Ophthalmologic Vascular Endothelial Growth Factor (VEGF) Inhibitors

Policy Number: 2026D0042AQ
Effective Date: July 1, 2026

➲ Instructions for Use

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Related Commercial Policies
- Maximum Dosage and Frequency
- Medical Benefit Therapeutic Equivalent Medications – Excluded Drugs

Community Plan Policy
- Ophthalmologic Vascular Endothelial Growth Factor (VEGF) Inhibitors

Related Medicare Advantage Policy
- Medicare Part B Step Therapy Programs

Coverage Rationale

➲ See Benefit Considerations

Ahzantive™ (aflibercept-mrbb), Enzeevu™ (aflibercept-abzv), Eydenzelt® (aflibercept-boav), Nufymco® (ranibizumab-leyk), Opuviz™ (aflibercept-yszy), and Yesafili™ (aflibercept-jbvf) have been added to the Review at Launch program. Some members may not be eligible for coverage of this medication at this time. Refer to the Medical Benefit Drug Policy titled Review at Launch for New to Market Medications for additional details.

This policy provides information about the use of certain specialty pharmacy medications administered by the intravitreal route for ophthalmologic conditions.

This policy refers to the following vascular endothelial growth factor (VEGF) inhibitors and dual VEGF/angiopoietin-2 (Ang-2) inhibitors:
- Avastin® (bevacizumab)
- Beovu® (brolucizumab-dbll)
- Byooviz™ (ranibizumab-nuna)
- Cimerli™ (ranibizumab-eqrn)
- Eylea® (aflibercept)
- Eylea® HD (aflibercept)
- Lucentis® (ranibizumab)
- Pavblu™ (aflibercept-ayyh)
- Vabysmo™ (faricimab-svoa)
- Any FDA-approved ophthalmologic VEGF or dual VEGF/Ang-2 inhibitor product not listed here*

*Any U.S. Food and Drug Administration approved ophthalmologic VEGF inhibitor product not listed by name in this policy will be considered non-preferred until reviewed by UnitedHealthcare.

Beovu® and Byooviz™ are typically excluded from coverage. Coverage reviews may be in place if required by law or the benefit plan. Refer to the Medical Benefit Drug Policy titled Medical Benefit Therapeutic Equivalent Medications – Excluded Drugs and the corresponding excluded drug list with preferred alternatives.

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Medical Necessity Plans

Avastin, Cimerli, Eylea, Eylea HD, Lucentis, Pavblu, and Vabysmo are the preferred ophthalmologic VEGF or dual VEGF/Ang-2 inhibitor products. Coverage will be provided for Avastin, Cimerli, Eylea, Eylea HD, Lucentis, Pavblu, and Vabysmo contingent on the coverage criteria in the General Requirements and Diagnosis-Specific Criteria sections.

Coverage for Beovu, Byooviz, or other non-preferred ophthalmologic VEGF or dual VEGF/Ang-2 inhibitor products will be provided contingent on the criteria in the Preferred Product Criteria, General Requirements and Diagnosis-Specific Criteria sections. In order to continue coverage, members already on Beovu, Byooviz, or other non-preferred ophthalmologic VEGF or dual VEGF/Ang-2 inhibitor products will be required to change therapy to Avastin, Cimerli, Eylea, Eylea HD, Lucentis, Pabvlu or Vabysmo unless they meet the criteria in the Preferred Product Criteria section.

*Preferred Product Criteria (For Medicare reviews, refer to the CMS section.**)*

Treatment with Beovu, Byooviz, or other non-preferred ophthalmologic VEGF or dual VEGF/Ang-2 inhibitor products is medically necessary for the indications specified in the policy when one of the following is met:

- **Both** of the following:
  - History of a trial of adequate dose and duration of Avastin, Cimerli, Eylea, Eylea HD, Lucentis, Pavblu, and Vabysmo, resulting in minimal clinical response; **and**
  - Physician attests that, in their clinical opinion, the clinical response would be expected to be superior with Beovu, Byooviz, or other non-preferred ophthalmologic VEGF or dual VEGF/Ang-2 inhibitor product, than experienced with Avastin, Cimerli, Eylea, Eylea HD, Lucentis, Pavblu, and Vabysmo

  or
- **Both** of the following:
  - History of intolerance, contraindication, or adverse event to Avastin, Cimerli, Eylea, Eylea HD, Lucentis, Pavblu, and Vabysmo; **and**
  - Physician attests that, in their clinical opinion, the same intolerance, contraindication, or adverse event would not be expected to occur with Beovu, Byooviz, or other non-preferred ophthalmologic VEGF or dual VEGF/Ang-2 inhibitor product

Non-Medical Necessity Plans

Any ophthalmologic VEGF or dual VEGF/Ang-2 inhibitor product is to be approved contingent on the coverage criteria in the General Requirements and Diagnosis-Specific Criteria sections.

General Requirements (Applicable to all Requests)

- For **initial therapy**, **all** of the following:
  - Diagnosis; **and**
  - Intravitreal VEGF or dual VEGF/Ang-2 inhibitor administration is no more than 12 doses per year per eye, regardless of diagnosis; **and**
  - Authorization is for no more than 12 months
- For **continuation of therapy**, **all** of the following:
  - Documentation of positive clinical response to anti-VEGF therapy; **and**
  - Intravitreal VEGF or dual VEGF/Ang-2 inhibitor administration is no more than 12 doses per year per eye, regardless of diagnosis; **and**
  - Authorization is for no more than 12 months

Diagnosis-Specific Requirements (Applicable to all Requests)

Avastin (bevacizumab) is proven and medically necessary for the treatment of:

- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)
- Macular edema following retinal vein occlusion (RVO)
- Myopic choroidal neovascularization (mCNV)
- Neovascular age-related macular degeneration (nAMD)
- Neovascular glaucoma (NVG)
- Neovascularization of the iris (NVI)
- Type I Retinopathy of Prematurity (ROP)

Beovu (brolucizumab) is proven and medically necessary for the treatment of:

- Diabetic macular edema (DME)

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- Neovascular age-related macular degeneration (nAMD)

Byooviz (ranibizumab-nuna) is proven and medically necessary for the treatment of:
- Macular edema following retinal vein occlusion (RVO)
- Myopic choroidal neovascularization (mCNV)
- Neovascular age-related macular degeneration (nAMD)

Cimerli (ranibizumab-eqrn) is proven and medically necessary for the treatment of:
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)
- Macular edema following retinal vein occlusion (RVO)
- Myopic choroidal neovascularization (mCNV)
- Neovascular age-related macular degeneration (nAMD)

Eylea (aflibercept) is proven and medically necessary for the treatment of:
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)
- Macular edema following retinal vein occlusion (RVO)
- Neovascular age-related macular degeneration (nAMD)
- Retinopathy of prematurity (ROP)

Eylea HD (aflibercept) is proven and medically necessary for the treatment of:
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)
- Macular edema following retinal vein occlusion (RVO)
- Neovascular age-related macular degeneration (nAMD)

Lucentis (ranibizumab) is proven and medically necessary for the treatment of:
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)
- Macular edema following retinal vein occlusion (RVO)
- Myopic choroidal neovascularization (mCNV)
- Neovascular age-related macular degeneration (nAMD)

Pavblu (aflibercept-ayyh) is proven and medically necessary for the treatment of:
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)
- Macular edema following retinal vein occlusion (RVO)
- Neovascular age-related macular degeneration (nAMD)

Vabysmo (faricimab-svoa) is proven and medically necessary for the treatment of:
- Diabetic macular edema (DME)
- Macular edema following retinal vein occlusion (RVO)
- Neovascular age-related macular degeneration (nAMD)

Additional Information

Avastin (bevacizumab) is supplied in sterile vials containing a solution of 25 mg/mL. Doses utilized in ophthalmic conditions generally range from 6.2 mcg to 2.5 mg. Therefore, bevacizumab vials are often divided into single-dose, prefilled syringes for intravitreal use by compounding pharmacies. Compounding pharmacies must comply with the United States Pharmacopeia (USP) General Chapter < 797 > : Pharmaceutical Compounding – Sterile Preparations, which sets standards for the compounding, transportation, and storage of compounded sterile products (CSP). The American Academy of Opthalmology recommends sourcing bevacizumab for intravitreal injections from a compounding pharmacy accredited by the Pharmacy Compounding Accrediation Board (PCAB), which adheres to these standards.

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

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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	Brand Name
C9257	Injection, bevacizumab, 0.25 mg	Avastin
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
J9035	Injection, bevacizumab, 10 mg	Avastin
Q5124	Injection, ranibizumab-nuna, biosimilar, (Byooviz), 0.1 mg	Byooviz
Q5128	Injection, ranibizumab-eqrn (Cimerli), biosimilar, 0.1 mg	Cimerli
Q5147	Injection, aflibercept-ayyh (Pavblu), biosimilar, 0.1 mg	Pavblu
Q5149	Injection, aflibercept-abzv (Enzeevu), biosimilar, 1 mg	Enzeevu
Q5150	Injection, aflibercept-mrbb (Ahzantive), biosimilar, 1 mg	Ahzantive
Q5153	Injection, aflibercept-yszy (Opuviz), biosimilar, 1 mg	Opuviz
Q5155	Injection, aflibercept-jbvf (Yesafili), biosimilar, 1 mg	Yesafili
Q5168	Injection, ranibizumab-leyk (Nufymco), biosimilar, 0.1 mg	Nufymco
Q5170	Injection, aflibercept-boav (Eydenzelt), biosimilar, 1 mg	Eydenzelt

Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
B39.5	Histoplasmosis duboisii						X		
B39.9	Histoplasmosis, unspecified						X		
E08.311	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy with macular edema	X	X	X	X	X	X		X
E08.319	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy without macular edema	X	X			X	X		X
E08.3211	Diabetes mellitus due to underlying condition with mild non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E08.3212	Diabetes mellitus due to underlying condition with mild non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E08.3213	Diabetes mellitus due to underlying condition with mild non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E08.3219	Diabetes mellitus due to underlying condition with mild non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E08.3291	Diabetes mellitus due to underlying condition with mild non-proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E08.3292	Diabetes mellitus due to underlying condition with mild non-proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X
E08.3293	Diabetes mellitus due to underlying condition with mild non-proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E08.3299	Diabetes mellitus due to underlying condition with mild non-proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E08.3311	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E08.3312	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E08.3313	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E08.3319	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E08.3391	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E08.3392	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X
E08.3393	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E08.3399	Diabetes mellitus due to underlying condition with moderate non-proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E08.3411	Diabetes mellitus due to underlying condition with severe non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E08.3412	Diabetes mellitus due to underlying condition with severe non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E08.3413	Diabetes mellitus due to underlying condition with severe non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E08.3419	Diabetes mellitus due to underlying condition with severe non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E08.3491	Diabetes mellitus due to underlying condition with severe non-proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E08.3492	Diabetes mellitus due to underlying condition with severe non-proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X
E08.3493	Diabetes mellitus due to underlying condition with severe non-proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E08.3499	Diabetes mellitus due to underlying condition with severe non-proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E08.3511	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E08.3512	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E08.3513	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E08.3519	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E08.3521	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye	X	X			X	X		X
E08.3522	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E08.3523	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral	X	X			X	X		X
E08.3529	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye	X	X			X	X		X
E08.3531	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye	X	X			X	X		X
E08.3532	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye	X	X			X	X		X
E08.3533	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral	X	X			X	X		X
E08.3539	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye	X	X			X	X		X
E08.3541	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E08.3542	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye	X	X			X	X		X
E08.3543	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral	X	X			X	X		X
E08.3549	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye	X	X			X	X		X
E08.3551	Diabetes mellitus due to underlying condition with stable proliferative diabetic retinopathy, right eye	X	X			X	X		X
E08.3552	Diabetes mellitus due to underlying condition with stable proliferative diabetic retinopathy, left eye	X	X			X	X		X
E08.3553	Diabetes mellitus due to underlying condition with stable proliferative diabetic retinopathy, bilateral	X	X			X	X		X
E08.3559	Diabetes mellitus due to underlying condition with stable proliferative diabetic retinopathy, unspecified eye	X	X			X	X		X
E08.3591	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E08.3592	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E08.3593	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E08.3599	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E08.37X1	Diabetes mellitus due to underlying condition with diabetic macular edema, resolved following treatment, right eye	X	X	X	X	X	X		X
E08.37X2	Diabetes mellitus due to underlying condition with diabetic macular edema, resolved following treatment, left eye	X	X	X	X	X	X		X
E08.37X3	Diabetes mellitus due to underlying condition with diabetic macular edema, resolved following treatment, bilateral	X	X	X	X	X	X		X
E08.37X9	Diabetes mellitus due to underlying condition with diabetic macular edema, resolved following treatment, unspecified eye	X	X	X	X	X	X		X
E09.311	Drug or chemical induced diabetes mellitus with unspecified diabetic retinopathy with macular edema	X	X	X	X	X	X		X
E09.3211	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E09.3212	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E09.3213	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E09.3219	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E09.3291	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E09.3292	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X
E09.3293	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E09.3299	Drug or chemical induced diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E09.3311	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E09.3312	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E09.3313	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E09.3319	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E09.3391	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E09.3392	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X
E09.3393	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E09.3399	Drug or chemical induced diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E09.3411	Drug or chemical induced diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E09.3412	Drug or chemical induced diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E09.3413	Drug or chemical induced diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E09.3419	Drug or chemical induced diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E09.3491	Drug or chemical induced diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E09.3492	Drug or chemical induced diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E09.3493	Drug or chemical induced diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E09.3499	Drug or chemical induced diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E09.3511	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E09.3512	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E09.3513	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E09.3519	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E09.3521	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye	X	X			X	X		X
E09.3522	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye	X	X			X	X		X
E09.3523	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E09.3529	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye	X	X			X	X		X
E09.3531	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye	X	X			X	X		X
E09.3532	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye	X	X			X	X		X
E09.3533	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral	X	X			X	X		X
E09.3539	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye	X	X			X	X		X
E09.3541	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye	X	X			X	X		X
E09.3542	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E09.3543	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral	X	X			X	X		X
E09.3549	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye	X	X			X	X		X
E09.3551	Drug or chemical induced diabetes mellitus with stable proliferative diabetic retinopathy, right eye	X	X			X	X		X
E09.3552	Drug or chemical induced diabetes mellitus with stable proliferative diabetic retinopathy, left eye	X	X			X	X		X
E09.3553	Drug or chemical induced diabetes mellitus with stable proliferative diabetic retinopathy, bilateral	X	X			X	X		X
E09.3559	Drug or chemical induced diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye	X	X			X	X		X
E09.3591	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E09.3592	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X
E09.3593	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E09.3599	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E09.37X1	Drug or chemical induced diabetes mellitus with diabetic macular edema, resolved following treatment, right eye	X	X	X	X	X	X		X
E09.37X2	Drug or chemical induced diabetes mellitus with diabetic macular edema, resolved following treatment, left eye	X	X	X	X	X	X		X
E09.37X3	Drug or chemical induced diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral	X	X	X	X	X	X		X
E09.37X9	Drug or chemical induced diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye	X	X	X	X	X	X		X
E10.311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema	X	X	X	X	X	X		X
E10.3211	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E10.3212	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E10.3213	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E10.3219	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E10.3291	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E10.3292	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E10.3293	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E10.3299	Type 1 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E10.3311	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E10.3312	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E10.3313	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E10.3319	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E10.3391	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E10.3392	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X
E10.3393	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E10.3399	Type 1 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E10.3411	Type 1 diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E10.3412	Type 1 diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E10.3413	Type 1 diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E10.3419	Type 1 diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E10.3491	Type 1 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E10.3492	Type 1 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X
E10.3493	Type 1 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E10.3499	Type 1 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E10.3511	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E10.3512	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E10.3513	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E10.3519	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E10.3521	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye	X	X			X	X		X
E10.3522	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye	X	X			X	X		X
E10.3523	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral	X	X			X	X		X
E10.3529	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye	X	X			X	X		X
E10.3531	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye	X	X			X	X		X
E10.3532	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye	X	X			X	X		X
E10.3533	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral	X	X			X	X		X
E10.3539	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E10.3541	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye	X	X			X	X		X
E10.3542	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye	X	X			X	X		X
E10.3543	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral	X	X			X	X		X
E10.3549	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye	X	X			X	X		X
E10.3551	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, right eye	X	X			X	X		X
E10.3552	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, left eye	X	X			X	X		X
E10.3553	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, bilateral	X	X			X	X		X
E10.3559	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye	X	X			X	X		X
E10.3591	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E10.3592	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E10.3593	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E10.3599	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E10.37X1	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, right eye	X	X	X	X	X	X		X
E10.37X2	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, left eye	X	X	X	X	X	X		X
E10.37X3	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral	X	X	X	X	X	X		X
E10.37X9	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye	X	X	X	X	X	X		X
E11.311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema	X	X	X	X	X	X		X
E11.3211	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E11.3212	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E11.3213	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E11.3219	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E11.3291	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E11.3292	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X
E11.3293	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E11.3299	Type 2 diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E11.3311	Type 2 diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E11.3312	Type 2 diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E11.3313	Type 2 diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E11.3319	Type 2 diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E11.3391	Type 2 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E11.3392	Type 2 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X
E11.3393	Type 2 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E11.3399	Type 2 diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E11.3411	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E11.3412	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E11.3413	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E11.3419	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E11.3491	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E11.3492	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X
E11.3493	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E11.3499	Type 2 diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E11.3511	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E11.3512	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E11.3513	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E11.3519	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E11.3521	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye	X	X			X	X		X
E11.3522	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye	X	X			X	X		X
E11.3523	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral	X	X			X	X		X
E11.3529	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye	X	X			X	X		X
E11.3531	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye	X	X			X	X		X
E11.3532	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E11.3533	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral	X	X			X	X		X
E11.3539	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye	X	X			X	X		X
E11.3541	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye	X	X			X	X		X
E11.3542	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye	X	X			X	X		X
E11.3543	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral	X	X			X	X		X
E11.3549	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye	X	X			X	X		X
E11.3551	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, right eye	X	X			X	X		X
E11.3552	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, left eye	X	X			X	X		X
E11.3553	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, bilateral	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E11.3559	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye	X	X			X	X		X
E11.3591	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E11.3592	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X
E11.3593	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E11.3599	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E11.37X1	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, right eye	X	X	X	X	X	X		X
E11.37X2	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, left eye	X	X	X	X	X	X		X
E11.37X3	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral	X	X	X	X	X	X		X
E11.37X9	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye	X	X	X	X	X	X		X
E13.311	Other specified diabetes mellitus with unspecified diabetic retinopathy with macular edema	X	X	X	X	X	X		X
E13.3211	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E13.3212	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E13.3213	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E13.3219	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E13.3291	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E13.3292	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X
E13.3293	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E13.3299	Other specified diabetes mellitus with mild non-proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E13.3311	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E13.3312	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E13.3313	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E13.3319	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E13.3391	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E13.3392	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X
E13.3393	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E13.3399	Other specified diabetes mellitus with moderate non-proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E13.3411	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E13.3412	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E13.3413	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E13.3419	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E13.3491	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E13.3492	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E13.3493	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E13.3499	Other specified diabetes mellitus with severe non-proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E13.3511	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, right eye	X	X	X	X	X	X		X
E13.3512	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, left eye	X	X	X	X	X	X		X
E13.3513	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, bilateral	X	X	X	X	X	X		X
E13.3519	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema, unspecified eye	X	X	X	X	X	X		X
E13.3521	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, right eye	X	X			X	X		X
E13.3522	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, left eye	X	X			X	X		X
E13.3523	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, bilateral	X	X			X	X		X
E13.3529	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula, unspecified eye	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E13.3531	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye	X	X			X	X		X
E13.3532	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, left eye	X	X			X	X		X
E13.3533	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, bilateral	X	X			X	X		X
E13.3539	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, unspecified eye	X	X			X	X		X
E13.3541	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, right eye	X	X			X	X		X
E13.3542	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, left eye	X	X			X	X		X
E13.3543	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, bilateral	X	X			X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E13.3549	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment, unspecified eye	X	X			X	X		X
E13.3551	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, right eye	X	X			X	X		X
E13.3552	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, left eye	X	X			X	X		X
E13.3553	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, bilateral	X	X			X	X		X
E13.3559	Other specified diabetes mellitus with stable proliferative diabetic retinopathy, unspecified eye	X	X			X	X		X
E13.3591	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, right eye	X	X			X	X		X
E13.3592	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, left eye	X	X			X	X		X
E13.3593	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, bilateral	X	X			X	X		X
E13.3599	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema, unspecified eye	X	X			X	X		X
E13.37X1	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, right eye	X	X	X	X	X	X		X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
E13.37X2	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, left eye	X	X	X	X	X	X		X
E13.37X3	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral	X	X	X	X	X	X		X
E13.37X9	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment, unspecified eye	X	X	X	X	X	X		X
H21.1X1	Other vascular disorders of iris and ciliary body, right eye						X		
H21.1X2	Other vascular disorders of iris and ciliary body, left eye						X		
H21.1X3	Other vascular disorders of iris and ciliary body, bilateral						X		
H21.1X9	Other vascular disorders of iris and ciliary body, unspecified eye						X		
H34.8110	Central retinal vein occlusion, right eye, with macular edema	X	X		X	X	X	X	X
H34.8111	Central retinal vein occlusion, right eye, with retinal neovascularization	X	X		X	X	X	X	X
H34.8112	Central retinal vein occlusion, right eye, stable	X	X		X	X	X	X	X
H34.8120	Central retinal vein occlusion, left eye, with macular edema	X	X		X	X	X	X	X
H34.8121	Central retinal vein occlusion, left eye, with retinal neovascularization	X	X		X	X	X	X	X
H34.8122	Central retinal vein occlusion, left eye, stable	X	X		X	X	X	X	X
H34.8130	Central retinal vein occlusion, bilateral, with macular edema	X	X		X	X	X	X	X
H34.8131	Central retinal vein occlusion, bilateral, with retinal neovascularization	X	X		X	X	X	X	X
H34.8132	Central retinal vein occlusion, bilateral, stable	X	X		X	X	X	X	X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
H34.8190	Central retinal vein occlusion, unspecified eye, with macular edema	X	X		X	X	X	X	X
H34.8191	Central retinal vein occlusion, unspecified eye, with retinal neovascularization	X	X		X	X	X	X	X
H34.8192	Central retinal vein occlusion, unspecified eye, stable	X	X		X	X	X	X	X
H34.821	Venous engorgement, right eye	X	X		X	X	X	X	X
H34.822	Venous engorgement, left eye	X	X		X	X	X	X	X
H34.823	Venous engorgement, bilateral	X	X		X	X	X	X	X
H34.829	Venous engorgement, unspecified eye	X	X		X	X	X	X	X
H34.8310	Tributary (branch) retinal vein occlusion, right eye, with macular edema	X	X		X	X	X	X	X
H34.8311	Tributary (branch) retinal vein occlusion, right eye, with retinal neovascularization	X	X		X	X	X	X	X
H34.8312	Tributary (branch) retinal vein occlusion, right eye, stable	X	X		X	X	X	X	X
H34.8320	Tributary (branch) retinal vein occlusion, left eye, with macular edema	X	X		X	X	X	X	X
H34.8321	Tributary (branch) retinal vein occlusion, left eye, with retinal neovascularization	X	X		X	X	X	X	X
H34.8322	Tributary (branch) retinal vein occlusion, left eye, stable	X	X		X	X	X	X	X
H34.8330	Tributary (branch) retinal vein occlusion, bilateral, with macular edema	X	X		X	X	X	X	X
H34.8331	Tributary (branch) retinal vein occlusion, bilateral, with retinal neovascularization	X	X		X	X	X	X	X
H34.8332	Tributary (branch) retinal vein occlusion, bilateral, stable	X	X		X	X	X	X	X
H34.8390	Tributary (branch) retinal vein occlusion, unspecified eye, with macular edema	X	X		X	X	X	X	X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
H34.8391	Tributary (branch) retinal vein occlusion, unspecified eye, with retinal neovascularization	X	X		X	X	X	X	X
H34.8392	Tributary (branch) retinal vein occlusion, unspecified eye, stable	X	X		X	X	X	X	X
H35.051	Retinal neovascularization, unspecified, right eye					X	X	X	
H35.052	Retinal neovascularization, unspecified, left eye					X	X	X	
H35.053	Retinal neovascularization, unspecified, bilateral					X	X	X	
H35.059	Retinal neovascularization, unspecified, unspecified eye					X	X	X	
H35.101	Retinopathy of prematurity, unspecified, right eye		X				X		
H35.102	Retinopathy of prematurity, unspecified, left eye		X				X		
H35.103	Retinopathy of prematurity, unspecified, bilateral		X				X		
H35.109	Retinopathy of prematurity, unspecified, unspecified eye		X				X		
H35.111	Retinopathy of prematurity, stage 0, right eye		X				X		
H35.112	Retinopathy of prematurity, stage 0, left eye		X				X		
H35.113	Retinopathy of prematurity, stage 0, bilateral		X				X		
H35.119	Retinopathy of prematurity, stage 0, unspecified eye		X				X		
H35.121	Retinopathy of prematurity, stage 1, right eye		X				X		
H35.122	Retinopathy of prematurity, stage 1, left eye		X				X		
H35.123	Retinopathy of prematurity, stage 1, bilateral		X				X		
H35.129	Retinopathy of prematurity, stage 1, unspecified eye		X				X		
H35.131	Retinopathy of prematurity, stage 2, right eye		X				X		
H35.132	Retinopathy of prematurity, stage 2, left eye		X				X		
H35.133	Retinopathy of prematurity, stage 2, bilateral		X				X		
H35.139	Retinopathy of prematurity, stage 2, unspecified eye		X				X		

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
H35.141	Retinopathy of prematurity, stage 3, right eye		X				X		
H35.142	Retinopathy of prematurity, stage 3, left eye		X				X		
H35.143	Retinopathy of prematurity, stage 3, bilateral		X				X		
H35.149	Retinopathy of prematurity, stage 3, unspecified eye		X				X		
H35.151	Retinopathy of prematurity, stage 4, right eye		X				X		
H35.152	Retinopathy of prematurity, stage 4, left eye		X				X		
H35.153	Retinopathy of prematurity, stage 4, bilateral		X				X		
H35.159	Retinopathy of prematurity, stage 4, unspecified eye		X				X		
H35.161	Retinopathy of prematurity, stage 5, right eye		X				X		
H35.162	Retinopathy of prematurity, stage 5, left eye		X				X		
H35.163	Retinopathy of prematurity, stage 5, bilateral		X				X		
H35.169	Retinopathy of prematurity, stage 5, unspecified eye		X				X		
H35.171	Retrolental fibroplasia, right eye		X				X		
H35.172	Retrolental fibroplasia, left eye		X				X		
H35.173	Retrolental fibroplasia, bilateral		X				X		
H35.179	Retrolental fibroplasia, unspecified eye		X				X		
H35.3210	Exudative age-related macular degeneration, right eye, stage unspecified	X	X	X	X	X	X	X	X
H35.3211	Exudative age-related macular degeneration, right eye, with active choroidal neovascularization	X	X	X	X	X	X	X	X
H35.3212	Exudative age-related macular degeneration, right eye, with inactive choroidal neovascularization	X	X	X	X	X	X	X	X
H35.3213	Exudative age-related macular degeneration, right eye, with inactive scar	X	X	X	X	X	X	X	X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
H35.3220	Exudative age-related macular degeneration, left eye, stage unspecified	X	X	X	X	X	X	X	X
H35.3221	Exudative age-related macular degeneration, left eye, with active choroidal neovascularization	X	X	X	X	X	X	X	X
H35.3222	Exudative age-related macular degeneration, left eye, with inactive choroidal neovascularization	X	X	X	X	X	X	X	X
H35.3223	Exudative age-related macular degeneration, left eye, with inactive scar	X	X	X	X	X	X	X	X
H35.3230	Exudative age-related macular degeneration, bilateral, stage unspecified	X	X	X	X	X	X	X	X
H35.3231	Exudative age-related macular degeneration, bilateral, with active choroidal neovascularization	X	X	X	X	X	X	X	X
H35.3232	Exudative age-related macular degeneration, bilateral, with inactive choroidal neovascularization	X	X	X	X	X	X	X	X
H35.3233	Exudative age-related macular degeneration, bilateral, with inactive scar	X	X	X	X	X	X	X	X
H35.3290	Exudative age-related macular degeneration, unspecified eye, stage unspecified	X	X	X	X	X	X	X	X
H35.3291	Exudative age-related macular degeneration, unspecified eye, with active choroidal neovascularization	X	X	X	X	X	X	X	X
H35.3292	Exudative age-related macular degeneration, unspecified eye, with inactive choroidal neovascularization	X	X	X	X	X	X	X	X
H35.3293	Exudative age-related macular degeneration, unspecified eye, with inactive scar	X	X	X	X	X	X	X	X
H35.351	Cystoid macular degeneration, right eye	X	X	X	X	X	X	X	X
H35.352	Cystoid macular degeneration, left eye	X	X	X	X	X	X	X	X

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Diagnosis Code	Description	Applies to HCPCS Code							
		J0177	J0178	J0179	J2777	J2778 Q5128	C9257 J9035	Q5124	Q5147
H35.353	Cystoid macular degeneration, bilateral	X	X	X	X	X	X	X	X
H40.841	Neovascular secondary angle closure glaucoma, right eye						X		
H40.842	Neovascular secondary angle closure glaucoma, left eye						X		
H40.843	Neovascular secondary angle closure glaucoma, bilateral						X		
H40.849	Neovascular secondary angle closure glaucoma, unspecified eye						X		
H40.89	Other specified glaucoma						X		
H44.2A1	Degenerative myopia with choroidal neovascularization, right eye					X	X	X	
H44.2A2	Degenerative myopia with choroidal neovascularization, left eye					X	X	X	
H44.2A3	Degenerative myopia with choroidal neovascularization, bilateral					X	X	X	
H44.2A9	Degenerative myopia with choroidal neovascularization, unspecified eye					X	X	X	

Background

Vascular endothelial growth factor (VEGF) is a protein that stimulates the growth, proliferation, and survival of vascular endothelial cells. VEGF plays a significant role in the development of new blood vessels (angiogenesis). Overproduction of VEGF can lead to abnormal blood vessel growth in the eye, contributing to various retinal diseases. Intravitreal VEGF inhibitors are designed to block this process, thereby preventing vision loss and improving visual outcomes. Intravitreal VEGF inhibitors work by binding to VEGF, preventing it from interacting with receptors on vascular endotheial cells. This action reduces vascular permeability, inhibits abnormal blood vessel growth, and decreases inflammation in the retina.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

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Proven

Neovascular Age-Related Macular Degeneration (nAMD)

Avastin (bevacizumab), Beovu (brolucizumab-dbll), Byooviz (ranibizumab-nuna), Cimerli (ranibizumab-eqrn), Eylea (aflibercept), Eylea HD (high-dose aflibercept), Lucentis (ranibizumab), Pavblu (aflibercept-ayyh), and Vabysmo (faricimab-svoa) are indicated for the treatment of neovascular age-related macular degeneration.

The efficacy and safety of bevacizumab versus ranibizumab was evaluated in a multi-center, single-blind, non-inferiority study conducted by the CATT Research Group in 1,208 patients with neovascular age-related macular degeneration (AMD). Participants were randomly assigned to receive intravitreal injections of either ranibizumab or bevacizumab on a monthly schedule or as needed with monthly evaluations. The primary outcome of the study was the mean change in visual acuity at one year, with a non-inferiority limit of 5 letters on the eye chart. The investigators reported that monthly administration of bevacizumab was equivalent to monthly administration of ranibizumab, with 8.0 and 8.5 letters gained, respectively. Results of as needed administration of the agents were determined to be equivalent, with bevacizumab recipients gaining 5.9 letters and ranibizumab recipients gaining 6.8 letters. Ranibizumab as needed was equivalent to monthly ranibizumab, while the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive, the mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 µm) than in the other groups (152 to 168 µm, p = 0.03 by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either treatment (p > 0.20). However, the proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern. Therefore, the investigators recommended that differences in rates of serious adverse events should be further studied. At one year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly.

Kodijkian et all also evaluated the relative efficacy and safety profile of bevacizumab versus ranibizumab intravitreal injections for the treatment of neovascular age-related macular degeneration (AMD) in a multicenter, prospective, noninferiority, double-masked, randomized clinical trial.. Patients (n = 501) aged ≥ 50 years were eligible if they presented with subfoveal neovascular AMD, with best-corrected visual acuity (BVCA) in the study eye of between 20/32 and 20/320 measured on the Early Treatment of Diabetic Retinopathy Study chart, and a lesion area of less than 12 optic disc areas (DA). Subjects were randomly assigned to intravitreal administration of bevacizumab (1.25 mg) or ranibizumab (0.50 mg), then followed for one year. A loading dose of three-monthly intravitreal injections was administered to all subjects, followed by an as-needed regimen (one injection in case of active disease) for the remaining 9 months with monthly follow-up. The main outcome measure was the mean change in visual acuity at one year, with a noninferiority limit of five letters. In the per protocol analysis, bevacizumab was noninferior to ranibizumab [bevacizumab minus ranibizumab + 1.89 letters; 95% confidence interval (CI), -1.16 to + 4.93, p < 0.0001]. The intention-to-treat analysis was concordant. The mean number of injections was 6.8 in the bevacizumab group and 6.5 in the ranibizumab group (p = 0.39). Both drugs reduced the central subfield macular thickness, with a mean decrease of 95 µm for bevacizumab and 107 µm for ranibizumab (p = 0.27). There were no significant differences in the presence of subretinal or intraretinal fluid at final evaluation, dye leakage on angiogram, or change in choroidal neovascular area. The proportion of patients with serious adverse events was 12.6% in the bevacizumab group and 12.1% in the ranibizumab group (p = 0.88). The proportion of patients with serious systemic or ocular adverse events was similar in both groups. Based on these results, bevacizumab was determined to be noninferior to ranibizumab for visual acuity at one year with similar safety profiles.

HAWK and HARRIER were two double-masked, multicenter, active-controlled, randomized phase 3 trials that compared brolucizumab, with aflibercept to treat neovascular age-related macular degeneration (nAMD). In the studies, patients (n = 1817) had untreated, active choroidal neovascularization due to age-related macular degeneration in the study eye. Patients were randomized to intravitreal brolucizumab 3 mg or 6 mg or aflibercept 2 mg. After loading with 3 monthly injections, brolucizumab-treated eyes received an injection every 12 weeks. If disease activity was present, dosing was adjusted to every 8 weeks. Patients receiving aflibercept were dosed every 8 weeks. The study was evaluating noninferiority in mean best-corrected visual acuity (BCVA) change from baseline to 48 weeks. Other key end points included the percentage of patients who maintained every 12-week dosing through 48 weeks and anatomic outcomes. At 48 weeks, each brolucizumab arm demonstrated noninferiority to aflibercept in BCVA change from baseline. Greater than 50% of brolucizumab 6 mg-treated eyes were maintained on every 12-week dosing for 48 weeks. At 16 weeks, after the same treatment exposure, fewer brolucizumab 6 mg-treated eyes had disease activity versus aflibercept in HAWK (24.0% vs. 34.5%; p = 0.001) and HARRIER (22.7% vs. 32.2%; p = 0.002). Greater central subfield thickness reductions from baseline to 48 weeks were observed with brolucizumab 6 mg versus aflibercept in HAWK (LS mean -172.8 µm vs. -143.7

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μm; p = 0.001) and HARRIER (LS mean -193.8 μm vs. -143.9 μm; p < 0.001). Anatomic retinal fluid outcomes favored brolucizumab over aflibercept. Overall, adverse event rates were generally the same with the two agents. The authors concluded that brolucizumab was noninferior to aflibercept in visual function at 48 weeks, and > 50% of brolucizumab 6 mg-treated eyes were maintained on every 12-week dosing through 48 weeks. Anatomic outcomes favored brolucizumab over aflibercept. Overall safety was similar for the two agents.

Two identically designed, randomized, multi-center, double-masked, active comparator-controlled, 2-year studies (TENAYA – NCT03823287 and LUCERNE – NCT03823300) assessed the safety and efficacy of faricimab in patients with nAMD. Patients (n = 1329) were newly diagnosed and treatment-naïve with ages ranging from 50 to 99 (mean = 75.9 years). Patients were randomized in a 1:1 ratio to one of two treatment arms: (1) aflibercept 2 mg administered fixed every 8 weeks after three initial monthly doses; and faricimab 6 mg administered by intravitreal injection every 4 weeks for the first 4 doses, followed by optical coherence tomography and visual acuity evaluations 8 and 12 weeks later to determine whether to give a 6 mg dose via intravitreal injection on one of the following three regimens: (1) Weeks 28 and 44 (Q16W dosing); (2) Weeks 24, 36, and 48 (Q12W dosing); or (3) Weeks 20, 28, 36, and 44 (Q8W dosing). At week 48, after 4 initial monthly doses in the faricimab arm, 45% of patients received Q16W dosing, 33% of patients received Q12W dosing, and the remaining 22% of patients received Q8W dosing. Both studies demonstrated non-inferiority to the comparator control (aflibercept) at the primary endpoint, defined as the mean change from baseline in Best Corrected Visual Acuity (BCVA) when averaged over the week 40, 44, and 48 visits and measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart. The primary endpoint analysis was a non-inferiority comparison for the mean change in BCVA between the aflibercept and the faricimab arm. In both studies, faricimab-treated patients had a non-inferior mean change from baseline in BCVA compared to patients treated with aflibercept. The clinical efficacy for the second year of the study has not been reviewed.

Woo et al. evaluated the equivalence of efficacy, similar safety, and similar immunogenicity of a ranibizumab biosimilar product (SB11) compared with the reference ranibizumab with neovascular age-related macular degeneration in a randomized, double-masked, parallel-group phase 3 equivalence study. The study was conducted in 75 centers in 9 countries from March 14, 2018, to December 9, 2019, among 705 participants 50 years or older with neovascular age-related macular degeneration with active subfoveal choroidal neovascularization lesions. Patients were randomized in a 1:1 ratio to receive intravitreous injection of either SB11 or ranibizumab, 0.5 mg, every 4 weeks through week 48. Preplanned interim analysis after all participants completed the week 24 assessment of primary efficacy end points at week 8 for change from baseline in best-corrected visual acuity (BCVA) and week 4 for central subfield thickness (CST), with predefined equivalence margins for adjusted treatment differences of −3 letters to 3 letters for BCVA and −36 μm to 36 μm for CST. Least-squares mean (SE) changes in BCVA from baseline at week 8 were 6.2 (0.5) letters in the SB11 group vs 7.0 (0.5) letters in the ranibizumab group. Least-squares mean (SE) changes in CST from baseline at week 4 were −108 (5) μm in the SB11 group vs −100 (5)μm in the ranibizumab group. Incidences of treatment-emergent adverse events [231 of 350 (66.0%) vs 237 of 354 (66.9%)], including serious treatment-emergent adverse events [44 of 350 (12.6%) vs 44 of 354 (12.4%)] and treatment-emergent adverse events leading to study drug discontinuation [8 of 350 (2.3%) vs 5 of 354 (1.4%)], were similar in the SB11 and ranibizumab groups. Immunogenicity was low, with a cumulative incidence of antidrug antibodies up to week 24 of 3.0% (10 of 330) in the SB11 group and 3.1% (10 of 327) in the ranibizumab group. These findings of equivalent efficacy and similar safety and immunogenicity profiles compared with ranibizumab support the use of SB11 for patients with neovascular age-related macular degeneration.

The clinical equivalence of ranibizumab-eqrn and reference ranibizumab was evaluated in a prospective, evaluation-masked, parallel-group, 48-week, phase 3 randomized study in patients with treatment-naïve, subfoveal choroidal neovascularization caused by neovascular age-related macular degeneration (nAMD). A total of 477 patients were randomly assigned to receive ranibizumab-eqrn (n = 238) or reference ranibizumab (n = 239) 0.5mg by intravitreal (IVT) injection in the study eye every 4 weeks. The primary end point was change from baseline in best-corrected visual acuity (BCVA) by Early Treatment Diabetic Retinopathy Study (ETDRS) letters at 8 weeks before the third IVT injection. Biosimilarity of ranibizumab-eqrn to its originator was assess via a 2-sided equivalence test, with an equivalence margin in BCVA of 3 ETDRS letters. The BCVA improved in both groups, with a mean improvement of + 5.1 (FYB201) and + 5.6 (reference ranibizumab) ETDRS letters at week 8. The analysis of covariance (ANCOVA) least squares mean difference for the change from baseline between ranibizumab-eqrn and reference ranibizumab was -0.4 ETDRS letters with a 90% confidence interval (CI) of -1.6 to 0.9. Primary end point was met as the 90% CI was within the predefined equivalence margin of -3.5 to 3.5. In the post hoc analysis, the ANCOVA least squares mean difference for the change from baseline in BCVA at week 8 between ranibizumab-eqrn and reference ranibizumab was –0.4 ETDRS letters, with a 95% CI of –1.9 to 1.1, again meeting the criteria for equivalence between drugs. In the per-protocol sensitivity analysis, the ANCOVA least squares mean difference for change in BCVA between ranibizumab-eqrn and reference ranibizumab at week 8 was –0.4 ETDRS letters, with a 90% CI of –1.7 to 0.9, also contained within the predefined equivalence margin. The frequency and type of ocular adverse events were comparable between treatment groups. Most adverse events were of mild or moderate intensity, and no clinically relevant differences were identified. The most frequent study drug-related adverse

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events in the ranibizumab-eqrn and reference ranibizumab groups, respectively, were cataract (0.0% and 2.1%), retinal pigment epithelium tear (0.4% and 1.3%), reduced visual acuity (0.0% and 1.3%), punctate keratitis (0.0% and 0.8%), vitreous hemorrhage (0.4% and 0.4%), eye pain (0.8% and 0.0%), increased gamma-glutamyl transferase level (0.4% and 0.4%), and increased intraocular pressure (1.3% and 0.8%). A total of 21.4% (ranibizumab-eqrn) and 27.6% (reference ranibizumab) of patients experienced adverse events related to the IVT injection procedure. The prevalence of treatment-emergent AEs associated with MedDRA preferred terms for intraocular inflammation was similar between FYB201 and reference ranibizumab groups. Of the patients treated with FYB201, 8.4% (20/238) experienced treatment-emergent AEs associated with intraocular inflammation terms, compared with 8.4% (20/239) of patients treated with reference ranibizumab. In both treatment groups, 0.8% of patients experienced treatment-emergent AEs possibly related to the investigational medicinal product, specifically iridocyclitis (n = 1) and conjunctivitis (n = 1) in the FYB201 group, and punctate keratitis (n = 2) in the reference ranibizumab group. Frequency and type of systemic AEs were also similar between FYB201 and reference ranibizumab groups, with the most frequent, respectively, being nAMD in the fellow eye (7.6% and 8.8%), nasopharyngitis (5.0% and 6.7%), hypertension (1.3% and 5.9%), and increased C-reactive protein level (4.2% and 2.1%). A slightly higher incidence of systemic serious AEs was observed in the reference ranibizumab arm (12.1%) compared with the FYB201 arm (7.1%). Three patients discontinued the study because of AEs, 1 in the FYB201 group (worsening of nAMD) and 2 in the reference ranibizumab group (unrelated benign pancreatic neoplasm and malignant tongue neoplasm of unspecified stage). In addition, AEs led to permanent or temporary withdrawal of study drug in an additional 9 patients, 5 in the FYB201 group and 4 in the reference ranibizumab group. In the FYB201 group, 3 patients had interruption of treatment due to mild nonserious AEs (1 with upper respiratory tract infection and 2 with conjunctivitis), and 2 patients had moderate AEs; 1 had a chalazion for which treatment was resumed at the subsequent visit without omitting an injection, and 1 had conjunctivitis for which the patient did not receive the last planned injection. In the reference ranibizumab group, mild nonserious AEs resulted in interruption of treatment in 3 patients (1 each of blepharospasm and visual acuity reduced, vascular anastomosis, and complications associated with device and viral infection), and 1 patient had severe endophthalmitis. Three patients died during the study (n = 2 in FYB201 group and n = 1 in the reference ranibizumab group), but none of the deaths were considered related to the study drug.

The efficacy of Eylea HD (aflibercept) for the treatment of nAMD was established in PULSAR, a randomized, double-masked, active-controlled study in 1,009 treatment-naïve patients with nAMD. Patients were randomly assigned to 1 of 3 treatment groups: (1) Eylea HD every 12 weeks following 3 initial monthly doses; (2) Eylea HD every 16 weeks following 3 initial monthly doses; or (3) Eylea 2 mg every 8 weeks following 3 initial monthly doses. The primary endpoint was the change from baseline in Best Corrected Visual Acuity (BCVA) at week 48 as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score. Both Eylea HD treatment arms were shown to be non-inferior and clinically equivalent to Eylea treatment with respect to the change in BCVA score at week 48 using the pre-specified non-inferiority margin of 4 letters.

Macular Edema Following Retinal Vein Occlusion (RVO)

Avastin (bevacizumab), Byooviz (ranibizumab-nuna), Cimerli (ranibizumab-eqrn), Eylea (aflibercept), Eylea HD (high-dose aflibercept), Lucentis (ranibizumab), Pavblu (aflibercept-ayyh), Vabysmo (faricimab-svoa) are indicated for the treatment of macular edema following retinal vein occlusion (RVO).

The efficacy and safety of intravitreal bevacizumab injections into eyes with macular edema secondary to central retinal vein occlusion (CRVO) was evaluated in a prospective clinical trial (n = 45 eyes) by Zhang et al. Study subjects were treated with 3 initial intravitreal bevacizumab injections of 1.25 mg at monthly intervals. Retreatment was based on central retinal thickness (CRT) measured by optical coherence tomography (OCT) performed monthly, while fluorescein angiography was performed every 3 months. Main outcome parameters were visual acuity (VA, using the Early Treatment of Diabetic Retinopathy Study protocol) and CRT in an 18-month follow-up period. Mean VA increased from 40.9 letters at baseline to 61.9 letters (+21 letters; $p < 0.001$) at month 18; CRT decreased from 572.3 µm at baseline to 273.2 µm at month 18 (-299.1 µm; $p < 0.001$). Neither age, duration of CRVO, baseline VA, nor baseline CRT was correlated with the change in VA. No drug-related systemic or ocular side effects were observed following intravitreal bevacizumab treatment.

The efficacy of intravitreal bevacizumab as the primary treatment of macular edema due to retinal vein occlusions was evaluated by Figueroa et al. in a study of patients diagnosed as having central retinal vein occlusion (CRVO) (n = 18 eyes) or branch retinal vein occlusion (BRVO) (n = 28 eyes) with visual acuity of less than 20/40 and macular edema (> 300 microm central retinal thickness). After an initial intravitreal injection of bevacizumab, re-treatment was performed if intraretinal or subretinal fluid with distortion of the foveal depression was found in optical coherence tomography. During a 6-month period, the mean number of injections per patient was 3.7 (BRVO group) and 4.6 (CRVO group). In the BRVO group, mean baseline logMAR visual acuity was 0.80 (SD 0.38) and macular thickness was 486.9 microm (SD 138.5 microm). After 6 months, mean logMAR visual acuity improved significantly to 0.44 (SD 0.34), $p < 0.001$. Mean macular thickness decreased significantly to 268.2 microm (SD 62.5 microm), $p < 0.001$. In the CRVO group, mean baseline logMAR visual acuity was 1.13 (SD 0.21) and macular thickness was 536.4 microm (SD 107.1 microm). Mean final

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logMAR visual acuity improved significantly to 0.83 (SD 0.45), p < 0.001. Mean macular thickness decreased significantly to 326.17 microm (SD 96.70 microm), p < 0.001. The investigators concluded that intravitreal bevacizumab is an effective primary treatment option for macular edema due to retinal occlusions. However, multiple injections are necessary to maintain visual and anatomic improvements.

The safety and efficacy of aflibercept were assessed in a 24-week, randomized, multi-center, double-masked, controlled study in patients with macular edema following BRVO. A total of 181 patients were treated and evaluable for efficacy (91 with aflibercept) in the VIBRANT study. In the study, patients were randomly assigned in a 1:1 ratio to either 2 mg aflibercept administered every 4 weeks (2Q4) or laser photocoagulation administered at baseline and subsequently as needed (control group). Protocol-specified visits occurred every 28 ±7 days. Patient ages ranged from 42 to 94 years with a mean of 65 years. In the VIBRANT study, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters in BCVA at week 24 compared to baseline. At week 24, the aflibercept 2 mg Q4 group was superior to the control group for the primary endpoint.

The safety and efficacy of ranibizumab were evaluated in a prospective, randomized, sham injection-controlled, double masked, multicenter trial in patients (n = 393) with macular edema after CRVO. Patients were randomized 1:1:1 to receive monthly intraocular injections of 0.3 or 0.5 mg of ranibizumab or sham injections. The primary efficacy outcome measure was mean change from baseline best-corrected visual acuity (BCVA) letter score at month 6. Secondary outcomes included other parameters of visual function and central foveal thickness (CFT). Mean [95% confidence interval (CI)] change from baseline BCVA letter score at month 6 was 12.7 (9.9-15.4) and 14.9 (12.6-17.2) in the 0.3 mg and 0.5 mg ranibizumab groups, respectively, and 0.8 (-2.0 to 3.6) in the sham group (p < 0.0001 for each ranibizumab group vs. sham). The percentage of patients who gained > or = 15 letters in BCVA at month 6 was 46.2% (0.3 mg) and 47.7% (0.5 mg) in the ranibizumab groups and 16.9% in the sham group (p < 0.0001 for each ranibizumab group vs. sham). At month 6, significantly more ranibizumab-treated patients (0.3 mg = 43.9%; 0.5 mg = 46.9%) had BCVA of > or = 20/40 compared with sham patients (20.8%; p < 0.0001 for each ranibizumab group vs. sham), and CFT had decreased by a mean of 434 microm (0.3 mg) and 452 microm (0.5 mg) in the ranibizumab groups and 168 microm in the sham group (p < 0.0001 for each ranibizumab group vs. sham). The median percent reduction in excess foveal thickness at month 6 was 94.0% and 97.3% in the 0.3 mg and 0.5 mg groups, respectively, and 23.9% in the sham group. The safety profile was consistent with previous phase III ranibizumab trials, and no new safety events were identified in patients with CRVO.

The safety and efficacy of faricimab-svoa were evaluated in two randomized, double-masked studies (BALATON – in patients with macular edema following branch retinal vein occlusion, and COMINO – in patients with macular edema following central retinal vein occlusion/hemiretinal vein occlusion). A total of 1,282 newly diagnosed, treatment-naive patients were enrolled in these studies. In both studies, patients were randomized to either faricimab-svoa 6 mg administered every 4 weeks or the control arm receiving aflibercept 2 mg administered every 4 weeks. The primary endpoint was the change from baseline in Best Corrected Visual Acuity (BCVA) at week 24, measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score. In both studies, Vabysmo demonstrated non-inferiority to Eylea for the primary endpoint. In BALATON, vision gains were +16.9 (CI 15.7, 18.1) eye chart letters in the faricimab-svoa arm and +17.5 letters (CI 16.3, 18.6) in the aflibercept arm at 24 weeks. In COMINO, vision gains were +16.9 letters (CI 15.4, 18.3) in the faricimab-svoa arm and +17.3 letters (CI 15.9, 18.8) in the aflibercept arm at 24 weeks.

The safety and efficacy of high-dose aflibercept was assessed in a randomized, multi-center, double-masked, active-controlled study (QUASAR) in patients with treatment naïve macular edema secondary to RVO. A total of 892 patients (425 with CRVO/HRVO and 467 with BRVO) were treated and analyzed for efficacy (591 with high-dose aflibercept). Patients were randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups: 1) High-dose aflibercept administered every 8 weeks, following 3 initial monthly doses (HDq8/3); 2) High-dose aflibercept administered every 8 weeks, following 5 initial Page 21 of 24 monthly doses (HDq8/5); 3) Aflibercept 2 mg administered every 4 weeks (2q4). Dosing intervals could be shortened or extended by 4-week increments based on protocol-defined visual and anatomic criteria. Intervals could be shortened beginning at week 16 for the HDq8/3 group, at week 24 for the HDq8/5 group and, if previously extended, at week 40 for the 2q4 group; intervals could be extended beginning at week 32 for the HDq8/3 and 2q4 groups and at week 40 for the HDq8/5 group. Patient ages ranged from 23 to 95 years with a mean of 65.9 years. At baseline, mean visual acuity was approximately 55 letters (range: 18 to 74 letters). The primary efficacy endpoint was the change from baseline in BCVA at week 36 as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score. Both high-dose aflibercept groups were shown to be non-inferior and clinically equivalent to aflibercept with respect to the change in BCVA score at week 36 using the pre-specified non-inferiority margin of 4 letters [LS mean change from baseline 17.0 vs. 17.1, -.1 (95% CI -2.0, 1.9) and 17.9 vs. 17.1, 0.8 (95% CI -1.1, 2.7)].

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Diabetic Macular Edema (DME)

Avastin (bevacizumab), Beovu (brolucizumab-dbll), Cimerli (ranibizumab-eqrn), Eylea (aflibercept), Eylea HD (high-dose aflibercept), Lucentis (ranibizumab), Pavblu (aflibercept-ayyh), and Vabysmo (faricimab-svoa) are indicated for the treatment of diabetic macular edema (DME).

Shoebi et al. reported the long-term results of intravitreal (IVT) bevacizumab injection alone or combined, at the time of first IVT bevacizumab injection, with IVT triamcinolone acetonide (IVT) for treatment of refractory DME. This randomized clinical trial enrolled 115 eyes of 101 patients with refractory DME and utilized three study arms: the IVB group (41 eyes) received three consecutive injections of 1.25 mg IVB at 6-week intervals; the IVB/IVT group (37 eyes) additionally received 2 mg of IVT at the time of first IVB injection; and the control (sham injection) group. Patients in the IVB and IVB/IVT groups were followed for a mean of 13.3 months and received retreatment with IVB alone whenever indicated. Main outcome measures were best corrected visual acuity (BCVA) and central macular thickness (CMT). The investigators found that at last follow up, CMT decreased significantly in the IVB group ($p = 0.013$), but it was not significant ($p = 0.13$) in the IVB/IVT group. Mean CMT improvement was 91 (95% CI, 20 to 161) microns and 57 (95% CI, -18 to 133) microns in the IVB and IVB/IVT groups, respectively. Mean BCVA improvement from baseline was 0.28 (95% CI, 0.18 to 0.38) logMAR ($p = 0.017$) in the IVB group and 0.19 (95% CI, 0.08 to 0.30) logMAR ($p = 0.001$) in the IVB/IVT group. There was no difference between the two groups in terms of visual improvement ($p = 0.42$). In generalized linear mixed model, only the time interval between the last injection and CMT measurement was statistically significant ($p = 0.04$). The same results were repeated for visual acuity ($p = 0.03$). Based upon these findings, the authors concluded that three loading doses of IVB (added doses if required) have long-term beneficial effects for treatment of refractory DME and that adding triamcinolone to this regimen provides no additional long-term benefit.

Nepomuceno et al compared visual acuity and spectral domain optical coherence tomography (SDOCT) outcomes associated with IV bevacizumab versus IVT ranibizumab for the management of DME in a prospective, randomized trial. Forty-eight patients (63 eyes) with center-involved DME were randomly assigned to receive 1.5 mg (0.06 cc) IV bevacizumab or 0.5 mg (0.05 cc) IV ranibizumab at baseline and monthly if central subfield thickness was greater than 275 µm. Forty-five patients (60 eyes) completed 48 weeks of follow-up. At baseline, mean ±standard error best-corrected visual acuity (BCVA) (logMAR) was 0.60 (20/80) ±0.05 in the IV bevacizumab group and 0.63 (20/85) ±0.05 in the IV ranibizumab group. A significant improvement in mean BCVA was observed in both groups at all study visits ($p < 0.05$); this improvement was significantly greater in the IV ranibizumab group compared with the IV bevacizumab group at weeks 8 ($p = 0.032$) and 32 ($p = 0.042$). A significant reduction in mean central subfield thickness was observed in both groups at all study visits compared with baseline ($p < 0.05$), with no significant difference in the magnitude of macular thickness reduction between groups. The mean number of injections was significantly higher ($p = 0.005$) in the IV bevacizumab group (9.84) than in the IV ranibizumab group (7.67). The investigators concluded that IV bevacizumab and IV ranibizumab are associated with similar effects on central subfield thickness in patients with DME through 1 year of follow-up. IV ranibizumab is associated with greater improvement in BCVA at some study visits, and the mean number of injections is higher in the IV bevacizumab group.

The safety and efficacy of ranibizumab were assessed in two phase III, randomized, multi-center, double-masked, controlled studies in patients with DME. Patients (n = 759) were randomized equally (1 eye per patient) to monthly 0.5 mg or 0.3 mg ranibizumab or sham injection. In the third year, sham patients, while still masked, were eligible to cross over to monthly 0.5 mg ranibizumab. Macular laser was available to all patients starting at month 3; panretinal laser was available as necessary. The main outcome measure was the proportion of patients gaining ≥ 15 Early Treatment Diabetic Retinopathy Study letters in BCVA from baseline at month 24. Visual acuity (VA) outcomes seen at month 24 in ranibizumab groups were consistent through month 36; the proportions of patients who gained ≥ 15 letters from baseline at month 36 in the sham/0.5 mg, 0.3 mg, and 0.5 mg ranibizumab groups were 19.2%, 36.8%, and 40.2%, respectively, in RIDE and 22.0%, 51.2%, and 41.6%, respectively, in RISE. In the ranibizumab arms, reductions in CFT seen at 24 months were, on average, sustained through month 36. After crossover to 1 year of treatment with ranibizumab, average VA gains in the sham/0.5 mg group were lower compared with gains seen in the ranibizumab patients after 1 year of treatment (2.8 vs. 10.6 and 11.1 letters). Per-injection rates of endophthalmitis remained low over time (~0.06% per injection). The incidence of serious adverse events potentially related to systemic vascular endothelial growth factor inhibition was 19.7% in patients who received 0.5 mg ranibizumab compared with 16.8% in the 0.3 mg group.

The safety and efficacy of aflibercept were assessed in two randomized, multi-center, double-masked, controlled studies in patients with DME. A total of 862 randomized and treated patients were evaluable for efficacy. Protocol-specified visits occurred every 28 ±7 days. Patient ages ranged from 23 to 87 years with a mean of 63 years. Of those, 576 were randomized to aflibercept groups in the two studies (VIVID and VISTA). In each study, patients were randomly assigned in a 1:1:1 ratio to 1 of 3 dosing regimens: (1) aflibercept administered 2 mg every 8 weeks following 5 initial monthly injections (aflibercept 2Q8); (2) aflibercept administered 2 mg every 4 weeks (aflibercept 2Q4); and 3) macular laser photocoagulation (at baseline and then as needed). Beginning at week 24, patients meeting a pre-specified threshold of

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vision loss were eligible to receive additional treatment: patients in the aflibercept groups could receive laser and patients in the laser group could receive aflibercept. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52 as measured by ETDRS letter score. Efficacy of both aflibercept 2Q8 and aflibercept 2Q4 groups was statistically superior to the control group. This statistically superior improvement in BCVA was maintained at week 100 in both studies.

The safety and efficacy of brolucizumab were assessed in two randomized, multi-center, double-masked, active controlled studies (KESTREL – NCT03481634 and KITE - NCT03481660) in patients with DME. A total of 926 patients were treated in these studies for 1 year (558 on brolucizumab and 368 on aflibercept 2 mg). Patient ages ranged from 23 to 87 years with a mean of 63 years. In KESTREL, patients were randomized in a 1:1:1 ratio to the following dosing regimens: (1) brolucizumab 6 mg administered once every 6 weeks for first 5 doses, followed by brolucizumab 6 mg every 8 or 12 weeks, (2) brolucizumab 3 mg administered once every 6 weeks for first 5 doses, followed by brolucizumab 3 mg every 8 or 12 weeks, and (3) aflibercept 2 mg administered once every 4 weeks for first 5 doses, followed by aflibercept 2 mg every 8 weeks. In KITE, patients were randomized in a 1:1 ratio to the following dosing regimens: (1) brolucizumab 6 mg administered once every 6 weeks for first 5 doses, followed by brolucizumab 6 mg every 8 or 12 weeks and (2) aflibercept 2 mg administered once every 4 weeks for first 5 doses, followed by aflibercept 2 mg every 8 weeks. In both studies, after the first five doses (Weeks 0, 6, 12, 18 and 24), brolucizumab patients were treated every 12 weeks, with the option of adjusting to an every 8-week dosing interval based on disease activity. Disease activity was assessed by changes in visual acuity and/or anatomical parameters, including CST and/or presence of IRF/SRF although the utility of the specific action parameters used has not been established. Disease activity was assessed by a physician during the first 12-week interval (at Weeks 32 and 36) and at each subsequent scheduled 12-week treatment visit. Patients who showed disease activity at any of these visits were adjusted to an every 8-week treatment interval. The comparator aflibercept was administered every 8 weeks after the first 5 monthly doses. The primary efficacy endpoint for both studies was the change from baseline to Week 52 in Best Corrected Visual Acuity (BCVA) as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score with the primary objective being to demonstrate non-inferiority of brolucizumab vs. aflibercept 2 mg. In both studies, brolucizumab was non-inferior to aflibercept 2 mg for the change in BCVA from baseline to Week 52 and the change from baseline over the period Week 40 through Week 52. After 5 initial q6w loading doses, the patients in the brolucizumab arm could have received between the minimum of 2 and maximum of 3 additional injections through Week 52. At Week 52, the median number of injections given over 12 months was 7 in patients treated with brolucizumab. Through Week 52, 55% (KESTREL) and 50% (KITE) of patients remained on brolucizumab every 12 weeks. The probability of remaining on every 12-week dosing from Week 36 to Week 52 was 88% and 95% in KESTREL and KITE, respectively. Treatment effects in evaluable subgroups (i.e., age, gender, baseline HbA1c, baseline visual acuity, baseline central subfield thickness, DME lesion type, duration of DME since diagnosis, retinal fluid status) in each study were generally consistent with the results in the overall population. In both studies, brolucizumab demonstrated a significant reduction from baseline in CST starting at Week 4 and continuing up to Week 52.

Two randomized, multi-center, double-masked, active comparator-controlled 2-year studies (YOSEMITE – NCT03622580 and RHINE – NCT03622593) assessed the safety and efficacy of faricimab in patients with DME. Patients (n = 1891) with diabetes were enrolled in the two studies with a total of 1262 patients treated with at least one dose of faricimab. Patient ages ranged from 24 to 91 years old (mean = 62.2 years). The overall population included both anti-VEGF naïve patients (78%) and patients who had been previously treated with a VEGF inhibitor prior to study participation (22%). The studies were identically designed, 2-year studies. Patients were randomized in a 1:1:1 ratio to one of three treatment regimens: (1) aflibercept Q8W, patients received fixed aflibercept 2 mg administered every 8 weeks (Q8W) after the first five monthly doses; (2) faricimab Q8W, patients received fixed faricimab 6 mg administered Q8W after the first six monthly doses; and (3) faricimab variable, patients received faricimab 6 mg administered every 4 weeks for at least four doses and until the central subfield thickness (CST) of the macula measured by optical coherence tomography was less than approximately 325 microns, then the interval of dosing was modified by up to 4 week interval extensions or reductions in up to 8 week interval increments based on CST and visual acuity disease activity criteria at study drug dosing visits. After 4 initial monthly doses, the patients in the faricimab variable arm could have received between the minimum of three and the maximum of eleven total injections through Week 56 inclusive. At Week 56, 32% of patients had completed at least one Q12W interval followed by one full Q16W interval. Seventeen percent (17%) of patients were treated on Q8W and/or Q4W dosing intervals through Week 56 (7% only on Q4W). These percentages are reflective of what happened within the conduct of these trials, but the percentages are not generalizable to a broader DME population due to the inclusion/exclusion criteria limited enrollment to a select subset of DME patients and that there is no empirical data that a similar magnitude would be observed if eligibility criteria allowed for broader enrollment. Both studies demonstrated non-inferiority to the comparator control (aflibercept) at the primary endpoint, defined as the mean change from baseline in BCVA at year 1 (average of the week 48, 52, and 56 visits), measured by the ETDRS Letter Score. The primary endpoint analysis was a non-inferiority comparison for the mean change in BCVA between the aflibercept and faricimab groups. In both studies, faricimab Q8W and faricimab variable treated patients had a mean change from baseline in BCVA that was non-inferior to the patients treated with aflibercept Q8W.

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The efficacy of high-dose aflibercept was established in PHOTON, a randomized, double-masked, active-controlled study in 658 patients with DME involving the center of the macula. Patients were randomly assigned to 1 of 3 treatment groups: (1) High-dose aflibercept every 12 weeks following 3 initial monthly doses; (2) High-dose aflibercept every 16 weeks following 3 initial monthly doses; or (3) Aflibercept 2 mg every 8 weeks following 5 initial monthly doses. The primary endpoint was the change from baseline in BCVA at week 48 as measured by the ETDRS letter score. Both high-dose aflibercept treatment arms were shown to be non-inferior and clinically equivalent to Eylea treatment with respect to the change in BCVA score at week 48 using the pre-specified non-inferiority margin of 4 letters.

Diabetic Retinopathy (DR)

Avastin (bevacizumab), Cimerli (ranibizumab-eqrn), Eylea (aflibercept), Eylea HD (high-dose aflibercept), Lucentis (ranibizumab), Pavblu (aflibercept-ayyh) are indicated for diabetic retinopathy (DR).

Ahmadieh et al. evaluated the effect of preoperative intravitreal bevacizumab (IVB) injections on the rate of early (≤ 4 weeks) post vitrectomy hemorrhage in patients (n = 68) with proliferative diabetic retinopathy. Subjects were randomly assigned to receive either 1.25 mg IVB (n = 35) one week prior to surgery or control (n = 33). The primary outcome measure was the incidence of early post vitrectomy hemorrhage. Secondary outcome measures included changes in best-corrected visual acuity (BCVA) and IVB-related adverse events. In the intention-to-treat analysis, the incidence of post vitrectomy hemorrhage 1 week and 1 month after surgery was significantly lower in the IVB group compared with the control group (p = 0.023 and p = 0.001, respectively). Mean BCVA improved from 1.88 logarithm of minimum angle of resolution (logMAR) units in both study groups before surgery to 0.91 logMAR units and 1.46 logMAR units 1 month after vitrectomy in the IVB and control groups, respectively (p = 0.001). Resolution of vitreous hemorrhage was observed in 9 eyes (25.7%) after IVB injection, obviating the need for vitrectomy; the corresponding figure was 2 eyes (6.1%) in the control group (p = 0.028). The per-protocol analysis included 16 eyes in the IVB group and 18 eyes in the control group; post vitrectomy hemorrhage occurred less frequently 1 week and 1 month after surgery in the IVB group compared with the control group (p = 0.033 and p = 0.003, respectively). Mean improvement in BCVA 1 month after vitrectomy was -1.05 logMAR units in the IVB group and -0.42 logMAR units in the control group (p = 0.004). No IVB-related complication was observed in the treatment group. The investigators concluded that IVB one week before vitrectomy appears to reduce the incidence of early post vitrectomy hemorrhage in diabetic patients. The need for vitrectomy may be decreased significantly in these cases as well.

In order to evaluate the safety and effectiveness of intravitreal bevacizumab (IVB) as an adjunct to vitrectomy, di Lauro et al. performed a randomized controlled trial on 72 eyes of 68 patients affected by vitreous hemorrhage (VH) and tractional retinal detachment (TRD) which occurred as a consequence of active proliferative diabetic retinopathy (PDR). Participants were assigned in a 1:1:1 ratio to receive a placebo injection or an intravitreal injection of 1.25 mg of bevacizumab, either 7 or 20 days before the vitrectomy. Complete ophthalmic examinations and color fundus photography were performed at baseline and 1, 6, 12, and 24 weeks after the surgery. In the placebo group, intraoperative bleeding occurred in 19 cases (79.1%), the use of endodiathermy was necessary in 13 patients (54.1%), relaxing retinotomy was performed on one patient (4.1%), and in four cases (16.6%) iatrogenic retinal breaks occurred. The surgical mean time was 84 minutes (SD 12 minutes). In subjects receiving IVB seven days prior to vitrectomy, intraoperative bleeding occurred in two cases (8.3%) and the use of endodiathermy was necessary in two patients (8.3%). No iatrogenic breaks occurred during the surgery. The surgical mean time was 65 minutes (SD 18 minutes). For those subjects receiving IVB twenty days before vitrectomy, intraoperative bleeding occurred in three cases (12.5%), the use of endodiathermy was necessary in three patients (1.5%), and an iatrogenic break occurred in one patient (4.1%) while the delamination of fibrovascular tissue was being performed. The surgical mean time was 69 minutes (SD 21 minutes). The average difference in the surgical time was statistically significant between the placebo group and the 7-day IVB group (p = 0.025), and between the placebo group and the 20-day IVB group (p = 0.031). At completion of surgery, the retina was completely attached in all eyes. The researchers concluded that best surgical results are achieved performing the IVB 7 days preoperatively.

The efficacy and safety of ranibizumab were derived from two phase III, randomized, multi-center, double-masked, controlled studies in patients with both DR and DME at baseline. Patients (n = 759) were randomized equally (1 eye per patient) to monthly 0.5 mg or 0.3 mg ranibizumab or sham injection. In the third year, sham patients, while still masked, were eligible to cross over to monthly 0.5 mg ranibizumab. Macular laser was available to all patients starting at month 3; panretinal laser was available as necessary. The main outcome measure was the proportion of patients gaining ≥ 15 Early Treatment Diabetic Retinopathy Study letters in BCVA from baseline at month 24. Visual acuity (VA) outcomes seen at month 24 in ranibizumab groups were consistent through month 36; the proportions of patients who gained ≥ 15 letters from baseline at month 36 in the sham/0.5 mg, 0.3 mg, and 0.5 mg ranibizumab groups were 19.2%, 36.8%, and 40.2%, respectively, in RIDE and 22.0%, 51.2%, and 41.6%, respectively, in RISE. In the ranibizumab arms, reductions in CFT seen at 24 months were, on average, sustained through month 36. After crossover to 1 year of treatment with ranibizumab, average VA gains in the sham/0.5 mg group were lower compared with gains seen in the ranibizumab patients after 1 year of treatment (2.8 vs. 10.6 and 11.1 letters). Per-injection rates of endophthalmitis remained low over

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time (~0.06% per injection). The incidence of serious adverse events potentially related to systemic vascular endothelial growth factor inhibition was 19.7% in patients who received 0.5 mg ranibizumab compared with 16.8% in the 0.3 mg group.

Efficacy and safety data of aflibercept in DR are derived from the VIVID, VISTA, and PANORAMA studies. In the VIVID and VISTA studies, an efficacy outcome was the change in the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (ETDRS-DRSS). The ETDRS-DRSS score was assessed at baseline and approximately every 6 months thereafter for the duration of the studies [see Clinical Studies (14.4)]. All enrolled patients had DR and DME at baseline. The majority of patients enrolled in these studies (77%) had moderate-to-severe nonproliferative diabetic retinopathy (NPDR) based on the ETDRS-DRSS. At week 100, the proportion of patients improving by at least 2 steps on the 25 of 28 ETDRS-DRSS was significantly greater in both aflibercept treatment groups (2Q4 and 2Q8) when compared to the control group.

Efficacy and safety data of Eylea HD in DR are derived from the PHOTON study. In the PHOTON study, a key efficacy outcome was the change in the ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS). The proportion of patients achieving ≥ 2-step improvement on ETDRS-DRSS was similar between the Eylea HD every 12 weeks and Eylea every 8 weeks. The Eylea HD every 16-week treatment arm did not meet the non-inferiority criteria for the proportion of patients with a ≥ 2-step improvement on ETDRS-DRSS and is not considered clinically equivalent to Eylea administered every 8 weeks.

Neovascular Glaucoma (NVG)

Ghosh et al. present the outcome of concomitant treatment with diode laser cyclophotocoagulation (CPC) and intravitreal bevacizumab (IVB) in painful eyes with poor visual potential in a case series of consecutively diagnosed neovascular glaucoma (NVG). Twelve patients (14 eyes) were treated with CPC and concurrent IVB 0.05 mL (1.25 mg). Study end-points were lowering of intraocular pressure (IOP), regression of anterior segment neovascularization, and resolution of pain. The mean preoperative IOP was 42.1 ±11.4 and was lowered to 16.6 ±7.1 mmHg at 1-month post-CPC. Anterior segment neovascularization regressed dramatically within 1 week of IVB in 12 eyes. Thirteen eyes reported persistent relief of ocular pain at 6 months following treatment. The authors concluded that combined IVB and CPC treatment for NVG provides rapid control of anterior segment neovascularization and may lead to improved symptomatic relief and IOP control.

To evaluate the effect of intravitreal bevacizumab injection in cases of neovascular glaucoma, Ghanem et al. studied 16 eyes of 16 patients with rubeosis iridis and secondary glaucoma. Patients were administered an intravitreal injection of bevacizumab (2.5 mg) and were followed for 2 months. Partial or complete regression of iris neovascularization was noted 1 week after injection of bevacizumab. Reproliferation of new vessels was detected in 25% of the cases after 2 months. The mean intraocular pressure (IOP) before injection was 28 ±9.3 mm Hg under topical β-blocker and systemic acetazolamide. One week after injection, the IOP decreased to 21.7 ±11.5 mm Hg (5 cases without anti-glaucoma drugs, 6 cases with topical β-blocker and 5 cases with both topical β-blocker and systemic acetazolamide). The authors concluded that intravitreal bevacizumab injection leads to regression of iris neovascularization with subsequent drop of IOP in eyes with neovascular glaucoma.

Moraczewski et al. report a retrospective, non-comparative, consecutive, interventional case series of the treatment of neovascular glaucoma with intravitreal bevacizumab in 56 eyes at the University of Miami, Florida, Bascom Palmer Eye Institute. The authors' impression both clinically and from a review of available literature is that early diagnosis and treatment of NVG with intravitreal bevacizumab may lead to improved outcomes. If bevacizumab is administered when the anterior chamber angle is open at the time of NVG diagnosis, it is postulated that IOP may be controlled without the need for surgical procedures. This study underscores the concept that, if followed long enough, the majority of patients regardless of initial angle status and initial IOP lowering, will require surgical intervention for the control of IOP. The cumulative proportion of eyes requiring a second injection of bevacizumab increases linearly with time and is related to recurrent or persistent iris neovascularization or angle neovascularization. Bevacizumab induced regression of neovascularization is often temporary and recurrence is possible, while panretinal photocoagulation provides a more permanent reduction of the ischemic angiogenic stimulus. At this institution, treatment of NVG with intravitreal bevacizumab is the standard of care, including: (1) Administering intravitreal bevacizumab at the time of diagnosis of NVG; (2) Administering panretinal photocoagulation shortly thereafter, and; (3) lowering IOP medically and via placement of a drainage device if necessary.

Myopic Choroidal Neovascularization (mCNV)

Avastin (bevacizumab), Byooviz (ranibizumab-nuna), Cimerli (ranibizumab-eqrn), and Lucentis (ranibizumab) are indicated for the treatment of choroidal neovascularization secondary to pathologic myopia.

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Cha DM et al compared the long-term efficacy of ranibizumab versus bevacizumab for myopic choroidal neovascularization (CNV) in retrospective, multicenter, comparative, non-randomized study in 64 consecutive patients [ranibizumab (n = 22) or bevacizumab (n = 42 patients)]. Best-corrected visual acuity (BCVA) and central foveal thickness (CFT) on optical coherence tomography were evaluated before and after treatment. All the patients were followed for at least 12 months. BCVA (logarithm of the minimal angle of resolution) improved from 0.63 ±0.30 to 0.43 ±0.27, 0.41 ±0.37, 0.40 ±0.39, 0.39 ±0.43, and 0.39 ±0.42 at 1, 2, 3, 6, and 12 months after treatment in the ranibizumab group, and from 0.67 ±0.28 to 0.52 ±0.31, 0.49 ±0.31, 0.4 7 ±0.31, 0.42 ±0.32, and 0.46 ±0.43 in the bevacizumab group (all $p < 0.05$ compared with baseline BCVA in each group). CFT decreased by 20.21%, 19.58%, and 22.43% from the baseline 304 ±76 μm at 3, 6, and 12 months after treatment in the former group, and by 15.20%, 15.67%, and 15.56% from the baseline 297 ±62 μm in the latter group (all $p < 0.05$ compared with baseline CFT in each group). BCVA improvement and CFT reduction did not statistically differ when compared at the same periods from treatment between 2 groups. Neither ocular nor systemic safety problems appeared during follow up. Researchers concluded that the outcomes of the study showed a similar functional and anatomical improvement after treatment for ranibizumab and bevacizumab in patients with myopic CNV over a 12-month follow-up period.

In a phase III, 12-month, randomized, double-masked, multicenter, active-controlled study, researchers evaluated the efficacy and safety of ranibizumab 0.5 mg, guided by visual acuity (VA) stabilization or disease activity criteria, versus verteporfin photodynamic therapy (vPDT) in patients (n = 277) with visual impairment due to myopic choroidal neovascularization (CNV). Patients were randomized to receive ranibizumab on day 1, month 1, and thereafter as needed guided by VA stabilization criteria (group I, n = 106); ranibizumab on day 1 and thereafter as needed guided by disease activity criteria (group II, n = 116); or vPDT on day 1 and disease activity treated with ranibizumab or vPDT at investigators' discretion from month 3 (group III, n = 55). Primary outcomes measured included average best-corrected visual acuity (BCVA) change from baseline to month 1 through months 3 (primary) and 6, mean BCVA change and safety over 12 months. Ranibizumab treatment in groups I and II was superior to vPDT based on mean average BCVA change from baseline to month 1 through month 3 [group I: + 10.5, group II: + 10.6 vs. group III: + 2.2 Early Treatment Diabetic Retinopathy Study (ETDRS) letters; both $p < 0.0001$]. Ranibizumab treatment guided by disease activity was noninferior to VA stabilization-guided retreatment based on mean average BCVA change from baseline to month 1 through month 6 (group II: + 11.7 vs. group I: + 11.9 ETDRS letters; $p < 0.00001$). Mean BCVA change from baseline to month 12 was + 13.8 (group I), + 14.4 (group II), and + 9.3 ETDRS letters (group III). At month 12, 63.8% to 65.7% of patients showed resolution of myopic CNV leakage. Patients received a median of 4.0 (group I) and 2.0 (groups II and III) ranibizumab injections over 12 months. No deaths or cases of endophthalmitis and myocardial infarction occurred. CONCLUSIONS: Ranibizumab treatment, irrespective of retreatment criteria, provided superior BCVA gains versus vPDT up to month 3. Ranibizumab treatment guided by disease activity criteria was noninferior to VA stabilization criteria up to month 6. Over 12 months, individualized ranibizumab treatment was effective in improving and sustaining BCVA and was generally well tolerated in patients with myopic CNV.

Yoon et al. compared visual outcomes after treatment with intravitreal antivascular endothelial growth factor (anti-VEGF) injection or photodynamic therapy (PDT) in patients with myopic choroidal (CNV). One hundred and forty-two eyes of 128 consecutive patients treated with anti-VEGF (ranibizumab or bevacizumab) and/or PDT for myopic choroidal neovascularization were retrospectively reviewed. Patients were categorized into 3 groups: PDT (51 eyes), anti-VEGF (63 eyes), and a combination group (PDT with anti-VEGF) (28 eyes). Corrected visual acuity values at baseline and 3, 6, 9, and 12 months after treatment were compared. The anti-VEGF group showed significant postoperative improvement in visual acuity compared with the PDT and combination groups ($p = 0.01$ and 0.04, respectively). The anti-VEGF group demonstrated visual improvement from baseline at every follow-up visit after treatment ($p = 0.04$, 0.02, 0.01, and 0.002, respectively). The anti-VEGF group showed visual improvement (Snellen equivalent) from 0.57 logarithm of the minimum angle of resolution (0.27) to 0.33 logarithm of the minimum angle of resolution (0.47) ($p = 0.01$). Furthermore, 98.4% of patients in the anti-VEGF group and 92.8% of those in the combination group lost < 15 letters from baseline visual acuity compared with 72.6% in the PDT group ($p = 0.001$ and 0.02, respectively). In the anti-VEGF group, 39.7% of patients improved from baseline by 15 or more letters compared with 17.7% in the PDT group ($p = 0.02$) and 21.4% in the combination group ($p = 0.07$). Based on these findings, the investigators concluded that intravitreal anti-VEGF injection is superior to PDT alone or a combination of PDT with anti-VEGF for treating myopic choroidal neovascularization.

Vadalà et al. assessed the efficacy and safety of ranibizumab in the treatment of choroidal neovascularisation (CNV) caused by pathologic myopia (PM) in a prospective, multicentre, interventional case series. Forty eyes of 39 consecutive patients with PM and CNV were treated with 'on demand' intravitreal injection of ranibizumab 0.5 mg. Final best corrected visual acuity (BCVA) and its change from baseline were the main outcome measures. Median follow-up was 13.3 ±2 (range 12-18) months. Fifteen eyes (37.5%) had previously been treated with photodynamic therapy (PDT). The mean baseline logarithm of the minimum angle of resolution (logMAR) BCVA was 0.68 ±0.34 (Snellen equivalent 20/131) and 21 ±16 letters. The final mean logMAR BCVA was 0.27 ±0.2 ($p = 0.008$) (20/42) and 40.5 ±14 letters ($p = 0.01$). Mean final VA improved in 82.5% of patients, in 60% by 3 or more lines (median number of lines gained 2.9). Age and previous

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PDT did not influence the results (p > 0.05). The mean number of injections was 2.8 ±1.2 (range 1-6). No ocular or systemic side effects were observed. Ranibizumab was an effective treatment for stabilizing and improving vision with a low number of injections in 92.5% of patients with myopic CNV in a long-term follow-up.

Retinopathy of Prematurity

In a prospective, controlled, randomized, stratified, multicenter trial, Mintz-Hittner et al. studied the efficacy of intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3 + retinopathy of prematurity (ROP). One hundred fifty infants were randomized to receive intravitreal bevacizumab (0.625 mg/0.025 ml) or conventional laser therapy, bilaterally. The primary ocular outcome was recurrence of ROP in one or both eyes requiring retreatment before 54 weeks' postmenstrual age. Of the 150 infants, 143 survived to 54 weeks. The 7 infants who died were not included in the primary outcome analysis. ROP recurred in 4 infants in the bevacizumab group [6 of 140 eyes (4%)] and 19 infants in the laser-therapy group [32 of 146 eyes (22%), p = 0.002]. A significant treatment effect was found for zone I ROP (p = 0.003) but not for zone II disease (p = 0.27). The authors concluded that intravitreal bevacizumab monotherapy, as compared with conventional laser therapy, in infants with stage 3 + retinopathy of prematurity showed a significant benefit for zone I but not zone II disease. Development of peripheral retinal vessels continued after treatment with intravitreal bevacizumab, but conventional laser therapy led to permanent destruction of the peripheral retina.

Geloneck et al. conducted a prospective, stratified, randomized, controlled, masked, multicenter clinical trial examining the efficacy of bevacizumab versus laser therapy for the treatment of zone I or zone II posterior stage 3 + retinopathy of prematurity (ROP) or aggressive posterior ROP (APROP) in preterm infants. Infants either received intravitreal bevacizumab or laser therapy, randomized by infant, also underwent cycloplegic retinoscopic refraction at an average age of 2.5 years. Pediatric and vitreoretinal ophthalmologists in 15 level 3 neonatal intensive care units in academic centers participated. Of the originally enrolled 150 infants (300 eyes) in the clinical trial, 13 infants (26 eyes) died (6 received intravitreal bevacizumab; 7 received laser) and 19 eyes had intraocular surgery (6 infants bilaterally). Thus, 45 eyes (19 infants bilaterally) were excluded, leaving 131 infants (255 eyes, including 21 eyes that received a successful second treatment for recurrence). The primary outcomes were spherical equivalent refractive outcomes and their distribution by ROP zone and treatment. Of the 131 eligible infants, refractions were available for only 109 (83.2%) and 211 of 255 eyes (82.7%). Mean (SD) spherical equivalent refractions were as follows: zone I, −1.51 (3.42) diopters (D) in 52 eyes that received intravitreal bevacizumab and −8.44 (7.57) D in 35 eyes that received laser treatment (p < .001); and zone II posterior, −0.58 (2.53) D in 58 eyes that received intravitreal bevacizumab and −5.83 (5.87) D in 66 eyes that received laser treatment (p < .001). Very high myopia (−8.00 D) occurred in zone I in 2 of 52 (3.8%) eyes that received intravitreal bevacizumab and in 18 of 35 (51.4%) eyes that received laser treatment (p < .001). Very high myopia occurred in zone II posterior in 1 of 58 (1.7%) eyes that received intravitreal bevacizumab and in 24 of 66 (36.4%) eyes that received laser treatment (p < .001). The authors concluded that more very high myopia was found in eyes that received laser treatment than in eyes that received intravitreal bevacizumab. This difference is possibly related to anterior segment development that is present with intravitreal bevacizumab but minimal or absent following laser treatment.

The efficacy and safety of aflibercept for the treatment of retinopathy of prematurity (ROP) was assessed in two randomized, 2-arm, open-label, parallel-group studies (BUTTERFLEYE and FIREFLEYE/FIREFLEYE NEXT). FIREFLEYE included 24 weeks of treatment and follow-up. FIREFLEYE NEXT was an observational follow-up of FIREFLEYE through week 52. The studies were conducted in 233 pre-term infants with ROP and compared Eylea treatment and laser photocoagulation therapy (laser). Eligible patients had a maximum gestational age at birth of 32 weeks or a maximum birth weight of 1500 g, had to weigh > 800 g on the day of treatment and had treatment-naïve ROP classified according to the International Classification for Retinopathy of Prematurity (IC-ROP 2005) in at least one eye with one of the following retinal findings: ROP Zone 1 Stage 1+, 2+, 3 or 3+, ROP Zone II Stage 2+ or 3+, or AP-ROP (aggressive posterior ROP). The primary efficacy endpoint of each study was the proportion of patients with absence of active ROP and unfavorable structural outcomes (retinal detachment, macular dragging, macular fold, retrolental opacity) at week 52 of chronological age. The proportion of patients without clinically significant reactivations of ROP who also did not develop unfavorable structural outcomes (78.7% to 79.6% with Eylea and 77.8% to 81.6% with laser) was higher in each arm of each study than would have been expected in infants who had not received treatment. Neither trial demonstrated superiority of one arm compared to the other arm. Neither trial demonstrated inferiority of one arm compared to the other arm.

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.

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Avastin (bevacizumab)

The statements below are for information only. Oncology indications for bevacizumab are listed in the NCCN Drugs & Biologics Compendium.

- Bevacizumab, in combination with intravenous 5-fluorouracil–based chemotherapy, is indicated for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum.
- Bevacizumab, in combination with fluoropyrimidine- irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients with metastatic colorectal cancer who have progressed on a first-line bevacizumab-containing regimen.
- Bevacizumab, in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer.
- Bevacizumab for treatment of glioblastoma, is indicated for the treatment of recurrent glioblastoma.
- Bevacizumab, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic cervical cancer.
- Bevacizumab, in combination with interferon alfa, is indicated for the treatment of metastatic renal cell carcinoma.
- Bevacizumab, in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by bevacizumab as a single agent, is indicated for the treatment of platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.
- Bevacizumab, in combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent, for stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection.
- Bevacizumab, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than 2 prior chemotherapy regimens.

Beovu (brolucizumab)

Beovu (brolucizumab) is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD) and diabetic macular edema (DME).

Byooviz (ranibizumab-nuna)

Byooviz (ranibizumab-nuna) is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD), macular edema following vein occlusion (RVO, and myoptic choroidal neovascularization (mCNV).

Cimerli (ranibizumab-eqrn)

Cimerli (ranibizumab-eqrn) 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), and myopic choroidal neovascularization (mCNV).

Eylea (aflibercept)

Eylea (aflibercept) 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), and retinopathy of prematurity (ROP).

Eylea HD (aflibercept)

Eylea HD (aflibercept) is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD), diabetic macular edema (DME), diabetic retinopathy (DR), and macular edema following retinal vein occlusion (RVO).

Lucentis (ranibizumab)

Lucentis (ranibizumab) 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, and myopic choroidal neovascularization (mCNV).

Pavblu (aflibercept-ayyh)

Pavblu (aflibercept-ayyh) 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), and diabetic retinopathy (DR).

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Vabysmo (faricimab)

Vabysmo (faricimab) is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD), diabetic macular edema (DME), and macular edema following retinal vein occlusion (RVO).

Centers for Medicare and Medicaid Services (CMS)

Medicare does not have a National Coverage Determination (NCD) for vascular endothelial growth factor (VEGF) inhibitors and dual VEGF/angiopoietin-2 (Ang-2) inhibitors: Cimerli® (ranibizumab-eqrn), Compounded Avastin® (bevacizumab), Lucentis® (ranibizumab), Eylea® (aflibercept), Eylea® HD (aflibercept), Beovu® (brolucizumab-dbll), Byooviz® (ranibizumab-nuna), Pavblu™ (aflibercept-ayyh), Vabysmo® (faricimab-svoa). Local Coverage Determinations (LCDs)/LCAs exist, refer to the LCDs/LCAs for Drugs and Biologicals, Coverage of, for Label and Off-Label Uses, Billing and Coding: Aflibercept (EYLEA®), and Billing and Coding: Intraocular Bevacizumab.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals.
(Accessed January 20, 2026)

**Preferred therapy criteria for Medicare Advantage members, refer to the Medicare Part B Step Therapy Programs.

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Policy History/Revision Information

Date	Summary of Changes
07/01/2026	**Applicable Codes** • Updated list of applicable HCPCS codes to reflect quarterly edits; added Q5149, Q5150, Q5153, Q5155, Q5168, and Q5170 **Supporting Information** • Archived previous policy version 2026D0042AP

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare 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, check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare 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.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare 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.

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