Medical Benefit Drug Policy

Vascular Endothelial Growth Factor Inhibitors for Ocular Diseases

Policy Number: MC/PC 036
Effective Date: March 1, 2025

Instructions for Use

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Related Policies

- n/a

Coverage Rationale

For the initial coverage the following will be required:

- **Compounded Avastin,** when prepared by a 503(B) Outsourcing Facility, the following diagnosis will be covered when prescribed by or in consultation with an ophthalmologist experienced in the treatment of retinal diseases:
  - Choroidal neovascularization secondary to pathologic myopia, angioid streaks/pseudoxanthoma elasticum, or ocular histoplasmosis syndrome (OHS) **or**
  - Diabetic macular edema (DME) **or**
  - Macular edema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) **or**
  - Neovascular age-related macular degeneration (AMD) **or**
  - Neovascular glaucoma **or**
  - Neovascularization of the iris (NVI) (rubeosis iridis) **or**
  - Proliferative diabetic retinopathy **or**
  - Type I retinopathy of prematurity

- **Beovu,** the following diagnosis will be covered when prescribed by or in consultation with an ophthalmologist experienced in the treatment of retinal diseases:
  - Neovascular (wet) age-related macular degeneration (nAMD) **or**
  - Diabetic macular edema (DME)

- **Vabysmo,** the following diagnosis will be covered when prescribed by or in consultation with an ophthalmologist experienced in the treatment of retinal diseases:
    - Neovascular (wet) age-related macular degeneration (nAMD) **or**
    - Diabetic macular edema (DME) **or**
    - Macular Edema following retinal vein occlusion (RVO)

- **Lucentis 0.3mg and Cimerli 0.3mg,** the following diagnosis will be covered when prescribed by or in consultation with an ophthalmologist experienced in the treatment of retinal diseases:
    - Diabetic macular edema (DME) **or**
    - Diabetic retinopathy (DR)

- **Lucentis 0.5mg, Cimerli 0.5mg, and Byooviz,** the following diagnosis will be covered when prescribed by or in consultation with an ophthalmologist experienced in the treatment of retinal diseases:
    - Neovascular (wet) age-related macular degeneration (nAMD) **or**
    - Macular edema following retinal vein occlusion (RVO) **or**
    - Myopic choroidal neovascularization (mCNV)

- **Eylea and Pavblu,** the following diagnosis will be covered when prescribed by or in consultation with an ophthalmologist experienced in the treatment of retinal diseases:
    - Neovascular (wet) age-related macular degeneration (nAMD) **or**
    - Macular edema following retinal vein occlusion (RVO) **or**
    - Diabetic macular edema (DME) **or**
    - Diabetic retinopathy (DR)

- **Eylea HD,** the following diagnosis will be covered when prescribed by or in consultation with an ophthalmologist experienced in the treatment of retinal diseases:
    - Neovascular (wet) age-related macular degeneration (nAMD) **or**
    - Diabetic macular edema (DME) **or**
    - Diabetic retinopathy (DR)

- **Eylea Injectable Vial,** when prescribed by or in consultation with an ophthalmologist experienced in the treatment of retinal diseases, the following will be required:
    - Diagnosis of retinopathy of prematurity (ROP) **and**
    - One of the following diagnoses:
        - Patient gestational age at birth less than or equal to 32 weeks
        - Patient birth weight less than or equal to 1500 grams **and**
    - Patient weight greater than 800 grams on day of treatment **and**
    - Retinopathy of prematurity (ROP) is present in at least one eye with one of the following classifications:
        - ROP zone 1, stage 1 plus, 2 plus, 3, or 3 plus
        - ROP zone 2, stage 2 plus or 3 plus
        - AP - ROP (aggressive posterior ROP)

- **Susvimo,** when prescribed by or in consultation with an ophthalmologist experienced in the treatment of retinal diseases, the following will be required:
    - Diagnosis of neovascular (wet) age-related macular degeneration (nAMD) **and**
    - Trial and positive response to at least 2 intravitreal injections

For the coverage on reauthorization the following will be required:

- **Compounded Avastin, Beovu, Byooviz, Cimerli, Eylea, Eylea HD, Lucentis, Pavblu, Susvimo, and Vabysmo,** when prescribed by or in consultation with an ophthalmologist experienced in the treatment of retinal diseases, the following will be required:
    - Documentation of positive clinical response to therapy (e.g., Improvement in Best Corrected Visual Acuity (BCVA) compared to baseline, stable vision)

- **Eylea Injectable Vial,** the following will be required when prescribed by or in consultation with an ophthalmologist experienced in the treatment of retinal diseases:
    - Documentation of positive clinical response to therapy as evidenced by the absence of active ROP and unfavorable structural outcomes (e.g., retinal detachment, macular dragging, macular fold, retrolental opacity)

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0177	Injection, aflibercept HD, 1 mg (Eylea HD)
J0178	Injection, aflibercept, 1 mg (Eylea)
J0179	Injection, brolucizumab-dbll, 1 mg (Beovu)
J2777	Injection, faricimab-svoa, 0.1 mg (Vabysmo)
J2778	Injection, ranibizumab, 0.1 mg (Lucentis)
J2779	Injection, ranibizumab, via intravitreal implant 0.1 mg (Susvimo)
J9035	Injection, bevacizumab, 10 mg (Avastin)
Q5124	Injection, ranibizumab-nuna, biosimilar 0.1 mg (Byooviz)
Q5128	Injection, ranibizumab-eqrn biosimilar, 0.1 mg (Cimerli)
Q5147	Injection, aflibercept-ayyh biosimilar, 1 mg (Pavblu)

ICD-10 Code	Description
E08.31	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy
E08.311	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy with macular edema

ICD-10 Code	Description
E08.319	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy without macular edema
E08.32	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy
E08.321	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy with macular edema
E08.3211	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy with macular edema, right eye
E08.3212	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy with macular edema, left eye
E08.3213	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy with macular edema, bilateral
E08.3219	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy with macular edema, unspecified eye
E08.329	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy without macular edema
E08.3291	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy without macular edema, right eye
E08.3292	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy without macular edema, left eye
E08.3293	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy without macular edema, bilateral
E08.3299	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy without macular edema, unspecified eye
E08.33	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy
E08.331	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy with macular edema
E08.3311	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy with macular edema, right eye
E08.3312	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy with macular edema, left eye
E08.3313	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy with macular edema, bilateral
E08.3319	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy with macular edema, unspecified eye
E08.339	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy without macular edema
E08.3391	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy without macular edema, right eye
E08.3392	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy without macular edema, left eye
E08.3393	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy without macular edema, bilateral
E08.3399	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy without macular edema, unspecified eye

ICD-10 Code	Description
E08.34	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy
E08.341	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy with macular edema
E08.3411	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy with macular edema, right eye
E08.3412	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy with macular edema, left eye
E08.3413	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E08.3419	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy with macular edema, unspecified eye
E08.349	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy without macular edema
E08.3491	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy without macular edema, right eye
E08.3492	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy without macular edema, left eye
E08.3493	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy without macular edema, bilateral
E08.3499	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy without macular edema, unspecified eye
E08.35	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy
E08.351	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema
E08.3511	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema, right eye
E08.3512	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema, left eye
E08.3513	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema, bilateral
E08.3519	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema, unspecified eye
E08.352	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment involving the macula
E08.3521	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye
E08.3522	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye
E08.3523	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral
E08.3529	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye
E08.353	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment not involving the macula

ICD-10 Code	Description
E08.3531	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye
E08.3532	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye
E08.3533	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral
E08.3539	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye
E08.354	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment
E08.3541	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye
E08.3542	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye
E08.3543	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral
E08.3549	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye
E08.355	Diabetes mellitus due to underlying condition with stable proliferative diabetic retinopathy
E08.3551	Diabetes mellitus due to underlying condition with stable proliferative diabetic retinopathy, right eye
E08.3552	Diabetes mellitus due to underlying condition with stable proliferative diabetic retinopathy, left eye
E08.3553	Diabetes mellitus due to underlying condition with stable proliferative diabetic retinopathy, bilateral
E08.3559	Diabetes mellitus due to underlying condition with stable proliferative diabetic retinopathy, unspecified eye
E08.359	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy without macular edema
E08.3591	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy without macular edema, right eye
E08.3592	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy without macular edema, left eye
E08.3593	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy without macular edema, bilateral
E08.3599	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy without macular edema, unspecified eye
E08.37X1	Diabetes mellitus due to underlying condition with diabetic macular edema, resolved following treatment, right eye
E08.37X2	Diabetes mellitus due to underlying condition with diabetic macular edema, resolved following treatment, left eye
E08.37X3	Diabetes mellitus due to underlying condition with diabetic macular edema, resolved following treatment, bilateral
E08.37X9	Diabetes mellitus due to underlying condition with diabetic macular edema, resolved following treatment, unspecified eye
E09.31	Drug or chemical induced diabetes mellitus with unspecified diabetic retinopathy

ICD-10 Code	Description
E09.311	Drug or chemical induced diabetes mellitus with unspecified diabetic retinopathy with macular edema
E09.319	Drug or chemical induced diabetes mellitus with unspecified diabetic retinopathy without macular edema
E09.32	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy
E09.321	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E09.3211	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, right eye
E09.3212	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye
E09.3213	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, bilateral
E09.3219	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, unspecified eye
E09.329	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema
E09.3291	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, right eye
E09.3292	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, left eye
E09.3293	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, bilateral
E09.3299	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, unspecified eye
E09.33	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy
E09.331	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E09.3311	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, right eye
E09.3312	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, left eye
E09.3313	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, bilateral
E09.3319	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, unspecified eye
E09.339	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema
E09.3391	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, right eye
E09.3392	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, left eye
E09.3393	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, bilateral

ICD-10 Code	Description
E09.3399	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, unspecified eye
E09.34	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy
E09.341	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E09.3411	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, right eye
E09.3412	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, left eye
E09.3413	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E09.3419	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, unspecified eye
E09.349	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema
E09.3491	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, right eye
E09.3492	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, left eye
E09.3493	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, bilateral
E09.3499	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, unspecified eye
E09.35	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy
E09.351	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema
E09.3511	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye
E09.3512	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye
E09.3513	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral
E09.3519	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye
E09.352	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula
E09.3521	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye
E09.3522	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye
E09.3523	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral
E09.3529	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye

ICD-10 Code	Description
E09.353	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula
E09.3531	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye
E09.3532	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye
E09.3533	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral
E09.3539	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye
E09.354	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment
E09.3541	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye
E09.3542	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye
E09.3543	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral
E09.3549	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye
E09.355	Drug or chemical induced diabetes mellitus with stable proliferative diabetic retinopathy
E09.3551	Drug or chemical induced diabetes mellitus with stable proliferative diabetic retinopathy, right eye
E09.3552	Drug or chemical induced diabetes mellitus with stable proliferative diabetic retinopathy, left eye
E09.3553	Drug or chemical induced diabetes mellitus with stable proliferative diabetic retinopathy, bilateral
E09.3559	Drug or chemical induced diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye
E09.359	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy without macular edema
E09.3591	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye
E09.3592	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye
E09.3593	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral
E09.3599	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye
E09.37X1	Drug or chemical induced diabetes mellitus with diabetic macular edema, resolved following treatment, right eye
E09.37X2	Drug or chemical induced diabetes mellitus with diabetic macular edema, resolved following treatment, left eye
E09.37X3	Drug or chemical induced diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral

ICD-10 Code	Description
E09.37X9	Drug or chemical induced diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye
E10.31	Type 1 diabetes mellitus with unspecified diabetic retinopathy
E10.311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E10.319	Type 1 diabetes mellitus with unspecified diabetic retinopathy without macular edema
E10.32	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy
E10.321	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E10.3211	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, right eye
E10.3212	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye
E10.3213	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, bilateral
E10.3219	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, unspecified eye
E10.329	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema
E10.3291	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, right eye
E10.3292	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, left eye
E10.3293	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, bilateral
E10.3299	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, unspecified eye
E10.33	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy
E10.331	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E10.3311	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, right eye
E10.3312	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, left eye
E10.3313	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, bilateral
E10.3319	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, unspecified eye
E10.339	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema
E10.3391	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, right eye
E10.3392	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, left eye
E10.3393	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, bilateral

ICD-10 Code	Description
E10.3399	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, unspecified eye
E10.34	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy
E10.341	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E10.3411	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, right eye
E10.3412	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, left eye
E10.3413	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E10.3419	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, unspecified eye
E10.349	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema
E10.3491	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, right eye
E10.3492	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, left eye
E10.3493	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, bilateral
E10.3499	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, unspecified eye
E10.35	Type 1 diabetes mellitus with proliferative diabetic retinopathy
E10.351	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema
E10.3511	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye
E10.3512	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye
E10.3513	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral
E10.3519	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye
E10.352	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula
E10.3521	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye
E10.3522	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye
E10.3523	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral
E10.3529	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye
E10.353	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula
E10.3531	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye
E10.3532	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye

ICD-10 Code	Description
E10.3533	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral
E10.3539	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye
E10.354	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment
E10.3541	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye
E10.3542	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye
E10.3543	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral
E10.3549	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye
E10.355	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy
E10.3551	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, right eye
E10.3552	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, left eye
E10.3553	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, bilateral
E10.3559	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye
E10.359	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema
E10.3591	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye
E10.3592	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye
E10.3593	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral
E10.3599	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye
E10.37X1	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, right eye
E10.37X2	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, left eye
E10.37X3	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral
E10.37X9	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye
E11.311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E11.319	Type 2 diabetes mellitus with unspecified diabetic retinopathy without macular edema
E11.32	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy
E11.321	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E11.3211	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, right eye
E11.3212	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye
E11.3213	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, bilateral
E11.3219	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, unspecified eye
E11.329	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema

ICD-10 Code	Description
E11.3291	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, right eye
E11.3292	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, left eye
E11.3293	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, bilateral
E11.3299	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, unspecified eye
E11.33	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy
E11.331	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E11.3311	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, right eye
E11.3312	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, left eye
E11.3313	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, bilateral
E11.3319	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, unspecified eye
E11.339	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema
E11.3391	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, right eye
E11.3392	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, left eye
E11.3393	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, bilateral
E11.3399	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, unspecified eye
E11.34	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy
E11.341	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E11.3411	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, right eye
E11.3412	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, left eye
E11.3413	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E11.3419	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, unspecified eye
E11.349	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema
E11.3491	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, right eye
E11.3492	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, left eye

ICD-10 Code	Description
E11.3493	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, bilateral
E11.3499	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, unspecified eye
E11.35	Type 2 diabetes mellitus with proliferative diabetic retinopathy
E11.351	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema
E11.3511	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye
E11.3512	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye
E11.3513	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral
E11.3519	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye
E11.352	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula
E11.3521	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye
E11.3522	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye
E11.3523	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral
E11.3529	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye
E11.353	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula
E11.3531	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye
E11.3532	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye
E11.3533	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral
E11.3539	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye
E11.354	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment
E11.3541	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye
E11.3542	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye
E11.3543	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral
E11.3549	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye
E11.355	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy
E11.3551	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, right eye
E11.3552	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, left eye

ICD-10 Code	Description
E11.3553	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, bilateral
E11.3559	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye
E11.359	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema
E11.3591	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye
E11.3592	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye
E11.3593	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral
E11.3599	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye
E11.37X1	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, right eye
E11.37X2	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, left eye
E11.37X3	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral
E11.37X9	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye
E13.311	Other specified diabetes mellitus with unspecified diabetic retinopathy with macular edema
E13.319	Other specified diabetes mellitus with unspecified diabetic retinopathy without macular edema
E13.3211	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, right eye
E13.3212	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, left eye
E13.3213	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, bilateral
E13.3219	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema, unspecified eye
E13.3291	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, right eye
E13.3292	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, left eye
E13.3293	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, bilateral
E13.3299	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema, unspecified eye
E13.3311	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, right eye
E13.3312	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, left eye
E13.3313	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, bilateral
E13.3319	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema, unspecified eye
E13.3391	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, right eye

ICD-10 Code	Description
E13.3392	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, left eye
E13.3393	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, bilateral
E13.3399	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema, unspecified eye
E13.3411	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, right eye
E13.3412	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, left eye
E13.3413	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, bilateral
E13.3419	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema, unspecified eye
E13.3491	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, right eye
E13.3492	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, left eye
E13.3493	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, bilateral
E13.3499	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema, unspecified eye
E13.3511	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye
E13.3512	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye
E13.3513	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral
E13.3519	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye
E13.3521	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye
E13.3522	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye
E13.3523	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral
E13.3529	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye
E13.3531	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye
E13.3532	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye
E13.3533	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral

ICD-10 Code	Description
E13.3539	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye
E13.3541	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye
E13.3542	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye
E13.3543	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral
E13.3549	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye
E13.3551	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, right eye
E13.3552	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, left eye
E13.3553	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, bilateral
E13.3559	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye
E13.3591	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye
E13.3592	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye
E13.3593	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral
E13.3599	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye
E13.37X1	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, right eye
E13.37X2	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, left eye
E13.37X3	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral
E13.37X9	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye
H34.8110	Central retinal vein occlusion, right eye, with macular edema
H34.8111	Central retinal vein occlusion, right eye, with retinal neovascularization
H34.8112	Central retinal vein occlusion, right eye, stable
H34.8120	Central retinal vein occlusion, left eye, with macular edema
H34.8121	Central retinal vein occlusion, left eye, with retinal neovascularization
H34.8122	Central retinal vein occlusion, left eye, stable
H34.8130	Central retinal vein occlusion, bilateral, with macular edema
H34.8131	Central retinal vein occlusion, bilateral, with retinal neovascularization
H34.8132	Central retinal vein occlusion, bilateral, stable
H34.8190	Central retinal vein occlusion, unspecified eye, with macular edema
H34.8191	Central retinal vein occlusion, unspecified eye, with retinal neovascularization
H34.8192	Central retinal vein occlusion, unspecified eye, stable

ICD-10 Code	Description
H34.83	Tributary (branch) retinal vein occlusion
H34.831	Tributary (branch) retinal vein occlusion, right eye
H34.8310	Tributary (branch) retinal vein occlusion, right eye, with macular edema
H34.8311	Tributary (branch) retinal vein occlusion, right eye, with retinal neovascularization
H34.8312	Tributary (branch) retinal vein occlusion, right eye, stable
H34.832	Tributary (branch) retinal vein occlusion, left eye
H34.8320	Tributary (branch) retinal vein occlusion, left eye, with macular edema
H34.8321	Tributary (branch) retinal vein occlusion, left eye, with retinal neovascularization
H34.8322	Tributary (branch) retinal vein occlusion, left eye, stable
H34.833	Tributary (branch) retinal vein occlusion, bilateral
H34.8330	Tributary (branch) retinal vein occlusion, bilateral, with macular edema
H34.8331	Tributary (branch) retinal vein occlusion, bilateral, with retinal neovascularization
H34.8332	Tributary (branch) retinal vein occlusion, bilateral, stable
H34.839	Tributary (branch) retinal vein occlusion, unspecified eye
H34.8390	Tributary (branch) retinal vein occlusion, unspecified eye, with macular edema
H34.8391	Tributary (branch) retinal vein occlusion, unspecified eye, with retinal neovascularization
H34.8392	Tributary (branch) retinal vein occlusion, unspecified eye, stable
H44.2A	Degenerative myopia with choroidal neovascularization
H44.2A1	Degenerative myopia with choroidal neovascularization, right eye
H44.2A2	Degenerative myopia with choroidal neovascularization, left eye
H44.2A3	Degenerative myopia with choroidal neovascularization, bilateral eye
H44.2A9	Degenerative myopia with choroidal neovascularization, unspecified eye
H35.1	Retinopathy of prematurity
H35.10	Retinopathy of prematurity, unspecified
H35.101	Retinopathy of prematurity, unspecified, right eye
H35.102	Retinopathy of prematurity, unspecified, left eye
H35.103	Retinopathy of prematurity, unspecified, bilateral
H35.109	Retinopathy of prematurity, unspecified, unspecified eye
H35.11	Retinopathy of prematurity, stage 0
H35.111	Retinopathy of prematurity, stage 0, right eye
H35.112	Retinopathy of prematurity, stage 0, left eye
H35.113	Retinopathy of prematurity, stage 0, bilateral
H35.119	Retinopathy of prematurity, stage 0, unspecified eye
H35.12	Retinopathy of prematurity, stage 1
H35.121	Retinopathy of prematurity, stage 1, right eye
H35.122	Retinopathy of prematurity, stage 1, left eye
H35.123	Retinopathy of prematurity, stage 1, bilateral
H35.129	Retinopathy of prematurity, stage 1, unspecified eye
H35.13	Retinopathy of prematurity, stage 2

ICD-10 Code	Description
H35.131	Retinopathy of prematurity, stage 2, right eye
H35.132	Retinopathy of prematurity, stage 2, left eye
H35.133	Retinopathy of prematurity, stage 2, bilateral
H35.139	Retinopathy of prematurity, stage 2, unspecified eye
H35.14	Retinopathy of prematurity, stage 3
H35.141	Retinopathy of prematurity, stage 3, right eye
H35.142	Retinopathy of prematurity, stage 3, left eye
H35.143	Retinopathy of prematurity, stage 3, bilateral
H35.149	Retinopathy of prematurity, stage 3, unspecified eye
H35.15	Retinopathy of prematurity, stage 4
H35.151	Retinopathy of prematurity, stage 4, right eye
H35.152	Retinopathy of prematurity, stage 4, left eye
H35.153	Retinopathy of prematurity, stage 4, bilateral
H35.159	Retinopathy of prematurity, stage 4, unspecified eye
H35.16	Retinopathy of prematurity, stage 5
H35.161	Retinopathy of prematurity, stage 5, right eye
H35.162	Retinopathy of prematurity, stage 5, left eye
H35.163	Retinopathy of prematurity, stage 5, bilateral
H35.169	Retinopathy of prematurity, stage 5, unspecified eye
H35.171	Retrolental fibroplasia, right eye
H35.172	Retrolental fibroplasia, left eye
H35.173	Retrolental fibroplasia, bilateral
H35.179	Retrolental fibroplasia, unspecified eye
H35.3110	Nonexudative age-related macular degeneration, right eye, stage unspecified
H35.3111	Nonexudative age-related macular degeneration, right eye, early dry stage
H35.3112	Nonexudative age-related macular degeneration, right eye, intermediate dry stage
H35.3113	Nonexudative age-related macular degeneration, right eye, advanced atrophic without subfoveal involvement
H35.3114	Nonexudative age-related macular degeneration, right eye, advanced atrophic with subfoveal involvement
H35.3120	Nonexudative age-related macular degeneration, left eye, stage unspecified
H35.3121	Nonexudative age-related macular degeneration, left eye, early dry stage
H35.3122	Nonexudative age-related macular degeneration, left eye, intermediate dry stage
H35.3123	Nonexudative age-related macular degeneration, left eye, advanced atrophic without subfoveal involvement
H35.3124	Nonexudative age-related macular degeneration, left eye, advanced atrophic with subfoveal involvement
H35.3130	Nonexudative age-related macular degeneration, bilateral, stage unspecified
H35.3131	Nonexudative age-related macular degeneration, bilateral, early dry stage
H35.3132	Nonexudative age-related macular degeneration, bilateral, intermediate dry stage

ICD-10 Code	Description
H35.3133	Nonexudative age-related macular degeneration, bilateral, advanced atrophic without subfoveal involvement
H35.3134	Nonexudative age-related macular degeneration, bilateral, advanced atrophic with subfoveal involvement
H35.3190	Nonexudative age-related macular degeneration, unspecified eye, stage unspecified
H35.3191	Nonexudative age-related macular degeneration, unspecified eye, early dry stage
H35.3192	Nonexudative age-related macular degeneration, unspecified eye, intermediate dry stage
H35.3193	Nonexudative age-related macular degeneration, unspecified eye, advanced atrophic without subfoveal involvement
H35.3194	Nonexudative age-related macular degeneration, unspecified eye, advanced atrophic with subfoveal involvement
H35.32	Exudative age-related macular degeneration
H35.321	Exudative age-related macular degeneration, right eye
H35.3210	Exudative age-related macular degeneration, right eye, stage unspecified
H35.3211	Exudative age-related macular degeneration, right eye, with active choroidal neovascularization
H35.3212	Exudative age-related macular degeneration, right eye, with inactive choroidal neovascularization
H35.3213	Exudative age-related macular degeneration, right eye, with inactive scar
H35.322	Exudative age-related macular degeneration, left eye
H35.3220	Exudative age-related macular degeneration, left eye, stage unspecified
H35.3221	Exudative age-related macular degeneration, left eye, with active choroidal neovascularization
H35.3222	Exudative age-related macular degeneration, left eye, with inactive choroidal neovascularization
H35.3223	Exudative age-related macular degeneration, left eye, with inactive scar
H35.323	Exudative age-related macular degeneration, bilateral
H35.3230	Exudative age-related macular degeneration, bilateral, stage unspecified
H35.3231	Exudative age-related macular degeneration, bilateral, with active choroidal neovascularization
H35.3232	Exudative age-related macular degeneration, bilateral, with inactive choroidal neovascularization
H35.3233	Exudative age-related macular degeneration, bilateral, with inactive scar
H35.329	Exudative age-related macular degeneration, unspecified eye
H35.3290	Exudative age-related macular degeneration, unspecified eye, stage unspecified
H35.3291	Exudative age-related macular degeneration, unspecified eye, with active choroidal neovascularization
H35.3292	Exudative age-related macular degeneration, unspecified eye, with inactive choroidal neovascularization
H35.3293	Exudative age-related macular degeneration, unspecified eye, with inactive scar
H35.33	Angioid streaks of macula
H35.351	Cystoid macular degeneration, right eye
H35.352	Cystoid macular degeneration, left eye
H35.353	Cystoid macular degeneration, bilateral
H35.81	Retinal edema
H40.89	Other specified glaucoma
H44.20	Degenerative myopia, unspecified eye

ICD-10 Code	Description
H44.21	Degenerative myopia, right eye
H44.22	Degenerative myopia, left eye
H44.23	Degenerative myopia, bilateral
H44.2A1	Degenerative myopia with choroidal neovascularization, right eye
H44.2A2	Degenerative myopia with choroidal neovascularization, left eye
H44.2A3	Degenerative myopia with choroidal neovascularization, bilateral eye
H44.2A9	Degenerative myopia with choroidal neovascularization, unspecified eye
H44.2B1	Degenerative myopia with macular hole, right eye
H44.2B2	Degenerative myopia with macular hole, left eye
H44.2B3	Degenerative myopia with macular hole, bilateral eye
H44.2B9	Degenerative myopia with macular hole, unspecified eye
H44.2C1	Degenerative myopia with retinal detachment, right eye
H44.2C2	Degenerative myopia with retinal detachment, left eye
H44.2C3	Degenerative myopia with retinal detachment, bilateral eye
H44.2C9	Degenerative myopia with retinal detachment, unspecified eye
H44.2D1	Degenerative myopia with foveoschisis, right eye
H44.2D2	Degenerative myopia with foveoschisis, left eye
H44.2D3	Degenerative myopia with foveoschisis, bilateral eye
H44.2D9	Degenerative myopia with foveoschisis, unspecified eye
H44.2E1	Degenerative myopia with other maculopathy, right eye
H44.2E2	Degenerative myopia with other maculopathy, left eye
H44.2E3	Degenerative myopia with other maculopathy, bilateral eye
H44.2E9	Degenerative myopia with other maculopathy, unspecified eye

Background

Vascular Endothelial Growth Factor (VEGF)
Angiogenesis is a complex process whereby interactions between stimulatory and inhibitory factors result in new blood vessel formation (*Solomon et al 2019*). The induction of angiogenesis is termed neovascularization (NV) (*Kuo 2023*). VEGF is a potent mitogen and vascular permeability factor that plays an important role in NV (*Folk et al 2010, Kuo 2023*). The dominant growth factor controlling angiogenesis is vascular endothelial growth factor-A (VEGF-A). VEGF-A is one member of the VEGF family, which also contains VEGF-B, VEGF-C, VEGF-D, or virus VEGF (VEGF-E), and placental growth factor (PIGF) (*Kuo 2023*). Inappropriate and excessive growth of blood vessels plays a causative role in retinal diseases such as neovascular age-related macular degeneration (nAMD), diabetic retinopathy (DR), diabetic macular edema (DME), and retinal vein occlusion (RVO) (*Kuo 2023, Solomon et al 2019*). Intravitreal (IVT) injection of drugs that inhibit VEGF can limit progression of nAMD and stabilize, or reverse, visual loss *Solomon et al 2019).*

Angiopoietin-2 (Ang-2)
The Ang/Tie2 pathway plays an important role in the regulation of vascular stability, in angiogenesis under physiological and pathological conditions, as well as in inflammation. Ang-1 and Ang-2 are key factors in vascular homeostasis, acting as ligands of the Tie2 receptor that is expressed on vascular endothelial cells. Ang-1 is a homeostatic factor that, when bound to Tie2, stabilizes the mature vasculature, promoting endothelial cell survival and barrier function, serving as a

molecular “brake” against vascular instability and inflammation. In contrast, Ang-2 acts as a vascular destabilization factor by blocking Ang-1-dependent Tie2 activation. This leads to dissociation of pericytes from existing vessels, thus increasing vessel plasticity, rendering vasculature amenable to endothelial barrier breakdown, fluid leakage, and sprouting of new vessels. This Ang-2 mediated vessel de-stabilization is a critical and required step towards sensitizing vessels for the further effects of proangiogenic growth factors such as VEGF-A (and other members of the VEGF family) as well as for pro-inflammatory cytokines such as tumor necrosis factor (TNF)-alpha, driving vascular beds towards angiogenesis, permeability, and inflammation (*Vabysmo dossier 2022*). Ang-2 levels can be upregulated by other pro-angiogenic factors, including VEGF-A, that promote vascular leakage and NV and have been shown to be increased during angiogenic stress triggered by hypoxia or hyperglycemia. In retinal diseases, Ang-2 and VEGF-A are upregulated and work synergistically to promote vascular instability.

Clinical Evidence

Neovascular Age-related Macular Degeneration (nAMD)

Solomon et al 2019 conducted a Cochrane systematic review of 16 randomized controlled trials (RCTs) of patients with nAMD (N = 6347) who were being treated with bevacizumab, pegaptanib, ranibizumab, or placebo. Aflibercept was excluded since its approval occurred after the protocol for the review had been submitted and because its mechanism of VEGF inhibition is slightly different than that of the other anti-VEGF agents. Six trials compared anti-VEGF treatment vs control, and 10 trials compared bevacizumab with ranibizumab. The primary outcome was the proportion of patients who gained ≥ 15 letters (≥ 3 lines) of best corrected visual acuity (BCVA) in the study eye measured on a VA chart (typically Early Treatment Diabetic Retinopathy Study [ETDRS] charts) with a logarithmic VA (logMAR) scale at 1 year of follow-up. The overall certainty of the evidence was moderate to high, and most trials had an overall low risk of bias. Compared with control, more patients who received IVT anti-VEGF agents had gained ≥ 15 letters of VA (risk ratio [RR] 4.19; 95% confidence interval [CI], 2.32 to 7.55; moderate-certainty evidence), had lost < 15 letters of VA (RR 1.40; 95% CI 1.27 to 1.55; high-certainty evidence), and showed mean improvement in VA (mean difference [MD] 6.7 letters; 95% CI, 4.4 to 9.0 in 1 pegaptanib trial; MD 17.8 letters; 95% CI, 16.0 to 19.7 in 3 ranibizumab trials; moderate-certainty evidence) after 1 year of follow-up. Improvements were also reported with anti-VEGF treatment in morphologic outcomes (eg, size of CNV, central retinal thickness [CRT]) (moderate certainty evidence).

VA outcomes after bevacizumab and ranibizumab were similar when the same RCTs compared the same regimens with respect to gain of ≥ 15 letters of VA (RR 0.95; 95% CI, 0.81 to 1.12; high-certainty evidence) and loss of < 15 letters of VA (RR 1.00; 95% CI, 0.98 to 1.02; high-certainty evidence); results showed similar mean improvement in VA (MD -0.5 letters; 95% CI, -1.5 to 0.5; high-certainty evidence) after 1 year of follow-up. Reduction in CRT was less among bevacizumab-treated than ranibizumab-treated patients after 1 year (MD -11.6 µm; 95% CI, -21.6 to -1.7; high-certainty evidence); however, this difference was not considered clinically meaningful. Results at 2 years for gain of ≥ 15 letters of VA were consistent with the 1-year outcomes (RR 0.84; 95% CI, 0.64 to 1.11; high-certainty evidence). The available information on adverse effects (AEs) with each medication did not suggest a higher incidence of potentially vision-threatening complications (VTC) with IVT injection compared with control interventions; however, clinical trials data may not have been sufficiently powered to detect rare safety outcomes.

Heier et al 2012 compared the safety and efficacy of aflibercept to that of ranibizumab in patients with nAMD in 2 similarly designed active-controlled (AC), double-blind (DB), multi-center (MC) RCTs known as VIEW 1 and VIEW 2 (N = 2419). The primary endpoint was noninferiority (margin of 10%) of the aflibercept regimens to ranibizumab in the proportion of patients losing < 15 letters on the ETDRS chart. Patients were randomized to IVT aflibercept 0.5 mg monthly (0.5q4), 2 mg monthly (2q4), 2 mg every 2 months after 3 initial monthly doses (2q8), or ranibizumab 0.5 mg monthly (Rq4).

All aflibercept groups were noninferior and clinically equivalent to monthly ranibizumab for the primary endpoint (the 2q4, 0.5q4, and 2q8 regimens were 95.1%, 95.9%, and 95.1%, respectively, for VIEW 1, and 95.6%, 96.3%, and 95.6%, respectively, for VIEW 2, whereas monthly ranibizumab was 94.4% in both studies). In a prespecified integrated analysis,

all aflibercept regimens were within 0.5 letters of the reference ranibizumab for mean change in BCVA. The proportions of patients gaining ≥ 15 letters from baseline to week 52 were similar in all treatment groups (29.4 to 34.8% with aflibercept vs 34.0% with ranibizumab). All aflibercept regimens also produced similar improvements in anatomic measures, ie, size of CNV and CRT vs ranibizumab. A *post hoc* analysis indicated similar proportions of aflibercept and ranibizumab-treated patients with a fluid-free retina. Ocular and systemic AEs were similar across treatment groups.

After the 52-week primary endpoint, a follow-up 96-week phase of the VIEW trials was conducted that required a switch to a variable (as needed [PRN], dosed at least every 12 weeks [q12w]) dosing schedule; interim injections were allowed based on assessment of anatomic and visual parameters (*Khurana et al 2019*, *Schmidt-Erfurth et al 2014*). At week 96, 42.5%, 53.9%, and 47.9% of eyes treated with Rq4, 2q4, and 2q8, respectively, received treatment at ≥ q12w intervals and 57.5%, 46.1%, and 52.1% of eyes received treatment at < q12w intervals during the second year. Among eyes receiving ≥ q12w dosing, the mean BCVA gains from baseline to week 52 were 8.7, 9.9, and 9.7 letters in the Rq4, 2q4, and 2q8, groups, respectively; at week 96, gains from baseline were maintained (8.5, 8.8, and 9.2 letters of improvement). Among eyes receiving < q12w dosing, mean BCVA gains from baseline to week 52 were 10.3, 9.7, and 8.9 letters in the Rq4, 2q4, and 2q8 groups. These gains were also largely maintained through the second year for all 3 groups (9.1, 7.7, and 8.1 letters of improvement from baseline at week 96).

The efficacy and safety of aflibercept HD (aflibercept 8 mg) were evaluated in an unpublished, ongoing, 3-year, Phase 2, DB, AC, MC, noninferiority RCT (PULSAR) in treatment-naïve patients with nAMD (Clinicaltrials.gov, Eylea HD dossier 2023). Patients were randomized to aflibercept 8 mg q12w (8q12), aflibercept 8 mg q16w (8q16), or aflibercept 2 mg q8w (2q8) following 3 initial monthly injections in all groups. In the aflibercept HD groups, patients could be treated as frequently as q8w based on protocol-defined visual and anatomic criteria, starting at week 16. The primary endpoint was change from baseline in BCVA at week 48 as measured by the ETDRS letter score. Both 8q12 and 8q16 treatments were shown to be noninferior and clinically equivalent to 2q8 treatment with respect to the change in BCVA score at week 48 using the pre-specified noninferiority margin of 4 letters. The mean change in BCVA score from baseline at week 48 was +6.7, +6.2, and +7.6 letters in the 8q12, 8q16, and 2q8 groups, respectively (least squares [LS] mean difference of -1.0 (95% CI, -2.9 to 0.9) and -1.1 (-3.0 to 0.7) with 8q12 and 8q16, respectively. In patients completing week 48, the mean number of injections administered was 5.2 in the 8q16 group (n = 312), 6.1 in the 8q12 group (n = 316), and 6.9 in the aflibercept 2q8 group (n = 309). At week 96, visual and anatomic benefits were sustained (Lanzetta et al 2023 [presentation]). The BCVA changes from baseline to week 96 (LS mean) were +6.6 letters in the 2q8 group; +5.6 letters in the 8q12 group (difference in LS mean vs 2q8, -1.01; 95% CI, -2.82 to 0.80; p = 0.00066 [nominal]), and +5.5 letters in the 8q16 group (difference in LS mean vs 2q8, -1.08; 95% CI, -2.87 to 0.71; p = 0.0007 [nominal]). Change in central subfield thickness (CST) was similar in the 3 treatment arms, with minimal fluctuations over the course of treatment. At weeks 60 and 96 respectively, 91% and 89% of patients receiving aflibercept 8q16 achieved ≥ q12w dosing intervals and 77% and 78% achieved ≥ q16w intervals, respectively. At week 96, 53% of patients receiving 8q16 achieved ≥ q20w intervals.

Some trials, mostly retrospective, have investigated the effects of aflibercept on patients resistant to either bevacizumab or ranibizumab therapy. Results from these studies are varied, with some reporting increased VA following aflibercept treatment in patients with persistent exudation, as well as no change in VA post-treatment (*Adrean et al 2022*, *Cho et al 2013, Kumar et al 2013, Messenger et al 2014, Wykoff et al 2014*). A review that collated 31 small retrospective studies of switching anti-VEGF agents in patients with nAMD from January 2010 to January 2017 found that switching from bevacizumab to ranibizumab mostly resulted in improvement in VA and anatomical outcomes (central macular thickness [CMT], CRT; 7/8 and 6/8 studies, respectively), whereas switching from ranibizumab to bevacizumab was less effective (no VA or anatomical improvement in 2/4 studies). Switching from either agent (bevacizumab and/or ranibizumab) to aflibercept resulted in improvement of retina anatomy in most cases (20/22 studies), but rarely in VA improvement (6/22 studies) (*Pikkel & Attas 2018*).

A 24-week, prospective, open-label (OL), uncontrolled trial evaluated aflibercept administered as 3 initial loading doses every 4 weeks (q4w), followed by further injections every 8 weeks (q8w) in 49 patients with treatment-resistant nAMD (*Chang et al 2014*). All 49 patients had received ≥ 4 ranibizumab injections within the 6 months before switching to

aflibercept. Among them, 40/49 (82%) patients had ranibizumab monotherapy and 7/49 (14%) had received ≥ 4 ranibizumab injections plus ≥ 1 bevacizumab injection within the 6 months before the commencement of the aflibercept study. One patient had received PDT and bevacizumab > 6 months before switching, and 1 patient had received bevacizumab > 6 months before baseline aflibercept treatment. BCVA improved by a mean of 6.9 letters and CRT was reduced by 89.4 µm at all follow-up visits compared with baseline ($p < 0.001$). At week 24, 55% of eyes improved by ≥ 5 letters, 26% improved by ≥ 10 letters, and 10% improved by ≥ 15 letters. Forty-three percent of eyes were stable (±5 letters compared with the baseline value). Only 1 patient (2%) lost > 5 letters. Further follow-up is required to determine whether these improvements can be maintained in the longer term.

The safety and efficacy of brolucizumab vs aflibercept for the treatment of previously untreated patients with nAMD were evaluated in two 2-year similarly designed AC, DB, MC, RCTs dubbed HAWK and HARRIER (N = 1817) (*Dugel et al 2019*). The primary endpoint was noninferiority in mean BCVA change from baseline to week 48 (margin: 4 letters). Patients were randomized to brolucizumab 3 mg (HAWK only) or 6 mg or aflibercept 2 mg. After loading with 3 monthly injections, brolucizumab-treated eyes received an injection q12w and were interval adjusted to q8w if disease activity was present; aflibercept-treated eyes received q8w dosing.

In both trials, each brolucizumab arm demonstrated noninferiority vs aflibercept in least squares (LS) mean BCVA change from baseline to week 48. In HAWK, brolucizumab 3 mg- and brolucizumab 6 mg-treated eyes gained 6.1 and 6.6 letters, respectively, vs 6.8 letters among aflibercept-treated eyes (LS mean; 95% CI for treatment difference, -2.5 to 1.3; p-value for noninferiority < 0.001 and 95% CI for treatment difference, -2.1 to 1.8; p-value for noninferiority < 0.001, respectively). In HARRIER, brolucizumab 6 mg-treated eyes gained 6.9 letters vs 7.6 letters among aflibercept-treated eyes (LS mean; 95% CI for treatment difference, -2.4 to 1.0; p-value for noninferiority < 0.001).

For brolucizumab-treated eyes, q12w dosing after loading was maintained through week 48 in 49.4% of patients (3 mg) and 55.6% (6 mg) in HAWK and 51.0% (6 mg) in HARRIER. Based on a confirmatory superiority analysis in HAWK at week 16, brolucizumab 6 mg-treated eyes demonstrated less disease activity vs aflibercept (24.5 vs 35.5%; 95% CI for treatment difference, -17.1 to -3.5; p = 0.001). In HARRIER, 22.7% of patients in the brolucizumab 6 mg arm had disease activity compared to 32.2% of patients on aflibercept (95% CI for treatment difference, -15.8 to -3.1; p = 0.002). Greater central subfield thickness (CST) reductions from baseline to week 48 were observed among eyes treated with brolucizumab 6 mg vs aflibercept in HAWK (LS mean -172.8 µm vs -143.7 µm; p = 0.001) and HARRIER (LS mean -193.8 µm vs -143.9 µm; p < 0.001). Intraretinal fluid (IRF)/subretinal fluid (SRF) was present in fewer brolucizumab-treated eyes vs aflibercept-treated eyes from baseline to week 16 in both trials (p < 0.001 for both trials). At week 48, subretinal pigment epithelium (sub-RPE) fluid was present in fewer brolucizumab 6 mg-treated eyes than aflibercept-treated eyes in both trials (p = 0.004 in HAWK and p < 0.001 in HARRIER). The overall safety profile (systemic and ocular) of brolucizumab was comparable to aflibercept and consistent with published data on other anti-VEGF treatments.

Dugel et al 2021 reported the 96-week outcomes from HAWK and HARRIER. Visual outcomes from week 48 to week 96 were consistent with the efficacy observed at week 48. In HAWK, the LS mean change ± standard error (SE) in BCVA from baseline to week 96 was 5.6 ± 0.79 letters for brolucizumab 3 mg, 5.9 ± 0.78 letters for brolucizumab 6 mg, and 5.3 ± 0.78 letters for aflibercept, whereas in HARRIER, it was 6.1 ± 0.73 letters for brolucizumab 6 mg and 6.6 ± 0.73 letters for aflibercept. The effect of brolucizumab on reducing CST and IRF/SRF was maintained through week 96 in both trials. The probability that an eye could be maintained on a q12w interval after loading to the disease activity assessment (DAA) at week 92 was 39.7% and 45.4% for the brolucizumab 3 mg and 6 mg treatment groups in HAWK, respectively, and 38.6% for the brolucizumab 6 mg group in HARRIER.

A MC, noninterventional cohort study involving 65 patients originally treated with ranibizumab in the pivotal Phase 3 trials (ANCHOR, MARINA) and an OL extension (HORIZON) assessed the long-term outcomes 7 to 8 years after initiation of therapy (*Rofagha et al 2013*). At a mean of 7.3 years (range, 6.3 to 8.5) after entry into ANCHOR or MARINA, 37% of study eyes met the primary endpoint of 20/70 or better BCVA, 23% achieved a BCVA of 20/40 or better, and 37% were legally blind (BCVA 20/200 or worse). Forty-three percent of study eyes had a stable or improved letter score (≥ 0-letter gain) compared with ANCHOR or MARINA baseline measurements, whereas 34% declined by ≥ 15 letters, with an overall

mean decline of 8.6 letters ($p < 0.005$). Since exit from the HORIZON study, study eyes had received a mean of 6.8 anti-VEGF injections during the mean 3.4-year interval; a subgroup of patients who received 11 or more anti-VEGF injections had a significantly better mean gain in letter score since HORIZON exit ($p < 0.05$).

A cohort study of the 5-year outcomes of patients originally enrolled in the 2-year, Phase 3 CATT trial comparing bevacizumab with ranibizumab for the treatment of nAMD (N = 647, 71% of survivors) found that ~50% of eyes had a VA of 20/40 or better and 20% had a VA of 20/200 or worse (*Maguire et al 2016*). Mean change in VA was -3.3 letters from baseline and -10.8 letters from 2 years. Among 467 eyes with fluorescein angiography (FA), mean total lesion area was 12.9 mm^2, a mean of 4.8 mm^2 larger than at 2 years. Among 555 eyes with spectral-domain optical coherence tomography (OCT), 83% had fluid. Mean foveal total thickness was 278 mm, a decrease of 182 mm from baseline and 20 mm from 2 years. The retina was abnormally thin (< 120 mm) in 36% of eyes. Between 2 and 5 years, the group originally assigned to ranibizumab for 2 years lost more VA than the bevacizumab group (-4 letters; $p = 0.008$).

The efficacy and safety of faricimab were evaluated in two Phase 3, identically designed, DB, AC, MC, noninferiority RCTs (TENAYA & LUCERNE) in 1329 patients ≥ 50 years of age with treatment-naïve nAMD (*Heier et al 2022*). Patients were randomized (1:1) to faricimab 6 mg up to every 16 weeks (q16w) based on protocol-defined DAAs at weeks 20 and 24 or aflibercept 2 mg q8w. In the primary analysis, study treatment was administered up to week 48. The primary endpoint was change in BCVA from baseline averaged over weeks 40, 44, and 48 (prespecified noninferiority margin of 4 letters).

Change in mean BCVA from baseline in the study eye at primary endpoint visits (average at weeks 40, 44, and 48) with faricimab was noninferior to aflibercept. In the primary analysis (intent-to-treat [ITT] population), adjusted mean gains in BCVA at primary endpoint visits in TENAYA were 5.8 letters (95% CI, 4.6 to 7.1) in the faricimab group and 5.1 letters (3.9 to 6.4) in the aflibercept group (treatment difference 0.7 letters; 95% CI, -1.1 to 2.5). In LUCERNE, vision gains were 6.6 letters (95% CI, 5.3 to 7.8) in the faricimab group and 6.6 letters (5.3 to 7.8) in the aflibercept group (treatment difference 0.0 letters; 95% CI, -1.7 to 1.8). Similar proportions of patients in each group of TENAYA and LUCERNE gained ≥ 10 or ≥ 15 ETDRS letters from baseline at primary endpoint visits. More than 95% of patients in the faricimab group in both studies avoided losing ≥ 15 letters of vision from baseline at primary endpoint visits. Comparable proportions of patients across treatment groups in both studies demonstrated BCVA Snellen equivalent of 20/40 or better (49.4 to 57.0%) and 20/200 or worse (6.4 to 7.9%) at primary endpoint visits. Treatment with faricimab dosed up to q16w resulted in CST reductions from baseline at all timepoints up to week 48, starting at 4 weeks after treatment initiation, and was comparable with aflibercept q8w. In both studies, adjusted mean changes in total CNV lesion area and total area of leakage from baseline with faricimab at week 48 were comparable with aflibercept. At week 48, approximately 80% of faricimab-treated patients in both TENAYA and LUCERNE were on 12-week or 16-week dosing intervals, with 107 (34.0%) patients in TENAYA and 104 (32.9%) patients in LUCERNE on extended dosing regimens of q12w, and 144 (45.7%) patients in TENAYA and 142 (44.9%) patients in LUCERNE on 16-week dosing. A 2-year OL extension study, AVONELLE-X, is ongoing to assess the long-term durability of faricimab.

Integrated safety and efficacy analyses for Susvimo in nAMD were conducted in the pivotal, Phase 3, open-label (OL), multi-center (MC), randomized, VA assessor-masked, active-controlled (AC), non-inferiority and equivalence Archway trial (*Holekamp et al 2021, Susvimo AMCP dossier 2021*) and supportive Phase 2 Ladder trial (*Campochiaro et al 2019*, *Susvimo AMCP dossier 2021*). Both studies enrolled patients previously treated with IVT anti-VEGF therapy who were known to be responsive to treatment. Therefore, the objective of these studies was to demonstrate maintenance of best corrected visual acuity (BCVA) rather than a gain in BCVA. Archway evaluated the safety and efficacy of Susvimo in 415 patients with nAMD. Patients were randomized 2:3 to IVT ranibizumab 0.5 mg monthly (n = 167) or Susvimo 100 mg/mL with fixed 24-week refill exchanges (n = 248). Eligible patients were ≥ 50 years of age and had an initial diagnosis of nAMD within the previous 9 months of screening, received ≥ 3 injections of an IVT anti-VEGF agent (ranibizumab, bevacizumab, or aflibercept) within the previous 6 months, a demonstrated response to anti-VEGF treatment defined as decrease in disease activity and stable or improved BCVA, and a BCVA of 34 letters (> 20/200). Patients with prior treatment for nAMD other than VEGF inhibitors were excluded. The primary endpoint was change from baseline in BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter(s) score averaged over weeks 36 and 40 (non-inferiority margin, -4.5 letters; equivalence margin, ±4.5 letters). The primary analysis was conducted when all patients completed

the week 40 visit or discontinued early. In total, 240 patients (96.8%) and 162 patients (97.0%) in the Susvimo and monthly IVT ranibizumab arms, respectively, completed study eye treatment through week 40. The most common reasons for study eye treatment discontinuation were adverse events (AEs) in the Susvimo arm (n = 5) and withdrawal by patient in the monthly IVT ranibizumab arm (n = 4). The results showed that Susvimo was both non-inferior and equivalent to IVT monthly ranibizumab. Adjusted mean change from baseline in BCVA score averaged over weeks 36 and 40 was +0.2 ETDRS letters (standard error [SE], 0.5 ETDRS letters) in the Susvimo arm and +0.5 ETDRS letters (SE, 0.6 ETDRS letters) in the monthly IVT ranibizumab arm. Difference in adjusted means between treatment arms was -0.3 ETDRS letters (95% confidence interval [CI], -1.7 to 1.1). Because the upper and lower limits of the 2-sided 95% CI were within the prespecified ±4.5-letter non-inferiority and equivalence margins, Susvimo was both clinically non-inferior and equivalent to monthly IVT ranibizumab in terms of BCVA change from baseline at the average of weeks 36 and 40. Susvimo-treated patients experienced a transient and reversible postsurgical drop of ~1 ETDRS line in vision after implant insertion, with vision returning to baseline by week 8. Thereafter, the 2 arms were similar, with minimal changes in BCVA from baseline through week 40.

Diabetic retinopathy (DR) & Diabetic Macular Edema (DME)

Virgili et al 2018 conducted a Cochrane systematic review of RCTs of patients with DME and moderate vision loss to compare the effectiveness and safety of the different anti-VEGF drugs using network meta-analysis methods (24 RCTs; N = 6007). Treatment groups included comparisons of aflibercept, bevacizumab, and ranibizumab to laser photocoagulation; comparisons of bevacizumab, ranibizumab, and pegaptanib to sham injections; and head-to-head comparisons of bevacizumab vs ranibizumab. Eleven studies assessed ranibizumab, 6 bevacizumab, 2 pegaptanib, and 3 aflibercept. The primary outcome was BCVA expressed as the proportion of patients with ≥ 15 ETDRS letters (≥ 3 lines or 0.3 logMAR) of improvement from baseline to 12 months.

Aflibercept, bevacizumab, and ranibizumab were all more effective than laser for improving vision by ≥ 3 lines after 1 year, since about 1 in 10 patients improve vision with laser and about 3 in 10 improve with anti-VEGF treatment. RR vs laser was 3.66 (95% CI, 2.79 to 4.79) for aflibercept; 2.47 (95% CI, 1.81 to 3.37) for bevacizumab; and 2.76 (95% CI, 2.12 to 3.59) for ranibizumab. On average, there was no change in mean BCVA with laser after 1 year, compared with a gain of 1 or 2 lines with anti-VEGF treatment (aflibercept and ranibizumab: high certainty evidence; bevacizumab: moderate certainty evidence).

When the anti-VEGF drugs were compared as monotherapy, all efficacy outcomes significantly favored aflibercept over ranibizumab and bevacizumab. Compared with ranibizumab and bevacizumab, aflibercept increased the chances of gaining ≥ 3 lines (17 studies, 4031 eyes) by about 30% with an RR of 0.75 (95% CI, 0.60 to 0.94) and 0.68 (95% CI, 0.53 to 0.86) vs ranibizumab and bevacizumab, respectively. For every 1000 patients treated with aflibercept, 92 fewer would gain ≥ 3 lines of VA at 1 year if treated with ranibizumab (22 to 148 fewer). The corresponding figures for mean BCVA change (21 studies, 2689 eyes) were a difference of 0.08 logMAR (95% CI, 0.05 to 0.11) and 0.08 logMAR (95% CI, 0.05 to 0.11) and were 38.90 µm (95% CI, 2.27 to 75.52) and 68.32 µm (95% CI, 28.69 to 107.96) for CRT change (16 studies, 3491 eyes), all favoring aflibercept. Ranibizumab and bevacizumab did not differ in terms of functional outcomes with an RR of gain 1.11 (95% CI, 0.87 to 1.43) and difference in mean VA change 0.00 logMAR (95% CI, -0.02 to 0.03). However, CRT reduction favored ranibizumab by -29.4 µm (95% CI, -58.2 to -0.70). The only large study that compared all 3 drugs found that aflibercept was superior to bevacizumab and ranibizumab for patients with lower VA (≤ 69 ETDRS or ~20/50 or 0.4 logMAR or worse), whereas differences between the 3 drugs were unimportant for patients with better vision. Two-year data were reported in only 4 RCTs. There was only 1 study for each comparison, making data unsuitable for a network meta-analysis. No signals of differences in overall safety were found between the 3 drugs, but the estimates were imprecise for cardiovascular events and death.

A Cochrane review of 23 RCTs with 1755 patients (2334 eyes) was conducted to assess the efficacy and safety of IVT VEGF inhibitors for the treatment of Proliferative DR (PDR) (*Martinez-Zapata et al 2023*). Studies in which anti-VEGFs were compared with another active treatment (panretinal photocoagulation [PRP] or vitrectomy), sham treatment, or no treatment were included. The mean glycosylated hemoglobin (HbA1c) was 8.45 for the PRP group and 8.25 for patients receiving anti-VEGFs alone or in combination. Twelve studies included patients with PDR, and patients in 11

studies had high-risk PDR (HRPDR). The number of patients per RCT was 76 (range, 15 to 305). Most studies had an unclear or high risk of bias. Ten trials contributed to the primary outcome analyses of mean VA. Two reported changes in VA from baseline, and the remaining 8 reported end of follow-up data. Three trials used bevacizumab, 1 assessed aflibercept, 1 used pegaptanib, and 5 used ranibizumab. Results showed that anti-VEGFs (aflibercept, bevacizumab, pegaptanib, or ranibizumab) ± PRP probably increase VA compared with PRP alone (MD -0.08 logMAR, 95% CI, -0.12 to -0.04; I2 = 28%; 10 RCTs, 1172 eyes); moderate-certainty evidence. Overall, there was low heterogeneity (I2 = 28%) and no evidence for any difference according to the type of anti-VEGF (test for subgroup differences p = 0.79). These results correspond to an improvement in VA of 4 letters (95% CI, 2 to 6). Anti-VEGFs ± PRP may increase regression of new vessels (MD -4.14 mm2; 95% CI, -6.84 to -1.43; I2 = 75%; 4 RCTs, 189 eyes; low-certainty evidence) and probably increase a complete regression of new vessels (RR 1.63; 95% CI, 1.19 to 2.24; I2 = 46%; 5 RCTs, 405 eyes; moderate certainty evidence).

Results for key secondary endpoints indicated that anti-VEGFs ± PRP:

- Probably reduce vitreous hemorrhage (RR 0.72; 95% CI, 0.57 to 0.90; I2 = 0%; 6 RCTs, 1008 eyes; moderate-certainty evidence).
- May reduce the need for vitrectomy compared with PRP alone (RR 0.67; 95% CI, 0.49 to 0.93; I2 = 43%; 8 RCTs, 1248 eyes; low-certainty evidence).
- May result in little to no difference in the quality of life compared with PRP alone (MD 0.62; 95% CI, -3.99 to 5.23; I2 = 0%; 2 RCTs, 382 patients; low-certainty evidence).

The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol S study was a MC, noninferiority RCT that compared the safety and efficacy of ranibizumab to panretinal photocoagulation (PRP) (a standard of care) in 305 patients with PDR (*Gross et al 2015*). The primary endpoint was mean VA change at 2 years (5 letter noninferiority margin). Mean VA letter improvement at 2 years was +2.8 in the ranibizumab group vs +0.2 in the PRP group (adjusted difference +2.2; 95% CI, -0.5 to +5.0; noninferiority p < 0.001). Mean treatment group difference in VA area under the curve over 2 years was +4.2 (95% CI, +3.0 to +5.4; p < 0.001). Visual field sensitivity loss was worse (MD 372 decibels [dB]; 95% CI, 213 to 531; p < 0.001), vitrectomy more frequent (15 vs 4%; difference 9%; 95% CI, 4 to 15%; p < 0.001), and DME development more frequent (28 vs 9%; difference 19%; 95% CI, 10 to 28%; p < 0.001) in the PRP vs ranibizumab group, respectively. A limitation of the study was that more than half the eyes in the PRP group (53%) received ranibizumab for DME; thus, the study essentially tested ranibizumab for PDR vs PRP plus ranibizumab when needed for DME treatment. One eye in the ranibizumab group developed endophthalmitis vs none in the PRP group. No significant differences between groups in rates of major cardiovascular events were identified. Five years of follow-up was completed by 187/277 patients (66% excluding deaths). The mean change in VA letter score was 3.1 and 3.0 for ranibizumab and PRP, respectively (adjusted difference 0.6; 95% CI, -2.3 to 3.5; p = 0.68); the mean VA was 20/25 (approximate Snellen equivalent) in both groups at 5 years. DME developed in 27 and 53 eyes in the ranibizumab and PRP groups, respectively (cumulative probabilities: 22 vs 38%; hazard ratio, 0.4; 95% CI, 0.3 to 0.7) *(Gross et al 2018*).

An unpublished 2-year, DB, MC, RCT (PANORAMA) evaluated the safety and efficacy of aflibercept in 402 patients with moderately severe to severe NPDR without central involvement compared to sham injections (*Regeneron Medical Information response letter 2019*). Patients were randomized to aflibercept 3 initial monthly 2 mg injections followed by 1 injection after 8 weeks, then 1 injection q16w (2q16); aflibercept 5 monthly 2 mg injections followed by 1 injection q8w (2q8); or sham injection. The primary endpoint was the percentage of patients improving by ≥ 2 steps from baseline in Diabetic Retinopathy Severity Scale (DRSS) score at week 24 (for the combined aflibercept treatment groups) and at week 52 (for aflibercept 2q8 and aflibercept 2q16) compared to sham injection. At week 52, efficacy in the aflibercept 2q16 and 2q8 groups was superior to the sham group for the primary endpoint. The proportion of patients with ≥ 2 steps of improvement in ETDRS-DRSS from baseline was 65.2%, 79.9%, and 15.0% for aflibercept 2q16, aflibercept 2q8, and sham, respectively (p < 0.01 vs sham for both aflibercept dosing regimens). Results were also significant for the combined aflibercept groups vs sham at 24 weeks. For the key secondary outcome of VTCs (defined as PDR/ASNV) and CI-DME, more patients in the sham group had events compared to patients receiving aflibercept (p < 0.003). There was a 76.3% reduction in VTCs and CI-DME in patients receiving aflibercept 2q16 and a 72.4% reduction in patients receiving

aflibercept 2q8 compared to sham. Ocular AEs occurred in 50.4%, 43.0%, and 44.8% of patients in the sham, aflibercept 2q16, and aflibercept 2q8 groups, respectively.

The efficacy and safety of brolucizumab compared with aflibercept for the treatment of DME were assessed in two 100-week, Phase 3, AC, DB, MC, pivotal, noninferiority RCTs, KESTREL and KITE (*Brown et al 2022*). Patients were randomized to brolucizumab 3 mg/6 mg or aflibercept 2 mg in KESTREL (n = 566) or to brolucizumab 6 mg or aflibercept 2 mg in KITE (n = 360). The brolucizumab groups received 5 loading doses q6w followed by q12w dosing, with optional adjustment to q8w if disease activity was identified at pre-defined assessment visits; the aflibercept groups received 5 doses q4w followed by fixed q8w dosing. The primary endpoint was BCVA change from baseline at week 52. At week 52, brolucizumab 6 mg was noninferior (margin of 4 letters) to aflibercept in mean change in BCVA from baseline (KESTREL, +9.2 letters vs +10.5 letters; KITE, +10.6 letters vs +9.4 letters; $p < 0.001$). The proportion of patients who gained ≥ 15 letters from baseline in BCVA or reached BCVA of ≥ 84 letters in the KESTREL study was generally comparable between the brolucizumab 6 mg arm and the aflibercept arm (37.0% vs 39.0%). This proportion was generally higher in the brolucizumab 6 mg arm at week 52 compared with the aflibercept arm (46.4% vs 37.6%) of the KITE study. In KITE, the LS mean change from baseline in CST showed superior improvements in the brolucizumab 6 mg arm (-187 μ m) compared with the aflibercept arm (-158 μ m), with an estimated difference of -29 μ m (95% CI, -49 to -10; p = 0.001). The proportions of patients achieving CST < 280 μ m were consistently higher in the brolucizumab arms at the first predefined DAA at week 32 and week 52. Compared with baseline, a lower proportion of patients with retinal fluid was observed in all treatment arms at all post-baseline visits in both studies.

At week 52, the proportions of patients with IRF and/or SRF in KESTREL were 60.3% and 73.3% in the brolucizumab 6 mg and aflibercept arms, respectively with a treatment difference of -13.2% (95% CI, -23.2 to -3.8). In KITE, the proportions of patients with IRF and/or SRF at week 52 were 54.2% in the brolucizumab 6 mg arm vs 72.9% in the aflibercept arm (treatment difference, -18.4%; 95% CI, -28.5 to -8.3). More than 50% of patients receiving brolucizumab in both studies (55.1% in the brolucizumab 6 mg arm in KESTREL and 50.3% in KITE) were maintained on q12w dosing through week 52. The gains in BCVA at week 52 achieved with brolucizumab 6 mg and aflibercept in both studies were maintained through week 100. The LS mean change from baseline in BCVA at week 100 in the brolucizumab 6 mg and aflibercept arms were: +8.8 letters vs +10.6 letters in KESTREL (treatment difference, -1.7 letters; 95% CI, -3.8 to 0.4) and +10.9 letters vs +8.4 letters in KITE (treatment difference, 2.6 letters; 95% CI, 0.2 to 4.9) (*Wykoff et al 2023*). In both studies, the reduction in CST achieved at week 52 was maintained through week 100 in each treatment arm. In both studies, fewer brolucizumab patients had IRF and/or SRF vs aflibercept. Results were achieved with 32.9% (KESTREL) and 47.5% (KITE) of brolucizumab patients maintained on q12w and q12w/q16w dosing, respectively.

The efficacy and safety of faricimab for the treatment of DME were evaluated in two Phase 3, identically-designed, DB, AC, MC, noninferiority RCTs (RHINE & YOSEMITE) in 1891 patients with vision loss secondary to CI-DME (*Wykoff et al 2022*). Patients were randomly assigned (1:1:1) to faricimab 6 mg q8w, faricimab 6 mg per personalized treatment interval (PTI), or aflibercept 2 mg q8w up to week 100. PTI dosing intervals were extended, maintained, or reduced (q4w up to q16w) based on disease activity at active dosing visits. The primary endpoint was mean change in BCVA at 1 year, averaged over weeks 48, 52, and 56 (defined as the primary endpoint visits). The noninferiority margin was 4 letters.

Both trials achieved noninferior 1-year vision gains with faricimab q8w or PTI vs aflibercept q8w in the ITT population. In YOSEMITE, adjusted mean BCVA change from baseline at the primary endpoint visits was 10.7 letters (97.52% CI, 9.4 to 12.0) in the faricimab q8w group and 11.6 letters (10.3 to 12.9) in the faricimab PTI group vs 10.9 letters (9.6 to 12.2) in the aflibercept q8w group (mean difference vs aflibercept q8w, -0.2 letters [-2.0 to 1.6] in the faricimab q8w group and 0.7 letters [-1.1 to 2.5] in the faricimab PTI group). Corresponding mean BCVA gains in RHINE were 11.8 letters (10.6 to 13.0) in the faricimab q8w group and 10.8 letters (9.6 to 11.9) in the faricimab PTI group vs 10.3 letters (9.1 to 11.4) in the aflibercept q8w group (MD vs aflibercept q8w, 1.5 letters [-0.1 to 3.2] in the faricimab q8w group and 0.5 letters [-1.1 to 2.1] in the faricimab PTI group). A higher proportion of faricimab-treated patients achieved absence of protocol-defined DME (CST < 325 µm) up to week 56 vs aflibercept. In Cochran-Mantel-Haenszel-weighted estimates, 77 to 87% of the faricimab q8w group and 80 to 82% of the faricimab PTI group in YOSEMITE achieved absence of DME at weeks 48 to 56, vs 64 to 71% of the aflibercept q8w group.

Corresponding proportions in RHINE were 85 to 90% in the faricimab q8w group and 83 to 87% in the faricimab PTI group vs 71 to 77% in the aflibercept q8w group. In YOSEMITE and RHINE, > 70% of patients in the PTI groups achieved q12w dosing or longer at 1 year. At the week 52 visit, 151 (53%) patients in YOSEMITE and 157 (51%) patients in RHINE achieved q16w dosing, and a further 60 (21%) patients in YOSEMITE and 62 (20%) patients in RHINE achieved dosing q12w. Approximately two-thirds of patients reached q12w or q6w dosing at week 52 without an interval reduction below q12w during year 1 (YOSEMITE, n = 194 [68%]; RHINE, n = 198 [64%]). In both trials, more faricimab-treated than aflibercept-treated patients achieved absence of IRF up to week 56. In YOSEMITE, weighted proportions of patients with absence of IRF at weeks 48 to 56 were greater for those receiving faricimab q8w (42 to 48%) and PTI (34 to 43%) vs aflibercept q8w (22 to 25%). In RHINE, 39 to 43% in the faricimab q8w group and 33 to 41% in the faricimab PTI group vs 23 to 29% in the aflibercept q8w group achieved absence of IRF. Absence of SRF was observed in 61 to 69% of patients across treatment groups and trials at baseline; weighted proportions increased to near 100% for all groups at week 16 and were maintained up to week 56. An OL extension study known as RHONE-X is ongoing to further evaluate the efficacy, safety, and durability of faricimab in the treatment of DME.

The efficacy and safety of aflibercept HD for the treatment of DME are being evaluated in PHOTON, an ongoing 96-week, Phase 2/3, AC, DB, MC, RCT comparing aflibercept 8q12 and 8q16 with aflibercept 2q8 (Eylea HD dossier 2023). Dosing intervals for patients in the 8q12 and 8q16 arms could be shortened during year 1 at specific timepoint assessments if certain protocol-defined criteria were met, and the minimal dosing interval for all pts was q8w. The primary endpoint is mean change from baseline in BCVA (ETDRS letters) at week 48 (noninferiority assessment at 4-letter margin). Both 8q12 and 8q16 treatments were shown to be noninferior and clinically equivalent to 2q8 treatment with respect to the change in BCVA score at week 48 using the pre-specified noninferiority margin of 4 letters. In patients completing week 48, the mean number of injections administered were 5.0 in the 8q16 group (n = 155), 6.0 in the 8q12 group (n = 298) and 7.9 in the aflibercept 2q8 group (n = 156). The mean changes in BCVA at week 96 for the 8q12 and 8q16 groups were noninferior to 2q8 with up to 6 fewer injections. The LS mean change from baseline to week 96 was +7.7 letters in the 2q8 group; +8.2 letters in the 8q12 group (difference in LS mean vs 2q8: +0.5; 95% CI, -1.6 to 2.5; $p < 0.0001$); and +6.6 letters in the 8q16 group (difference in LS mean vs 2q8: -1.1; 95% CI, -3.3 to 1.1; $p = 0.0044$) (Do 2023 [presentation]). Through week 96, 89% of 8 mg patients maintained ≥ 12-week dosing intervals. At week 96, 44% of all 8 mg patients had assigned intervals ≥ q20w. Patients were assigned to 24-week dosing intervals if they continued to meet extension criteria but did not have enough time to complete the interval within the 96-week study period. A total of 27% of all 8 mg patients had assigned intervals ≥ q24w at week 96.

The efficacy and safety of aflibercept HD for the treatment of DR are derived from the key secondary endpoint of PHOTON, ie, the proportion of patients with ≥ 2-step improvement in DRSS from baseline to week 48. Aflibercept 8q12 achieved noninferiority vs 2q8 at a margin of 15% (treatment difference, 1.98; 95% CI, -6.61 to 10.57). The 8q16 group did not demonstrate noninferiority vs 2q8 (treatment difference, -7.52; 95% CI, -16.88 to 1.84). Overall, 93% of patients treated with aflibercept 8 mg maintained dosing intervals of ≥ 12 weeks through week 48; 91% in the 8q12 group and 89% in the 8q16 group maintained their randomized dosing interval. The mean number of aflibercept injections administered through week 48 was 7.7 (8 planned injections per original dosing schedule) 5.7 (6 planned injections), and 4.9 (5 planned injections) injections in the aflibercept 2q8, 8q12, and 8q16 groups, respectively.

A systematic review of 24 studies evaluated the efficacy of switching to a different VEGF inhibitor for refractory DME (*Madjedi et al 2022*). Various definitions of refractory DME were used across the included studies. Overall, the most common definition of refractory DME employed in the included studies was a CRT > 300 μm or reduction in CRT < 10% after ≥ 3 to 6 prior anti-VEGF injections. The review included mostly retrospective studies. All studies reported a statistically significant anatomical reduction following the switch from IVT bevacizumab to IVT ranibizumab. Most (62.5%) studies found a statistically significant improvement in BCVA after switching from IVT bevacizumab to IVT ranibizumab, but 37.5% found no significant improvement. Switching to IVT aflibercept from either IVT ranibizumab or bevacizumab was associated with moderate to significant improvement in CST. Statistically significant reductions in CST from pre-switch baseline were reported in all 3 included studies. Statistically significant improvements in BCVA were reported in 2 of the 3 studies. A statistically significant reduction in CST was reported in 4 of 5 studies evaluating a

switch from IVT ranibizumab to IVT aflibercept. Three of the 5 included studies reported a statistically significant improvement in BCVA after switching to IVT aflibercept.

Retinal Vein Occlusion (RVO)

The efficacy and safety of the VEGF inhibitors for preserving or improving vision in patients with ME secondary to BRVO and CRVO were evaluated in 2 Cochrane systematic reviews conducted by *Mitry et al 2013* and *Braithwaite et al 2014*, respectively. The primary outcome was the proportion of patients with an improvement from baseline in BCVA of ≥ 15 letters on the ETDRS.

Two studies of patients with non-ischemic BRVO (1 RCT, 1 quasi-RCT; N = 427) were included in the analysis by *Mitry et al*. In the larger 12-month trial (N = 397), the percentage of patients who had an improvement from baseline of ≥ 15 letters by month 6 was 55.2% (0.3 mg) and 61.1% (0.5 mg) in the ranibizumab groups and 28.8% in the sham group (RR 1.92; 95% CI, 1.41 to 2.61 favoring 0.3 mg vs sham; and RR 2.12; 95% CI, 1.57 to 2.87 favoring 0.5 mg vs sham, respectively). After 6 monthly injections, 91.0% of patients receiving 0.3 mg ranibizumab and 84.7% of patients receiving 0.5 mg ranibizumab had CMT ≤ 250 µm, which suggests that the monthly anti-VEGF regimen was able to eliminate ME in most patients. Although repeated injections of ranibizumab appeared to have a favorable effect on the primary outcome, approximately 50% of the ranibizumab 0.3 mg group and 45% of the ranibizumab 0.5 mg group received rescue laser treatment; no data were provided on this subgroup and a proportion of the visual gain reported may be attributed to this treatment. The smaller trial (N = 30) compared bevacizumab with macular grid laser photocoagulation (GLP) followed up for 12 months. In the bevacizumab group, 12/15 patients achieved a 15-letter improvement in BCVA at 12 months compared with 8/15 in the GLP group. An improvement in mean VA and a reduction in CMT were demonstrated to be statistically significant in both groups. The bevacizumab group had a greater improvement in mean VA and a greater reduction in CMT compared with the GLP group. The study was underpowered to detect a difference in the primary outcome of a ≥ 15 letter gain.

In *Braithwaite et al*, high-quality evidence from 6 RCTs (N = 937) showed that patients receiving IVT anti-VEGF treatment (aflibercept, bevacizumab, pegaptanib, ranibizumab) were 2.71 times more likely to gain ≥ 15 letters of VA at 6 months compared to patients treated with sham injections (RR 2.71; 95% CI, 2.10 to 3.49). High-quality evidence from 5 trials suggested anti-VEGF treatment was associated with an 80% lower risk of losing ≥ 15 letters of VA at 6 months compared to sham injection (RR 0.20; 95% CI, 0.12 to 0.34). Moderate-quality evidence from 3 trials (N = 481) indicated that the mean reduction from baseline to 6 months in CRT was 267.4 µm (95% CI, 211.4 to 323.4) greater in patients treated with anti-VEGF agents than in those treated with sham.

Two unpublished Phase 3, DB, MC RCTs (BALATON, N = 553 and COMINO, N = 729) compared the efficacy and safety of faricimab to aflibercept in patients with ME due to BRVO or CRVO/HRVO, respectively (*Genentech Medical Information response letter 2023*). The primary endpoint of each study was the change in BCVA from baseline at 24 weeks. Secondary endpoints included change in CST and drying of retinal fluid from baseline to week 24. Both trials met their primary endpoints and demonstrated that vision gains associated with faricimab were noninferior to aflibercept at week 24. Vision gains were seen in both faricimab- and aflibercept-treated patients and were comparable between both treatment arms. The adjusted mean BCVA change from baseline was +16.9 ETDRS letters in the faricimab arm vs +17.5 ETDRS letters in the aflibercept arm in BALATON (treatment difference, -0.6 letters; 95% CI, -2.2 to 1.1). The corresponding results for COMINO were: +16.9 letters for faricimab vs +17.3 letters for aflibercept (treatment difference, -0.4 letters; 95% CI, -2.5 to 1.6). The proportion of patients gaining or avoiding a loss of vision was comparable between patients treated with faricimab and aflibercept.

In BALATON, 56.1% of patients in the faricimab group and 60.4% in the aflibercept group gained ≥ 15 letters. A total of 99.6% of patients in the faricimab group and 98.6% in the aflibercept group avoided a BCVA loss of ≥ 15 letters. In COMINO, 56.6% of patients in the faricimab group and 58.1% in the aflibercept group gained ≥ 15 letters. A total of 96.2% of patients in the faricimab group and 96.7% in the aflibercept group avoided a BCVA loss of ≥ 15 letters. Comparable reductions in CST were observed in both the faricimab and aflibercept treatment arms.Long-term treatment results up to 72 weeks showed that all patients in both studies received faricimab using a treat and extend (TAE) dosing

regimen. Data showed extension of faricimab treatment intervals up to every 4 months while maintaining the vision gains achieved in the first 24 weeks of the trials. Robust and sustained drying of retinal fluid was observed from baseline up to week 72, as measured by reduction in CST.

Myopic Choroidal Neovascularization (mCNV)

A meta-analysis of 3 RCTs (N = 158 eyes) evaluated the efficacy of bevacizumab and ranibizumab for the treatment of CNV secondary to PM (*Hu et al 2019*). Compared with baseline, at 1, 3, 6, and 12 months after bevacizumab or ranibizumab treatment, BCVA was significantly increased. There was no significant difference between the 2 groups in increasing BCVA from baseline at 1 month, 3 months, 6 months, or 12 months (MD at 12 months, -0.04 logMAR; 95% CI, -0.15 to 0.08; Z = 0.64, 95% CI, -0.15 to 0.08, p = 0.52). No significant difference between groups was observed in the number of injections received (MD, -0.67; 95% CI, -1.83 to 0.49; Z = 1.13, 95% CI, -1.83 to 0.49, p = 0.26; I^2 = 86%) or the effect on CNV stabilization (RR 1.05, 95% CI, 0.83 to 1.33; p = 0.67; I^2 = 71%).

Meta-analysis of common retinal disorders

Pham et al 2019 conducted a systematic review and random-effects meta-analysis to evaluate the comparative effectiveness and safety of bevacizumab, ranibizumab, and aflibercept for patients with nAMD, DME, ME due to RVO and mCNV. Nineteen RCTs (N = 7459) in patients with nAMD (n = 12), DME (n = 3), RVO-ME (n = 2) and mCNV (n = 2) were included.

Vision gain was not significantly different in patients with nAMD, DME, RVO-ME, and mCNV treated with bevacizumab vs ranibizumab. Similarly, vision gain was not significantly different between nAMD patients treated with aflibercept vs ranibizumab. There were no RCTs that directly compared bevacizumab and aflibercept. In the DRCR.net Protocol T trial (N = 620), patients with DME and high baseline VA treated with aflibercept, bevacizumab, or ranibizumab achieved similar vision gains (≥ 15 ETDRS letters) at 12 months (RR of bevacizumab vs aflibercept: 0.91 [95% CI, 0.50 to 1.65]; RR of aflibercept vs ranibizumab: 1.18 [95% CI, 0.64 to 2.17]). In patients with low baseline VA (BCVA < 69 letters), aflibercept was associated with higher vision gains than bevacizumab or ranibizumab at 12 months (RR of bevacizumab vs aflibercept: 0.62 [95% CI, 0.47 to 0.81]; RR of aflibercept vs ranibizumab: 1.35 [95% CI, 1.06 to 1.72]) but this was not maintained at 24 months (RR of bevacizumab vs aflibercept: 0.90 [95% CI, 0.69 to 1.16]; RR of aflibercept vs ranibizumab: 1.05 [95% CI, 0.82 to 1.35]). Rates of systemic serious AEs (SSAEs) were similar for the 3 drugs.

Retinopathy of Prematurity (ROP)

The efficacy and safety of aflibercept vs laser photocoagulation for the treatment of ROP in infants born at GA ≤ 32 weeks were evaluated in 2 pivotal Phase 3, OL, MC, noninferiority RCTs known as FIREFLEYE (*Stahl et al 2022*) and BUTTERFLEYE (*unpublished, Regeneron Medical Information response letter 2023*). In FIREFLEYE, 118 infants were randomized to receive aflibercept 0.4 mg IVT or transpupillary conventional laser photocoagulation. The primary endpoint was the proportion of infants without active ROP and unfavorable structural outcomes 24 weeks after starting treatment. BUTTERFLEYE randomized 127 infants to aflibercept 0.4 mg IVT or laser. The primary endpoint was the proportion of infants with absence of active ROP and unfavorable structural outcomes at week 52 of chronological age. Most patients were treated bilaterally in both studies.

In FIREFLEYE, treatment success was 85.5% (90% credible interval [CrI], 78.0 to 91.3) compared with 82.1% (90% CrI, 70.5 to 90.8) with laser photocoagulation. The between-group difference was 3.4% (1-sided 95% CrI, -8.0 to ∞) in favor of IVT aflibercept. However, because the lower limit of the 95% CrI for the treatment difference was -8.0%, and not greater than the prespecified value of -5.0%, noninferiority could not be concluded. Retreatment was required for 17.8% of eyes in the aflibercept group and 9.7% in the laser photocoagulation group. No infant received more than 2 doses (1 retreatment) per eye. In total, 8.2% of eyes in the aflibercept group (10.7% of infants) received any second treatment modality, which was rescue treatment with laser photocoagulation in 4.8% (95% CI, 1.9 to 9.6%) of eyes (6.7% of infants). In total, 12.5% of eyes (13.2% of infants) in the laser photocoagulation group received any second treatment modality, which was rescue treatment with aflibercept in 11.1% (95% CI, 4.9 to 20.7%) of eyes (10.5% of infants).

In BUTTERFLEYE, 79.6% of patients in the aflibercept group (N = 93) and 77.8% of patients in the laser group (N = 27) achieved absence of active ROP and unfavorable structural outcomes (adjusted difference 1.81%; 95.1% CI, -15.7 to 19.3). Because the lower bound of the 95% CI was not greater than -5.0%, noninferiority could not be concluded. From baseline to week 52, 15.1% of patients in the aflibercept group (N = 93) and 18.5% of patients in the laser group (N = 27) required retreatment (adjusted difference -3.66%; 95.1% CI, -19.9 to 12.5). Five-year extension trials of FIREFLEYE and BUTTERFLEYE are ongoing.

Clinical Guidelines

- The 2019 AAO AMD Preferred Practice Pattern recommends early detection and prompt treatment of nAMD to improve visual outcomes. Management options for AMD include observation, antioxidant vitamin and mineral supplements, IVT injection of anti-VEGF agents, PDT, and laser photocoagulation surgery. The choice of anti-VEGF agent should be individually tailored based on discussion between the patient and physician. The VEGF inhibitors have demonstrated improved visual and anatomic outcomes compared with other therapies. Presently, there does not appear to be a significant difference in efficacy between ranibizumab and bevacizumab. Anti-VEGF therapies have become first-line therapy for treating and stabilizing most cases of nAMD and a Cochrane systematic review demonstrates the effectiveness of these agents to maintain VA (Good quality, Strong recommendation). The guidelines note that ophthalmologists should provide appropriate informed consent with respect to the off-label status of bevacizumab. Symptoms suggestive of post-injection endophthalmitis or retinal detachment require prompt evaluation following administration of VEGF inhibitors.
    - The PRN regimens using ranibizumab appear to have efficacy and safety comparable to fixed monthly regimens over 1 year of treatment, but they do not maintain the initial visual gains with longer follow-up. Caution should be used when dosing PRN bevacizumab, as it may be slightly less effective than other monthly anti-VEGF regimens and other PRN anti-VEGF regimens. A continuous, variable dosing regimen that attempts to individualize therapy, commonly referred to as treat and extend (TAE) is frequently used in clinical practice as an alternative to the 2 treatment approaches above. Prospective studies have shown similar efficacy between monthly and TAE for bevacizumab and ranibizumab.
    - PDT and laser photocoagulation are less commonly used. PDT is an option where the classic component is > 50% of the lesion. Juxtafoveal CNV is an off-label indication for PDT but may be considered in select cases. Thermal laser photocoagulation surgery may be considered for extrafoveal classic CNV or juxtapapillary CNV but is rarely used.
- The 2019 AAO Diabetic Retinopathy Preferred Practice Pattern describes the management of DR based on the severity of the retinopathy as well as the presence and type of DME. IVT anti-VEGF therapy is considered the initial treatment choice for CI-DME and as a possible alternative for PDR. Laser photocoagulation remains the preferred treatment for non-center involved (NCI-DME) and PRP surgery remains the mainstay treatment for PDR. Specific management may vary on a case-by-case basis for the individual patient.
- According to the 2019 AAO Retinal Vein Occlusions Preferred Practice Pattern, ME may complicate both CRVOs and BRVOs. First-line treatment for the associated ME is the use of anti-VEGF agents. IVT corticosteroids, with the associated risk of glaucoma and cataract formation, have demonstrated efficacy. Also, laser photocoagulation in BRVO has a potential role in treatment.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Beovu is a human vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Diabetic Macular Edema (DME)

Byooviz, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Myopic Choroidal Neovascularization (mCNV)

Cimerli, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with:

- 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)

Eylea is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)
- Retinopathy of Prematurity (ROP)

Eylea HD is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (nAMD)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)

Lucentis, a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with:

- 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)

Pavblu is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)

Susvimo (ranibizumab injection), a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with Neovascular (wet) Age-related Macular Degeneration (AMD) who have previously responded to at least two intravitreal injections of a VEGF inhibitor.

Vabysmo is a vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) inhibitor indicated for the treatment of patients with:

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

- Diabetic Macular Edema (DME)
- Macular Edema Following Retinal Vein Occlusion (RVO)

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Policy History/Revision Information

Date	Summary of Changes
9/20/2023	Approved by OptumRx P&T Committee
04/17/2024	Annual Review. New indication added for Vabysmo. Updates to coverage rationale, applicable codes, clinical evidence, FDA and reference sections.
2/20/2025	Annual Review. Addition of Eylea HD and Pavblu to policy. Updated references.

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Archived Policy Versions (Internal Only)

Effective Date	Policy Number	Policy Title
mm/dd/yyyy – mm/dd/yyyy	######	Title of Policy Hyperlinked to KL or Other Internal Location

Nondiscrimination & Language Access Policy

Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:
Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If *you* believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

Hindi: _यान द_: य_द आप ि हंदी बोलते ह_ तो आपके ि लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_।1-800-332-6501 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-800-332-6501 (TTY: 711).

Korean: 주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다.1-800-332-6501 (TTY: 711)번으로 전화해 주십시오.

Polish: UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer1-800-332-6501 (TTY: 711).

Russian: ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода.Звоните 1-800-332-6501 (телетайп: 711).

Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al1-800-332-6501 (TTY: 711).

Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1-800-332-6501 (TTY: 711).

Traditional Chinese: 注意：如果您使用繁體中文， 您可以免費獲得語言援助服務。請 致電 1-800-332-6501 (TTY: 711)

Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-800-332-6501 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzscht, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1-800-332-6501 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1-800-332-6501 (TTY: 711).

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