Eylea administered every 8 weeks.

Results of the subgroups (e.g., age, gender, race, ethnicity, baseline BCVA and prior DME treatment) on the proportion of patients who achieved a ≥2-step improvement on the ETDRS-DRSS from baseline to week 48 were, in general, consistent with those in the overall population.

Summary of Evidence

Based on the results of the studies provided to the U.S. Food and Drug Administration for consideration of approval, intravitreal injections of aflibercept (Eylea®) may be considered medically necessary for the treatment of diabetic macular edema, or macular edema following retinal vein occlusion (RVO) (central retinal vein occlusion [CRVO] and branch retinal vein occlusion [BRVO]); diabetic retinopathy (DR); treatment of neovascular (wet) age-related macular degeneration (AMD); treatment of choroidal neovascularization (CNV; includes myopic CNV or mCNV) due to angioid streaks, central serous chorioretinopathy, choroidal retinal neovascularization, secondary to pathologic myopia, choroidal retinal neovascularization, degenerative progressive high myopia, choroidal rupture or trauma, idiopathic choroidal neovascularization, multifocal choroiditis, pathologic myopia, presumed ocular histoplasmosis syndrome, and uveitis, and retinopathy of prematurity (ROP).

Based on the results of the studies provided to the U.S. Food and Drug Administration for consideration of approval, intravitreal injections of aflibercept (Eylea® HD) may be considered medically necessary for individuals who have tried and failed, or has a clinical reason to avoid intravitreal injection(s) of bevacizumab (Avastin™) as an anti-VEGF (vascular endothelial growth

factor) therapy for neovascular (wet) age-related macular degeneration (AMD; diabetic macular edema (DME); or diabetic retinopathy (DR).

Based on the results of the studies provided to the U.S. Food and Drug Administration for consideration of approval, intravitreal injections of aflibercept-ayyh (Pavblu™) may be considered medically necessary for individuals who have tried and failed, or has a clinical reason to avoid intravitreal injections of bevacizumab (Avastin™) as an anti-VEGF vascular endothelial growth factor) therapy for neovascular (wet) age-related macular degeneration (AMD; macular edema following retinal vein occlusion; diabetic macular edema (DME); or diabetic retinopathy (DR).

Continuation of aflibercept (Eylea® and Eylea® HD) or aflibercept-ayyh (Pavblu™) therapy may be considered medically necessary for all members (including new members) who are currently receiving the requested medication through a previously authorized pharmacy or medical benefit, when dosing is in accordance with an authoritative source, and who are experiencing benefit from therapy as evidenced by disease stability or disease improvement.

Intravitreal injection of aflibercept (Eylea® and Eylea® HD) or aflibercept-ayyh (Pavblu™) is considered experimental, investigational and/or unproven for the treatment of all other ophthalmological indications.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	67028
HCPCS Codes	J0177, J0178, Q5147, [Deleted 4/2024: C9161]

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
05/15/2025	Document updated with literature review. The following change was made to Coverage: Added: continuation therapy and initial therapy statements with conditional criteria for aflibercept-ayyh (Pavblu™). Added reference 7. Title changed from Aflibercept.
02/01/2025	Document updated. The following change was made to Coverage: Added language regarding drug shortages/recalls to “Initial Therapy” criteria. No new references added.
05/15/2024	Document updated. The following change was made to Continuation Therapy in Coverage for both Eylea and Eylea HD: removed “through a previously authorized pharmacy or medical benefit” in the statement “Continuation of aflibercept (Eylea®) [or Eylea® HD] therapy may be considered medically necessary for all members (including new members…” Now reads: Continuation of aflibercept (Eylea®) [or Eylea® HD] therapy may be considered medically necessary for all Members (including new members): who are currently receiving the requested medication, AND who

	are experiencing benefit from therapy as evidenced by disease stability or disease improvement, AND when dosing is in accordance with an authoritative source." No new references added.
05/01/2024	Document updated with literature review. The following change was made to Coverage: Added: Continuation therapy of Eylea® HD may be considered medically necessary for all members (including new members) who are currently receiving the requested medication through a previously authorized pharmacy or medical benefit, when dosing is in accordance with an authoritative source, and who are experiencing benefit from therapy as evidenced by disease stability or disease improvement. Intravitreal injection of Eylea® HD may be considered medically necessary contingent on the following coverage criteria: Individual has tried and failed, or has a clinical reason to avoid intravitreal injection(s) of bevacizumab (Avastin™) as an anti-VEGF (vascular endothelial growth factor) therapy for the following conditions: Neovascular (Wet) Age-Related Macular Degeneration (nAMD); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR). Added Eylea® HD to the experimental, investigational and/or unproven statement for all other ophthalmological indications. Title changed from Aflibercept (Eylea®). Reference 6 added; others revised.
10/01/2023	Document updated. The following change was made to Coverage: Added preferred criteria for bevacizumab (Avastin™). No new references added.
06/01/2023	Document updated with literature review. The following change was made to Coverage: Added "retinopathy of prematurity (ROP)" to list of medically necessary indications. Added reference 5; updated reference 1.
07/15/2022	Document updated. The following changes were made to Coverage: Aflibercept (Eylea™) may be considered medically necessary for the indications listed in Coverage. Aflibercept (Eylea™) was also previously addressed on OTH903.020 Intravitreal Angiogenesis Inhibitors for Choroidal Vascular Conditions. Medical document divided into OTH903.020 Bevacizumab for Ophthalmological Indications; OTH903.027 Aflibercept; OTH903.043 Brolucizumab-dbll. Title changed from: Intravitreal Angiogenesis Inhibitors for Retinal Vascular Disorders.
04/15/2022	Document updated with literature review. The following changes were made to Coverage: 1) Aflibercept (Eylea™): Removed FDA labelled indication (editorial change) for neovascular (wet) age-related macular degeneration as this condition is addressed on medical policy 903.020; 2) Pegaptanib (Macugen®): added term "sodium" to state "pegaptanib sodium" and removed diabetic retinopathy from the medically necessary coverage statement; Added references 38, 66-68, 70, 73, 75-81; others updated, some removed.
04/01/2022	Document updated. Coverage for ranibizumab (Lucentis®) was removed and is now addressed on OTH903.041 Ranibizumab Injections, Implants and Biosimilars.

04/1/2020	Document updated with literature review. Coverage for Eylea for diabetic retinopathy in patients with diabetic macular edema was revised to diabetic retinopathy. References and rationale revised.
10/15/2018	Reviewed. No changes.
11/01/2017	Document updated with literature review. The following wording was removed from the Lucentis™ medically necessary coverage statement "proliferative" and "as an adjunctive treatment to vitrectomy or photocoagulation" following the U.S. Food and Drug Administration-approved labeling. The following NOTEs were added in the Coverage section: "NOTE 2: Bevacizumab (Avastin™) is a recognized, viable, cost-effective anti-VEGF (vascular endothelial growth factor) alternative treatment"; and "NOTE 5: For conditions resulting from wet age-related macular degeneration, (e.g., retinal detachment, refer to medical policy OTH903.020, Intravitreal Angiogenesis Inhibitors for Choroidal Vascular Conditions, for the appropriate U.S. Food and Drug Administration approved drug for coverage information."
7/15/2016	Reviewed. No changes.
12/1/2015	Document updated with literature review. The following indication was added to the medically necessary coverage statement intravitreal injection of aflibercept (Eylea™): "Diabetic retinopathy in patients with diabetic macular edema." Otherwise, coverage unchanged.
11/15/2014	Document updated with literature review. The following was added as an approved U.S. Food and Drug Administration labeled indication for aflibercept (Eylea™): Intravitreal injection of aflibercept (Eylea™) may be considered medically necessary for the treatment of macular edema following retinal vein occlusion, inclusive of branch retinal vein occlusion. The Rationale and References were revised.
10/1/2014	New medical document. Intravitreal injection of ranibizumab (Lucentis™) or bevacizumab (Avastin™) may be considered medically necessary for the treatment of specifically listed retinal vascular conditions. Intravitreal injection of pegaptanib (Macugen®) may be considered medically necessary for the treatment of diabetic macular edema and diabetic retinopathy. Intravitreal injection of aflibercept (Eylea™) may be considered medically necessary for the treatment of macular edema following central retinal vein occlusion and for diabetic macular edema. Intravitreal injection of bevacizumab (Avastin™) may be considered medically necessary for the treatment of specific retinal or macular conditions. Intravitreal injection of ranibizumab (Lucentis™) or bevacizumab (Avastin™) is considered experimental, investigational and/or unproven for the treatment of all other retinal vascular disorders. Intravitreal injection of aflibercept (Eylea™) is considered experimental, investigational and/or unproven for all other ophthalmologic indications listed in the coverage. CPT/HCPCS code(s) updated. Significant revisions were made to entire medical policy document.

	This topic was previously addressed on OTH903.020, Intravitreal Angiogenesis Inhibitors for Choroidal Vascular Conditions.