Policy Number	**OTH903.041**
Policy Effective Date	**01/01/2026**

Ranibizumab Injections, Implants and Biosimilars

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Related Policies (if applicable)
None

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 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

Ranibizumab (Lucentis®), Ranibizumab-nuna (Byooviz™), Ranibizumab-eqrn (Cimerli™)

Intravitreal injection of ranibizumab (Lucentis®), ranibizumab-nuna (Byooviz™) or ranibizumab-eqrn (Cimerli™) **may be considered medically necessary** when the individual has one of the following conditions:

- Diabetic macular edema (DME);
- Diabetic retinopathy (DR);
- Macular edema following central retinal vein occlusion (CRVO);
- Macular edema following branch retinal vein occlusion (BRVO);
- Neovascular (wet) age-related macular degeneration (AMD);
- Neovascular glaucoma;
- Rubeosis (neovascularization of the iris); or
- 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.

NOTE 1: Byooviz™ (ranibizumab-nuna) is a biosimilar to Lucentis® (ranibizumab injection).

NOTE 2: Cimerli™ (ranibizumab-eqrn) is a biosimilar to, and interchangeable with, Lucentis® (ranibizumab injection), for the conditions noted above.

Ranibizumab (Susvimo®)
Intravitreal injections of ranibizumab (Susvimo®) via the Susvimo ocular implant **may be considered medically necessary** for the treatment of individuals who have previously responded to at least two intravitreal injections of a vascular endothelial growth factor (VEGF) inhibitor AND have one of the following indications:

- Neovascular (wet) Age-related Macular Degeneration (AMD)
- Diabetic Macular Edema (DME); or
- Diabetic Retinopathy (DR).

Intravitreal injections of ranibizumab (Lucentis®), ranibizumab (Susvimo®), ranibizumab-nuna (Byooviz™), or ranibizumab-eqrn (Cimerli™) **are considered experimental, investigational and/or unproven** for all other indications.

Policy Guidelines

None.

Description

Angiogenesis inhibitors such as ranibizumab are being evaluated for the treatment of retinal circulation. They can be given via intraocular injections as a treatment for disorders of choroidal and retinal circulation. Ophthalmic disorders affecting the choroidal circulation include age-related macular degeneration (AMD or ARMD), central serous chorioretinopathy (CSC), pathologic myopia, presumed ocular histoplasmosis syndrome, angioid streaks, idiopathic choroidal neovascularization (CNV), uveitis, choroidal rupture, or trauma, and chorioretinal scars. Ophthalmic disorders affecting the retinal circulation include proliferative diabetic macular edema (DME), diabetic retinopathy (DR), central (CRVO) or branch retinal vein occlusion (BRVO), and retinopathy of prematurity (ROP).

Vascular endothelial growth factor (VEGF) has been implicated in the pathogenesis of a variety of ocular vascular conditions characterized by neovascularization and macular edema. The macula, with the fovea at its center, has the highest photoreceptor concentration and is where visual detail is discerned. Anti-VEGF agents are used to treat CNV associated with ARMD and are being evaluated for the treatment of disorders of retinal circulation (e.g., DME, macular edema following retinal vein occlusion, ROP).

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.

Ranibizumab binds extracellular VEGF to inhibit the angiogenesis pathway. Ranibizumab is an antibody fragment that does not possess the fragment crystallizable domain and is directed at all isoforms of VEGF-A receptors.

Diabetic Macular Edema and Diabetic Retinopathy

Diabetic retinopathy 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 such as ranibizumab, reduce permeability and block the pathway leading to new blood vessel formation (angiogenesis), and 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 and Branch Retinal Vein Occlusions

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.

Age-Related Macular Degeneration

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.

Myopic Choroidal Neovascularization

Myopia, or nearsightedness, is a common condition where objects further away are blurry while those close are clear. It is one of the leading causes of visual impairment in the world; and one of the most feared complications of myopia, is the development of CNV. Myopic CNV (mCNV) can occur in patients with any degree of myopia, even in the absence of characteristic degenerative retinal changes.

Although some information is available regarding the genetics of pathologic myopia (PM), the genetic factors specifically associated with the development and presentation of myopic CNV are not yet fully understood. One study found a correlation between the COL8A1 gene and the presence of myopic CNV. Interestingly, this gene encodes chains of collagen type VIII, one of the major components of Bruch membrane and choroidal stroma. Mutations in this gene might lead to the structural changes frequently observed in patients with PM. Alterations in SERPINF1, the gene that encodes pigment epithelium–derived factor, may also be related to CNV progression.

In addition to genetic factors, structural and hemodynamic mechanisms have been suggested to contribute to the development of myopic CNV. Excessive elongation of the globe is presumed to cause mechanical stress, with retinal damage and imbalance of proangiogenic and antiangiogenic factors resulting in CNV. The axial elongation promotes alteration in collagen proteins that subsequently leads to degenerative changes in the retina, choroid, and sclera. A chain of molecular and inflammatory events may occur because of this mechanical and structural stress. The amacrine cells in the retina are thought to play a part in this process.

Compared to unaffected individuals, patients with PM had significantly higher levels of inflammatory factors such as high-sensitivity C-reactive protein and complement factors C3 and CH50; these findings strongly suggest that inflammation is involved in myopic CNV. Another hypothesis suggests that hemodynamic changes at the level of the choroid lead to choroidal thinning and hypoperfusion, predisposing to CNV development.

Regulatory Status

Lucentis® (Genentech) was first approved for the treatment of patients with neovascular AMD. In 2010, Lucentis™ was approved by the U.S. Food and Drug Administration (FDA) for the treatment of macular edema following retinal vein occlusion. In 2012, Lucentis® was approved for the treatment of DME and in 2015 it was approved for the treatment of proliferative DR in patients with DME. In 2017,

the FDA approved a label change for DR to not include any limitations for that that diagnosis. Therefore, Lucentis® is approved for DR in patients. (1)

Susvimo™ (Genentech) was approved in October 2021 as a refillable implant containing ranibizumab that is surgically implanted into the eye during a one-time, outpatient procedure. (2, 3)

Byooviz™ (Samsung Bioepis Co., Ltd) is the first ophthalmology biosimilar approved in the United States and is the first biosimilar to Lucentis. It was approved in September 2021 based on a review of safety and efficacy data demonstrating Byooviz is biosimilar to Lucentis. (4, 5)

Cimerli™ (Coherus BioSciences, Inc.) was approved by the FDA on August 2, 2022, as a biosimilar to Lucentis. It is interchangeable with Lucentis for the following indications:

- Neovascular (wet) age-related macular degeneration (AMD);
- Macular edema following retinal vein occlusion (RVO);
- Diabetic macular edema (DME);
- Diabetic retinopathy (DR);
- Myopic choroidal neovascularization (mCNV).

Per the prescribing information for Cimerli: "An interchangeable product (IP) is a biological product that is approved based on data demonstrating that it is highly similar to an FDA-approved reference product (RP) and that there are no clinically meaningful differences between the products; it can be expected to produce the same clinical result as the RP in any given patient; and if administered more than once to a patient, the risk in terms of safety or diminished efficacy from alternating or switching between use of the RP and IP is not greater than that from the RP without such alternation or switch. Interchangeability of Cimerli has been demonstrated for the condition(s) of use, strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information." (6)

Rationale

Lucentis® (1, 4, 6)

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

The safety and efficacy of Lucentis were assessed in three randomized, double-masked, sham- or active-controlled studies in patients with neovascular AMD. A total of 1323 patients (Lucentis 879, control 444) were enrolled in the three studies.

Studies AMD-1 and AMD-2
In Study AMD-1, patients with minimally classic or occult (without classic) choroidal neovascularization (CNV) lesions received monthly Lucentis 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections. Data are available through Month 24. Patients treated with Lucentis in Study AMD-1 received a mean of 22 total treatments out of a possible 24 from Day 0 to Month 24.

In Study AMD-2, patients with predominantly classic CNV lesions received one of the following: 1) monthly Lucentis 0.3 mg intravitreal injections and sham photodynamic therapy (PDT); 2) monthly Lucentis 0.5 mg intravitreal injections and sham PDT; or 3) sham intravitreal injections and active PDT. Sham PDT (or active PDT) was given with the initial Lucentis (or sham) intravitreal injection and every 3 months thereafter if fluorescein angiography (FA) showed persistence or recurrence of leakage. Data are available through Month 24. Patients treated with Lucentis in Study AMD-2 received a mean of 21 total treatments out of a possible 24 from Day 0 through Month 24.

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 12 months compared with baseline. Almost all Lucentis-treated patients (approximately 95%) maintained their visual acuity. Among Lucentis-treated patients, 31% to 37% experienced a clinically significant improvement in vision, defined as gaining 15 or more letters at 12 months. The size of the lesion did not significantly affect the results. Detailed results are shown in Table 1, Table 2, and Figure 1 below.

Table 1. Visual Acuity Outcomes at Month 12 and Month 24 in Study AMD-1

Outcome Measure	**Month**	**Sham n=229**	**Lucentis 0.5 mg n=230**	**Estimated Difference (95% CI)[a]**
Loss of <15 letters in visual acuity (%)	12	60%	91%	30% (23%, 37%)
	24	56%	89%	33% (26%, 41%)
Gain of ≥15 letters in visual acuity (%)	12	6%	31%	25% (18%, 31%)
	24	4%	30%	25% (18%, 31%)

Mean change in visual acuity (letters (SD)	12	-11.0 (17.9)	+6.3 (14.1)	17.1 (14.2, 20.0)
	24	-15.0 (19.7)	+5.5 (15.9)	20.1 (16.9, 23.4)

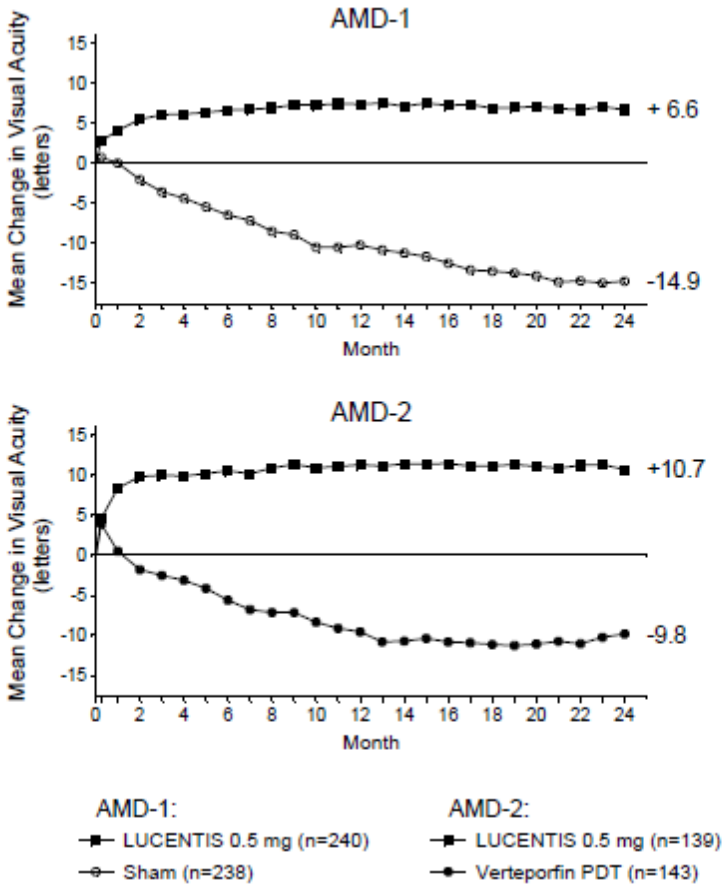
[a] Adjusted estimate based on the stratified model; p<0.01.
CI: confidence interval; SD: standard deviation.

Table 2. Visual Acuity Outcomes at Month 12 and Month 24 in Study AMD-2

Outcome Measure	**Month**	**Sham n=229**	**Lucentis 0.5 mg n=230**	**Estimated Difference (95% CI)[a]**
Loss of <15 letters in visual acuity (%)	12	66%	98%	32% (24%, 40%)
	24	65%	93%	28% (19%, 37%)
Gain of ≥15 letters in visual acuity (%)	12	11%	37%	26% (17%, 36%)
	24	9%	37%	29% (20%, 39%)
Mean change in visual acuity (letters (SD)	12	-8.5 (17.8)	+11.0 (15.8)	19.8 (15.9, 23.7)
	24	-9.1 (18.7)	+10.9 (17.3)	20 (16.0, 24.4)

[a] Adjusted estimate based on the stratified model; p<0.01.
CI: confidence interval; SD: standard deviation.

Figure 1. Mean Change in Visual Acuity[a] from Baseline to Month 24 in Study AMD-1 and Study AMD-2



[a] Visual acuity was measured at a distance of 2 meters.

Patients in the group treated with Lucentis had minimal observable CNV lesion growth, on average. At Month 12, the mean change in the total area of the CNV lesion was 0.1-0.3-disc areas (DA) for Lucentis versus 2.3-2.6 DA for the control arms. At Month 24, the mean change in the total area of the CNV lesion was 0.3-0.4 DA for Lucentis versus 2.9-3.1 DA for the control arms.

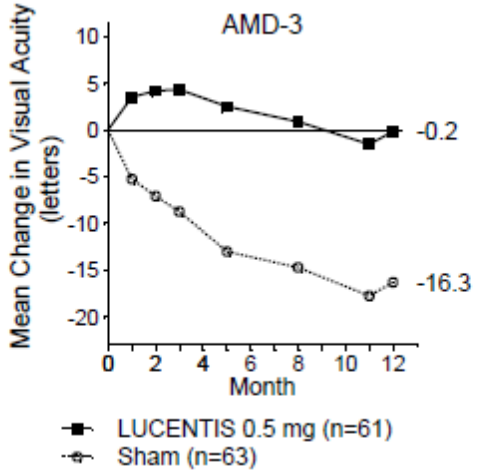
Study AMD-3

Study AMD-3 was a randomized, double-masked, sham-controlled, 2-year study designed to assess the safety and efficacy of Lucentis in patients with neovascular AMD (with or without a classic CNV component). Data are available through Month 12. Patients received Lucentis 0.3 mg or 0.5 mg intravitreal injections or sham injections once a month for three consecutive doses, followed by a dose administered once every 3 months for 9 months. A total of 184 patients were enrolled in this study (Lucentis 0.3 mg, 60; Lucentis 0.5 mg, 61; sham, 63); 171 (93%) completed 12 months of this study. Patients treated with Lucentis in Study AMD-3

received a mean of six total treatments out of a possible 6 from Day 0 through Month 12.

In Study AMD-3, the primary efficacy endpoint was the mean change in visual acuity at 12 months compared with baseline (see Figure 2). After an initial increase in visual acuity (following monthly dosing), on average, patients dosed once every 3 months with Lucentis lost visual acuity, returning to baseline at Month 12. In Study AMD-3, almost all Lucentis-treated patients (90%) lost fewer than 15 letters of visual acuity at Month 12.

Figure 2. Mean Change in Visual Acuity from Baseline in Month 12 in Study AMD-3



Study AMD-4
Study AMD-4 was a randomized, double-masked, active treatment-controlled, two-year study designed to assess the safety and efficacy of Lucentis 0.5 mg administered monthly or less frequently than monthly in patients with neovascular AMD. Patients randomized to the Lucentis 0.5 mg less frequent dosing arm received three monthly doses followed by monthly assessments where patients were eligible to receive Lucentis injections guided by pre-specified re-treatment criteria. A total of 550 patients were enrolled in the two 0.5 mg treatment groups with 467 (85%) completing through Month 24. Data are available through Month 24.

Clinical results at Month 24 remain similar to that observed at Month 12.

From Month 3 through Month 24, visual acuity decreased by 0.3 letters in the 0.5 mg less frequent dosing arm and increased by 0.7 letters in the 0.5 mg monthly arm (see Figure 3). Over this 21-month period, patients in the 0.5 mg less frequent

dosing and the 0.5 mg monthly arms averaged 10.3 and 18.5 injections, respectively. The distribution of injections received in the less frequent dosing arm is shown in Figure 4.

Figure 3. Mean Change in Visual Acuity from Baseline to Month 24 in Study AMD-4

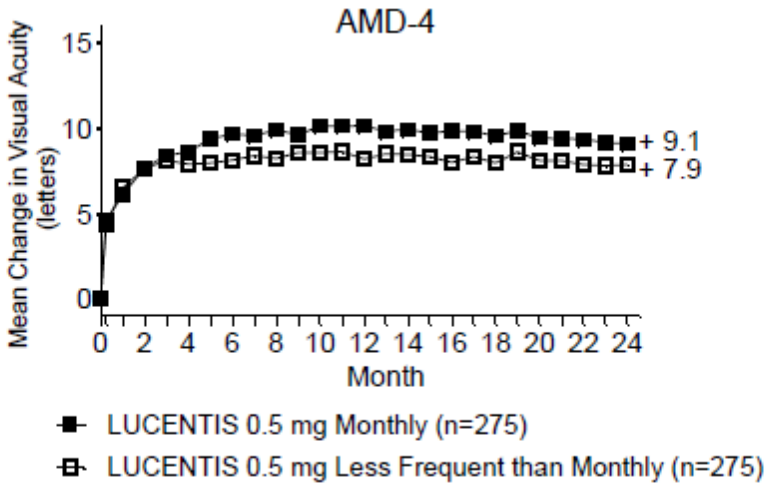
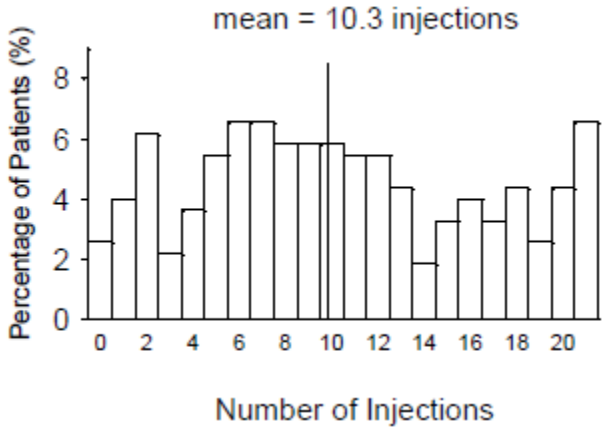


Figure 4. Distribution of Injections from Month 3 to Month 24 in the Less Frequent Dosing Arm in Study AMD-4



Macular Edema Following Retinal Vein Occlusion (RVO)

The safety and efficacy of Lucentis were assessed in two randomized, double-masked, 1-year studies in patients with macular edema following RVO. Sham controlled data are available through Month 6. Patient age ranged from 20 to 91 years, with a mean age of 67 years. A total of 789 patients (Lucentis 0.3 mg, 266 patients; Lucentis 0.5 mg, 261 patients; sham, 262 patients) were enrolled, with 739 (94%) patients completing through Month 6. All patients completing Month 6 were

eligible to receive Lucentis injections guided by pre-specified re-treatment criteria until the end of the studies at Month 12.

In Study RVO-1, patients with macular edema following branch or hemi-RVO, received monthly Lucentis 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections for 6 months. All patients were eligible for macular focal/grid laser treatment beginning at Month 3 of the 6-month treatment period. Macular focal/grid laser treatment was given to 26 of 131 (20%) patients treated with 0.5 mg Lucentis and 71 of 132 (54%) patients treated with sham.

In Study RVO-2, patients with macular edema following central RVO received monthly Lucentis 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections for 6 months.

At Month 6, after monthly treatment with 0.5 mg Lucentis, the following clinical results were observed:

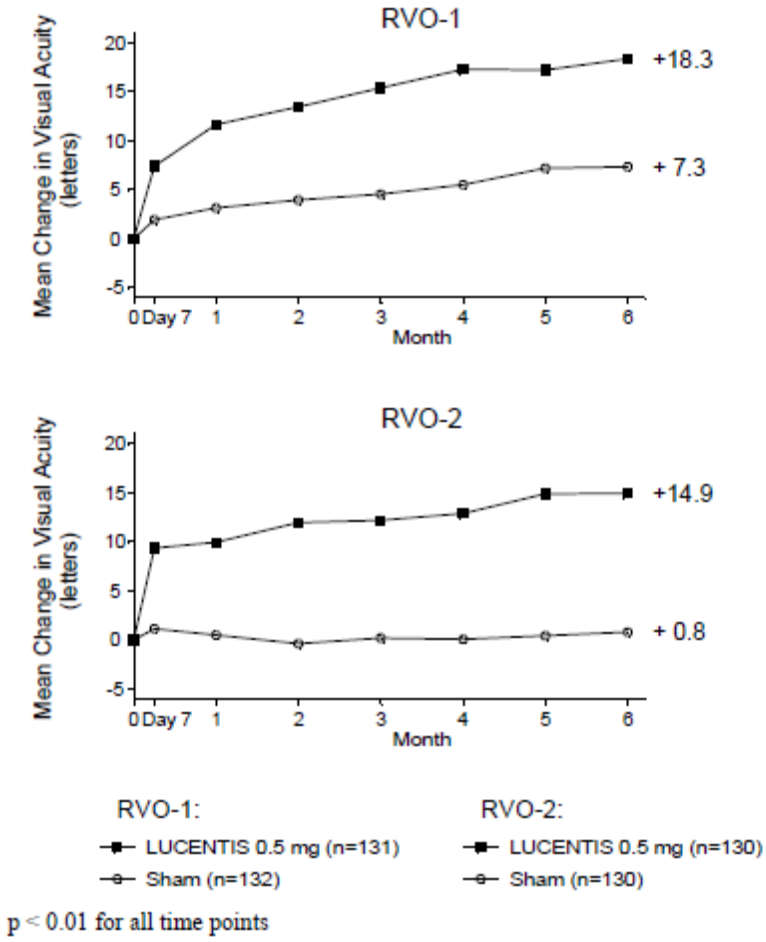
Table 3. Visual Acuity Outcomes at Month 6 in Study RVO-1 and Study RVO-2

Outcome Measures	**Study[a]**	**Sham**	**Lucentis 0.5 mg**	**Estimated Difference (95% CI)[b]**
Gain of ≥15 letters in visual acuity (%)	RVO-1	29%	61%	31% (20%, 43%)
Gain of ≥15 letters in visual acuity (%)	RVO-2	17%	48%	30% (20%, 41%)

[a] RVO-1: Sham, n=131; Lucentis 0.5 mg, n =132; RVO-2: Sham, n = 130; Lucentis 0.5 mg, n=130.

[b] Adjusted estimate based on stratified model; p<0.01.

Figure 5. Mean Change in Visual Acuity from Baseline to Month 6 in Study RVO-1 and Study RVO-2



$p < 0.01$ for all time points

Diabetic Macular Edema (DME)

Efficacy and safety data of Lucentis are derived from studies D-1 and D-2. All enrolled patients had diabetic retinopathy (DR) and DME at baseline.

The safety and efficacy of Lucentis were assessed in two randomized, double-masked, 3-year studies. The studies were sham-controlled through Month 24. Patient age ranged from 21 to 91 years, with a mean age of 62 years. A total of 759 patients (Lucentis 0.3 mg, 250 patients; Lucentis 0.5 mg, 252 patients; sham, 257 patients) were enrolled, with 582 (77%) completing through Month 36.

In Studies D-1 and D-2, patients received monthly Lucentis 0.3 mg or 0.5 mg intravitreal injections or monthly sham injections during the 24-month controlled treatment period. From Months 25 through 36, patients who previously received sham were eligible to receive monthly Lucentis 0.5 mg and patients originally randomized to monthly Lucentis 0.3 mg or 0.5 mg continued to receive their assigned dose. All patients were eligible for macular focal/grid laser treatment

beginning at Month 3 of the 24-month treatment period or panretinal photocoagulation (PRP) as needed. Through Month 24, macular focal/grid laser treatment was administered in 94 of 250 (38%) patients treated with Lucentis 0.3 mg and 185 of 257 (72%) patients treated with sham; PRP was administered in 2 of 250 (1%) patients treated with Lucentis 0.3 mg and 30 of 257 (12%) patients treated with sham.

Compared to monthly Lucentis 0.3 mg, no additional benefit was observed with monthly treatment with Lucentis 0.5 mg. At Month 24, after monthly treatment with Lucentis 0.3 mg, the following clinical results were observed:

Table 4. Visual Acuity Outcomes at Month 24 in Study D-1 and D-2

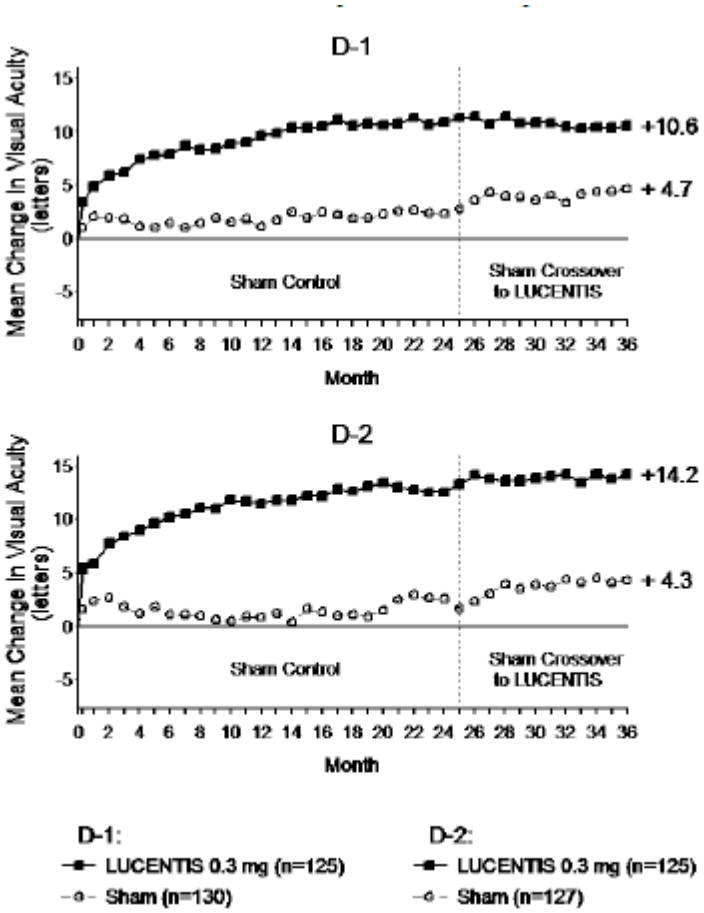
Outcome Measure	**Study[a]**	**Sham**	**Lucentis 0.3 mg**	**Estimated Difference (95% CI)[b]**
Gain of ≥15 letters in visual acuity (%)	D-1	12%	34%	21% (11%, 30%)
	D-2	18%	45%	24% (14%, 35%)
Loss of <15 letters in visual acuity (%)	D-1	92%	98%	7% (2%, 13%)
	D-2	90%	98%	8% (2%, 14%)
Mean change in visual acuity (letters)	D-1	2.3	10.9	8.5 (5.4, 11.5)
	D-2	2.6	12.5	9.6 (6.1, 13.0)

CI: confidence interval.

[a] D-1: Sham, n =130; Lucentis 0.3 mg, n=125; D-2: Sham, n=127; Lucentis 0.3 mg, n=125.

[b] Adjusted estimate based on stratified model; p≤0.01.

Figure 6. Mean Change to Visual Acuity from Baseline to Month 36 in Study D-1 and Study D-2



$p < 0.01$ for all time points comparing LUCENTIS 0.3 mg to sham through Month 24

Visual acuity outcomes observed at Month 24 in patients treated with Lucentis 0.3 mg were maintained with continued treatment through Month 36 in both DME studies. Patients in the sham arms who received Lucentis 0.5 mg beginning at Month 25 achieved lesser VA gains compared to patients who began treatment with Lucentis at the beginning of the studies.

In Studies D-1 and D-2, patients received monthly injections of Lucentis for 12 or 36 months, after which 500 patients opted to continue in the long-term follow-up study. Of 298 patients who had at least 12 months of follow-up from Month 36, 58 (19.5%) patients maintained vision with no further therapy. The remaining 202 patients were followed for less than 12 months.

Diabetic Retinopathy

Efficacy and safety data of Lucentis are derived from Studies D-1, D-2 and D-3. All enrolled patients in Studies D-1 and D-2 had DR and DME at baseline. Study D-3 enrolled DR patients both with and without DME at baseline.

Of the 759 patients enrolled in Studies D-1 and D-2, 746 patients had a baseline assessment of fundus photography. Patients had baseline Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scores (ETDRS-DRSS) ranging from 10 to 75. At baseline, 62% of patients had non-proliferative diabetic retinopathy (NPDR) (ETDRS-DRSS less than 60) and 31% had proliferative diabetic retinopathy (PDR) (ETDRS-DRSS greater than or equal to 60). The ETDRS-DRSS could not be graded in 5% of patients at baseline, and 2% of patients had absent or questionable DR at baseline. Approximately 20% of the overall population had prior PRP.

After monthly treatment with Lucentis 0.3 mg, the following clinical results were observed (Table 5; Figure 7):

Table 5. ≥3-Step and ≥2-Step Improvement at Month 24 in Study D-1 and Study D-2

Outcome Measure	**Study[a]**	**Sham**	**Lucentis 0.3 mg**	**Estimated Difference (95% CI)[b]**
≥3-step improvement from baseline in ETDRS-DRSS[c]	D-1	2%	17%	15% (7%, 22%)
	D-2	0%	9%	9% (4%, 14%)
≥2-step improvement from baseline in ETDRS-DRSS[d]	D-1	4%	39%	35% (26%, 44%)
	D-2	7%	37%	31% (21%, 40%)

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

[a] D-1: Sham, n=124; Lucentis 0.3 mg, n=117; D-2: Sham, n=115; Lucentis 0.3 mg, n=117.

[b] Adjusted estimate based on stratified model.

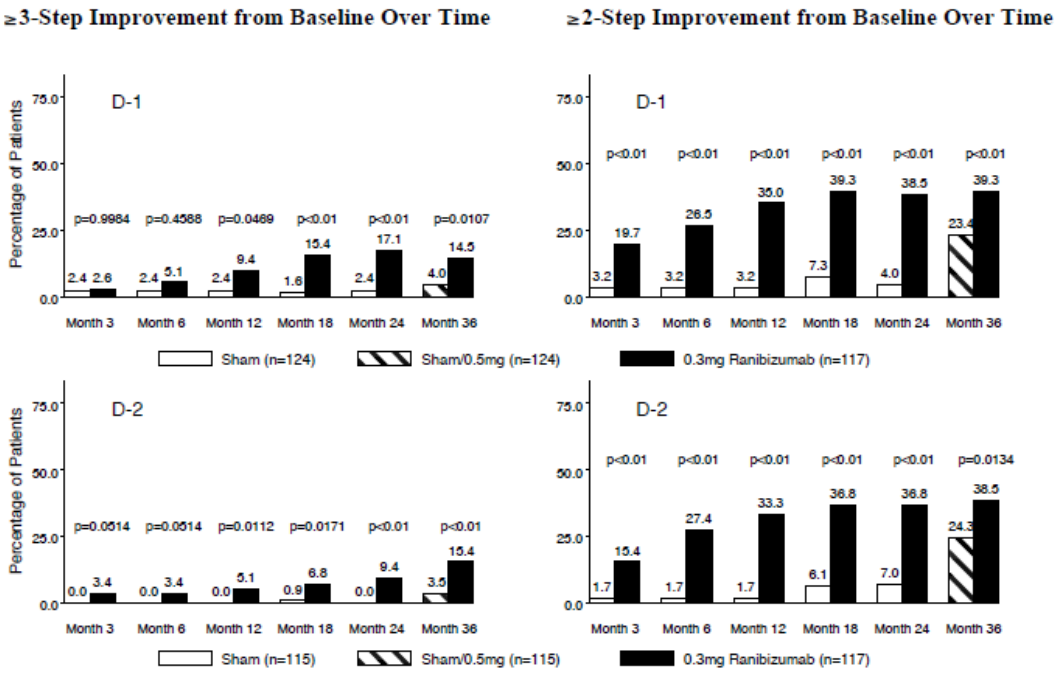
[c] $p < 0.05$ for all time points comparing Lucentis 0.3 mg to sham from month 12 through month 24.

[d] $p < 0.05$ for all time points comparing Lucentis 0.3 mg to sham from Month 3 through Month 24.

At Month 24, DR improvement by ≥3-steps in ETDRS-DRSS from baseline in subgroups examined (e.g., age, gender, race, baseline visual acuity, baseline HbA1c, prior DME therapy at baseline, baseline DR severity (NPDR, PDR)) were generally consistent with the results in the overall population.

The difference in the proportion of patients treated with Lucentis 0.3 mg compared to sham who achieved DR improvement based on the ETDRS-DRSS was observed as early as Month 3 for ≥2-step improvement or at Month 12 for ≥3-step improvement.

Figure 7. Proportion of Patients with a ≥3-Step and ≥2-Step Improvement from Baseline in ETDRS Diabetic Retinopathy Severity Level over Time in Study D-1 and Study D-2



Study D-3 enrolled DR patients with and without DME; 88 (22%) eyes with baseline DME and 306 (78%) eyes without baseline DME and balanced across treatment groups. Study D-3 was a randomized, active-controlled study where patient age ranged from 20 to 83 with a mean age of 51 years. A total of 394 study eyes from 305 patients, including 89 who had both eyes randomized, were enrolled (Lucentis, 191 study eyes; pan-retinal photocoagulation; 203 study eyes). All eyes in the Lucentis group received a baseline 0.5 mg intravitreal injection followed by 3

monthly intravitreal injections, after which treatment was guided by pre-specified retreatment criteria. Patients had baseline ETDRS-DRSS ranging from 20 to 85. At baseline, 11% of eyes had NPDR (ETDRS-DRSS less than 60), 50% had mild-to-moderate PDR (ETDRS-DRSS equal to 60, 61, or 65), and 37% had high-risk PDR (ETDRS-DRSS greater than or equal to 71).

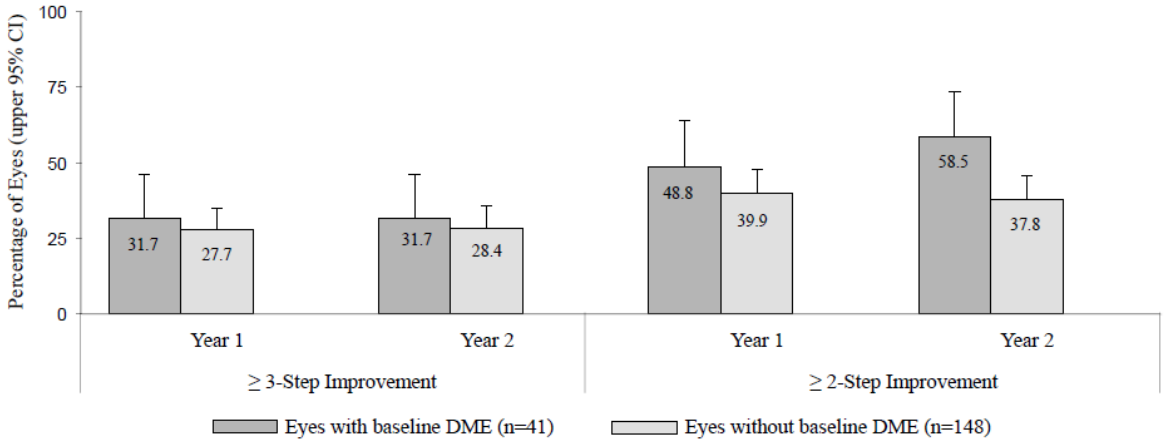
An analysis of data from Study D-3 demonstrated that at Year 2 in the Lucentis group, 31.7% and 28.4% of eyes in the subgroups with baseline DME and without baseline DME, respectively, had ≥ 3-step improvement from baseline in ETDRS-DRSS.

Table 6. Proportion of Eyes with a ≥3-Step and ≥2-Step Improvement from Baseline in ETDRS-DRSS at Year 2 in Study D-3

	Lucentis Group	
Outcome Measure (in ETDRS-DRSS)	**Eyes with Baseline DME n = 41**	**Eyes without Baseline DME n = 148**
≥ 3-step improvement from baseline 95% CI for percentage	13 (31.7%) (17.5%, 46.0%)	42 (28.4%) (21.1%, 35.6%)
≥ 2-step improvement from baseline 95% CI for percentage	24 (58.5%) (43.5%, 73.6%)	56 (37.8%) (30.0%, 45.7%)

ETDRS-DRSS: Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scores; DME: Diabetic Macular Edema; CI: confidence interval.

Figure 8. Proportion of Eyes in the Lucentis group with ≥ 3-Step and ≥ 2-Step Improvement from Baseline in ETDRS-DRSS at Year 1 and Year 2 in Study D-3



Myopic Choroidal Neovascularization (mCNV)

The efficacy and safety data of Lucentis were assessed in a randomized, double-masked, active-controlled 3-month study in patients with mCNV. Patients age ranged from 18 to 87 years, with a mean age of 55 years. A total of 276 patients (222 patients in the Lucentis treated Groups I and II; 55 patients in the active control PDT group) were enrolled. Patients randomized to the Lucentis groups received injections guided by prespecified re-treatment criteria. The retreatment criteria in Group I were vision stability guided, with the Best Corrected Visual Acuity (BCVA) at the current visit being assessed for changes compared with the two preceding monthly BCVA values. The retreatment criteria in Group II were disease activity guided, based on BCVA decrease from the previous visit that was attributable to intra- or sub-retinal fluid or active leakage secondary to mCNV as assessed by optical cohearence tomography (OCT) and/or FA compared to the previous monthly visit.

Visual gains for the two Lucentis 0.5 mg treatment arms were superior to the active control arm. The mean change in BCVA from baseline at Month 3 was: +12.1 letters for Group I, +12.5 letters for Group II and +1.4 letters for the PDT group. (Figure 9; Table 7). Efficacy was comparable between Group I and Group II.

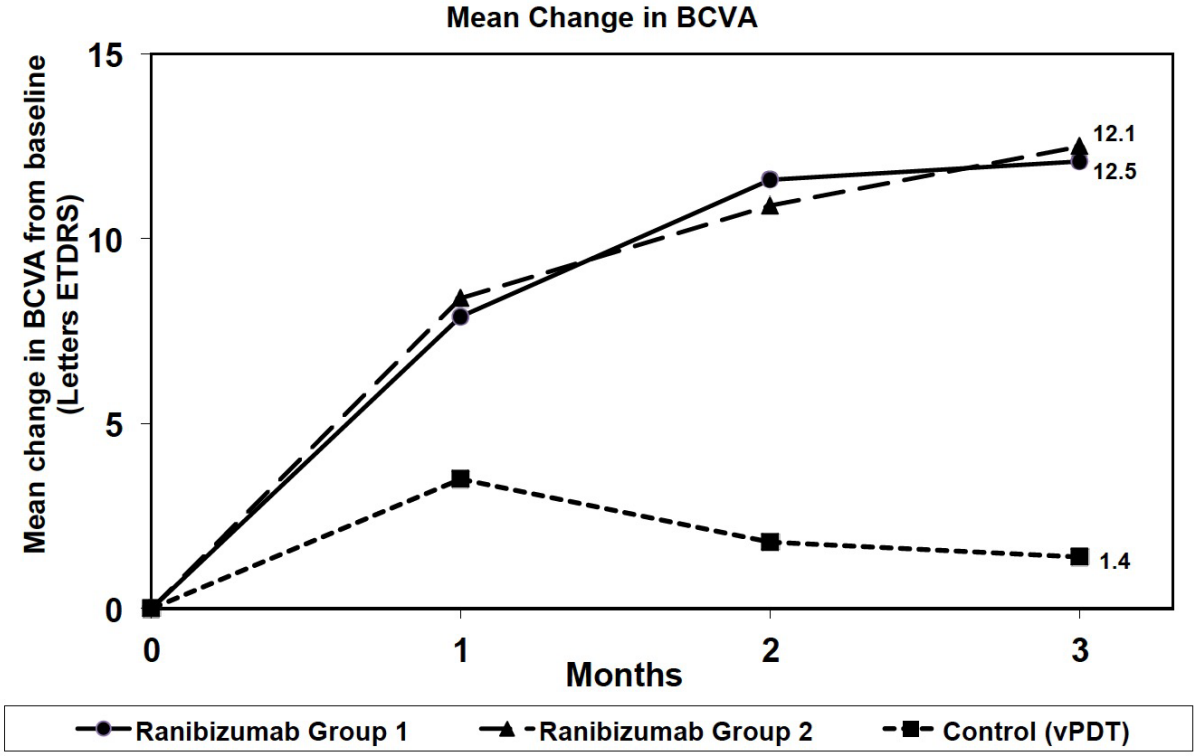
Table 7. Mean Change in Visual Acuity and Proportion of Patients who Gained ≥15 letters from Baseline at Month 3

Study Arms	Mean change in BCVA from baseline (Letters)		Proportion of patients who gained ≥15 letters from baseline	
	Mean (SD)	Estimated Difference (95% CI)[a]	Percent	Estimated Difference (95% CI)[a]
Group I	12.1 (10.2)	10.9 (7.6, 14.3)	37.1	22.6 (9.5, 35.7)
Group II	12.5 (8.8)	11.4 (8.3, 14.5)	40.5	26.0 (13.1, 38.9)
Control (PDT)	1.4 (12.2)		14.5	

[a] Adjusted estimates based on stratified models; $p < 0.01$

BCVA: Best Corrected Visual Acuity; PDT: photodynamic therapy; CI: confidence interval; SD: standard deviation.

Figure 9. Mean Change in Visual Acuity from Baseline to Month 3 in mCNV Study



The proportion of patients who gained ≥15 letters (ETDRS) by Month 3 was 37.1% and 40.5% for Lucentis Groups I and II, respectively and 14.5% for the PDT group. The mean number of injections between baseline and Month 3 was 2.5 and 1.8 for Groups I and II, respectively. 41% of patients received 1, 2 or 3 injections between baseline and Month 3 with no injections afterwards.

Susvimo™ (2)

The clinical efficacy and safety of Susvimo (ranibizumab injection) was assessed in a randomized, visual assessor-masked, active treatment-controlled study (Archway-NCT03677934) in patients with AMD. A total of 415 patients (248 in the Susvimo arm and 167 in the intravitreal ranibizumab arm) were enrolled and treated in this study.

Patients were diagnosed with nAMD within the 9 months prior to screening and received ≥ 3

doses of anti-VEGF intravitreal agents in the study eye within the last 6 months prior to

screening. Each patient was required to have demonstrated a response to an anti-VEGF

intravitreal agent prior to randomization. Patients were randomized in a 3:2 ratio to receive
continuous delivery of Susvimo (ranibizumab injection) via the Susvimo implant every 24
weeks or 0.5 mg intravitreal ranibizumab injections every 4 weeks. For patients randomized to
the Susvimo arm, supplemental treatment with 0.5 mg intravitreal ranibizumab injections was
available at Weeks 16, 20, 40, 44, 64, 68, 88, and 92, if needed. In the first 24 weeks, 1.6% of
patients assessed for supplemental treatment received 1 or more supplemental treatment(s) and in the following 24 weeks, 5.4% of patients assessed for supplemental treatment received 1 or more supplemental treatment(s).

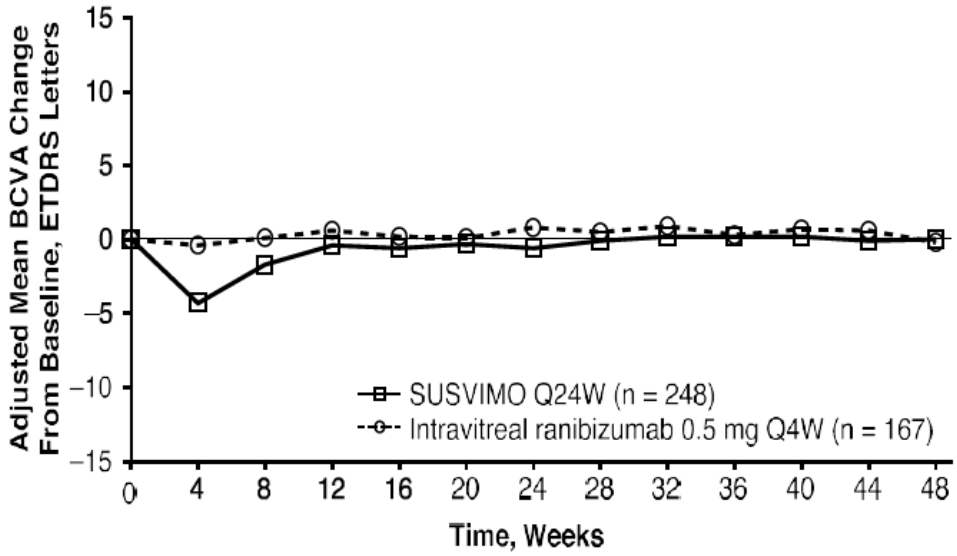
The primary efficacy endpoint of change from baseline in distance BCVA score averaged over Week 36 and Week 40 demonstrated that Susvimo was equivalent to intravitreal ranibizumab injections administered every 4 weeks. Detailed efficacy
results are shown in Table 8 and Figure 10 below.

Table 8. Visual Acuity Outcomes at Week 40 in Archway (GR40548) Study

Outcome Measure[a]	**Susvimo (100 mg/mL n=248**	**Intravitreal ranibizumab 0.5 mg (10 mg/mL) n=167**	**Difference (95% CI)[b]**
Adjusted mean change from baseline in BCVA score average over weeks 36 and 40	0.2	0.5	-0.3 (-1.7, 1.1)[c]

BCVA: Best corrected visual acuity; CI: confidence interval.
[a] BCVA measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart at a starting distance of 4 meters.
[b] All estimates are adjusted estimates based on a mixed-effect model with repeated measures. Susvimo arm intravitreal ranibizumab arm. 95% is a rounding of 95.03% CI; The type 1 error was adjusted for interim sensitivity monitoring.
[c] Equivalence margins were ±4.5 letters.

Figure 10. Adjusted Mean change from Baseline in Best Corrected Visual Acuity in study
eye through Week 48 in the Archway (GR40548) study[a], [b]



[a] Prior to study treatment, a median of 4 doses of anti-VEGF intravitreal agents were administered in the study eye of patients in the SUSVIMO and intravitreal ranibizumab arms.
[b] Decrease in BCVA at Week 4 during post-operative recovery period.
Q24W = every 24 weeks; Q4W = every 4 weeks

Consistent results were observed across patient subgroup analyses for mean change from
baseline in BCVA score (age, gender, number of prior anti-VEGF intravitreal injections, and
baseline BCVA score).

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	J2778, J2779, J3490, J3590, Q5124, Q5128, [Deleted 6/30/2022 C9093]

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Centers for Medicare and Medicaid Services (CMS)

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Policy History/Revision	
Date	**Description of Change**
01/01/2026	New medical document.