Subject: Beovu (brolucizumab)	**Original Effective Date:** Q1 2020
Policy Number: MCP-354	**Revision Date(s):**
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Disclaimer

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

Summary of Evidence/Position

This policy addresses Beovu (brolucizumab) for the treatment of neovascular (wet) age-related macular degeneration (nAMD) when appropriate criteria are met when appropriate criteria are met.

The intent of this policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical studies, nationally recognized authoritative references and current peer-reviewed scientific literature. The information outlined in the Molina Clinical Policy includes but is not limited to a review of evidence based information obtained from the following sources Evaluation of New and Existing Technologies (UM 10). This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

Beovu (brolucizumab-dbll)

Human vascular endothelial growth factor (VEGF) inhibitor

Humanized monoclonal single-chain antibody fragment which binds to vascular endothelial growth factor A (VEGF-A); prevents the factor from stimulating the growth of fragile and permeable new blood vessels associated with wet AMD.

A humanized single-chain antibody fragment differs from currently available full length monoclonal antibodies VEGF inhibitors due to its small size, single-chain antibody fragments which can provide enhanced tissue penetration and rapid clearance from systemic circulation.

The Beovu molecule is engineered to deliver the highest concentration of drug, providing more active binding agents than other anti-VEGFs. By inhibiting VEGF, Beovu suppresses the growth of abnormal blood vessels and the potential for fluid leakage into the retina (Dugel P, et al.).

Indicated for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD)

Wet age-related macular degeneration (wet AMD) includes activating the vascular endothelial growth factor A (VEGF-A) pathway which signals blood vessels to grow abnormally in the eye's retina, which may cause fluid leakage and vision loss.

Wet AMD is a chronic, degenerative eye disease caused by an excess of VEGF, a protein that promotes the growth of abnormal blood vessels underneath the macula, the area of the retina responsible for sharp, central vision (National Eye Institute). Fluid that leaks out of these abnormal blood vessels disrupts the normal retinal structure and ultimately damages the macula (National Eye Institute; WHO; NHS Choices).

The FDA approval of Beovu was based on the phase 3 HAWK and HARRIER trials
The approval was based on data from two phase III, prospective, double-masked, multicenter studies (HAWK and HARRIER) that compared the efficacy and safety of Beovu to aflibercept (Eylea) in 1817 patients with neovascular AMD for 96-weeks. Patients were 50 years or older with untreated, active choroidal neovascularization lesions secondary to age-related macular degeneration.

HAWK (NCT02307682) and HARRIER (NCT02434328) are the first and only global head-to-head trials in patients with wet AMD that prospectively demonstrated efficacy at week 48 using an innovative q12w/q8w regimen, with a majority of patients on q12w immediately following the loading phase2. Both studies are 96-week prospective, randomized, double-masked multi-center studies and part of the Phase III clinical development of Beovu2. The studies were designed to compare the efficacy and safety of intravitreal injections of brolucizumab 6 mg (HAWK and HARRIER) and 3 mg (HAWK only) versus aflibercept 2 mg in patients with wet AMD2.

HAWK (NCT02307682) and HARRIER (NCT02434328) trials (published in a single report; Dugel et al., 2019)

Both studies were designed to provide a head-to-head comparison of brolucizumab to aflibercept (Eylea) in the treatment of nAMD.

In the HAWK study, patients were randomized 1:1:1 to receive brolucizumab 3mg or 6mg every 8 or 12 weeks, or aflibercept 2mg every 8 weeks after the first 3 monthly doses.

In the HARRIER study, patients were randomized 1:1 ratio to receive brolucizumab 6mg every 8 or 12 weeks, or aflibercept 2mg every 8 weeks after the first 3 monthly doses.

The primary endpoint of both studies was non-inferiority of Beovu to Eylea in least squares (LS) mean best corrected visual acuity (BCVA) change from baseline to week 48.

Visual acuity outcomes were comparable across treatment arms, with BCVA changes (least-squares mean) ranging from 6 to 8 ETDRS letters at week 48, demonstrating the non-inferiority of brolucizumab.

Mean central subfield thickness (secondary end point) was significantly lower at 16 and 48 weeks in the brolucizumab 6-mg treatment arm than in the aflibercept arm in both studies ($P = .0016$ and $P < .0001$ at week 16 and $P = .0023$ and $P < .0001$ at week 48 in HAWK and HARRIER, respectively). These results were maintained in year 2 of the study.

Both studies also showed approximately 30% of Beovu-treated patients gained at least 15 letters at Week 48.

Fewer patients experienced intra-retinal (IRF) and/or sub-retinal fluid (SRF) with Beovu as well. Through Week 48, 56% and 51% of patients were maintained on the 12-week dosing regimen in the HAWK and HARRIER studies, respectively.

Patients in the brolucizumab arms could be switched to every-8-week dosing if disease activity was observed according to protocol- defined changes in VA or intraretinal fluid.

The overall safety profile of brolucizumab was similar to that of aflibercept. Brolucizumab is contraindicated in those who have ocular or periocular infections, active intraocular inflammation or known hypersensitivity to brolucizumab or any of the product's excipients. Signs and symptoms of hypersensitivity reactions include rash, itching, urticaria, erythema, or severe intraocular inflammation. The most frequent adverse events that occurred in at least 5% of patients were reduced VA, conjunctival or retinal hemorrhage, vitreous floaters, pain, dry eye, cataract, and vitreous detachment.

Brolucizumab provides an additional VEGF inhibitor treatment option for wet AMD. Other VEGF inhibitors indicated for wet AMD include Eylea and Lucentis. While brolucizumab did not demonstrate superiority for the primary endpoint, key secondary outcomes did favor brolucizumab over aflibercept (Eylea).

Brolucizumab is administered every 12 weeks whereas the recommended dosing frequency for Eylea is every 8 weeks. However, in the clinical trials about 50% of brolucizumab-treated patients required dosing every 8 weeks. While the dosing frequency for Eylea can be extended to every 12 weeks after one year of effective therapy, it may not be as effective as the recommended every 8-week dosing regimen for some patients. The recommended dosing frequency for Lucentis is once every month.

PREFERRED AGENT: Avastin (bevacizumab)

Avastin (bevacizumab) is the preferred agent for the treatment of AMD and documentation of the failure of Avastin is required prior to authorization of Beovu (brolucizumab).

There is no evidence to support the use of one VEGF-Inhibitor over another as the clinical trials provided data that showed comparability, none showed superiority. Results from the CATT research group indicate that bevacizumab and ranibizumab have equivalent effects on visual acuity for the treatment of ARMD when administered according to the same schedule.

Bevacizumab is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF). VEGF is the major angiogenic stimulus responsible for the formation of choroidal neovascularization and so represents a new paradigm in the treatment of retinovascular disease. Bevacizumab is FDA-approved for intravenous use in the treatment of metastatic colorectal, metastatic breast, and non-small cell lung cancer.

Bevacizumab was investigated first as a systemic intravenous treatment for AMD and then as an intravitreal injection (1.25 mg) before the FDA approved ranibizumab. [Michels S, et al. 2005; Avery RL, et al. 2006; AAO Retina/Vitreous Panel. Preferred Practice Pattern Guidelines. Age-Related Macular Degeneration.]

Based on published reports and compelling evidence of bevacizumab's safety and efficacy for use in a number of ophthalmic conditions, intravitreal bevacizumab is increasingly being administered as an off-label treatment in the United States and has been used in the treatment of the following off-label conditions that have not responded to other accepted therapies, including:

- *Neovascular (wet) age-related macular degeneration*
- *Diabetic macular edema*
- *Central retinal vein occlusion*
- *Venous tributary (branch) occlusion*
- *Proliferative diabetic retinopathy*
- *Neovascular glaucoma; Adjunct*

Comparative trials and uncontrolled case series reported improvements in visual acuity and decreased retinal thickness by OCT (Optical Coherence Tomography) following intravitreal bevacizumab treatment.

Intravitreal injection of bevacizumab has been used for the treatment of neovascular age-related macular degeneration (AHFS 2019). Results of several randomized controlled studies suggest that intravitreal bevacizumab has similar efficacy as ranibizumab in improving visual acuity. In one study, the incidence of serious systemic adverse effects (primarily hospitalizations) appeared to be higher with bevacizumab compared with ranibizumab; however, other studies, including a systematic review of 9 randomized controlled studies, directly comparing intravitreal injections of bevacizumab and ranibizumab in patients with neovascular age-related macular degeneration have found no such difference.

The Comparison of AMD Treatment Trials (CATT) was a multicenter clinical trial that compared the safety and effectiveness of bevacizumab to ranibizumab and an individualized dosing regimen (as-needed, or PRN) to monthly injections.

The primary outcome was the mean change in visual acuity at 1 year, with a non-inferiority limit of 5 letters on the eye chart. Bevacizumab administered monthly was equivalent to ranibizumab administered monthly. Bevacizumab administered as needed was equivalent to ranibizumab as needed. Ranibizumab PRN was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive.

Further follow-up at two years showed that the two drugs remained comparable in both efficacy and safety but the PRN arms together did not perform as well in terms of maintaining the visual gains at the end of year one compared with the two monthly injection arms, especially in the bevacizumab PRN group. (Martin DF, et al. 2012)

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.

Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN) [IVAN Study Investigators 2012, 2013]
The IVAN, enrolled 610 patients and found that for the primary outcome of best visual acuity at two years, bevacizumab was neither non-inferior nor inferior to ranibizumab. There was no difference in mortality, atherothrombotic events, or hospital admission between the two drugs. A meta-analysis combining results from one-year data of the CATT trial and two-year data from the IVAN trial found that bevacizumab was non-inferior to ranibizumab for visual acuity; additional randomized trials comparing the two drugs at two years also demonstrated non-inferiority for bevacizumab (Kodjikian L, et al. 2013) or equivalent efficacy (Berg K, et al. 2016)

The American Academy of Ophthalmology (AAO) supports the use of intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab and ranibizumab) is the most effective way to manage neovascular AMD and represents the first-line of treatment. AAO supports the use of bevacizumab for treatment of age-related macular degeneration as a recommendation with high importance to clinical care.

In a letter to the Centers for Medicare and Medicaid Services (CMS) in April 2006, the AAO stated that "*It supports reimbursement for treating age-related macular degeneration (AMD) with intravitreal injections of bevacizumab, to meet the medical needs of many patients who have not responded to therapy with ocular photodynamic therapy (OPT) with verteporfin or intravitreal pegaptanib*". The letter also stated that "*intravitreal bevacizumab, sold under the brand Avastin, is being used by "a large number of retinal specialists (who) believe that it is reasonable and medically necessary for treatment of some patients with neovascular AMD.*" The Academy advised that while "*the scientific studies related to the use of intravitreal injections of bevacizumab for the treatment of neovascular AMD are supportive*," they are "*not conclusive of its safety and efficacy*." The AAO's support for coverage is limited to "*such patients who are deemed by their treating physician to have failed FDA-approved therapies, or in the judgment of their treating physician, based on his/her experience, are likely to have greater benefit from the use of intravitreal bevacizumab."*

FDA Indications

Neovascular (wet) age-related macular degeneration Treatment of neovascular (wet) age-related macular degeneration

Available as: 6mg/0.05mL solution in a single-dose vial. Each vial should only be used for the treatment of a single eye.

Approved by the FDA: October 8, 2019

CLASSIFICATION: An Ophthalmic Agent; Vascular Endothelial Growth Factor (VEGF) inhibitor

Coverage Criteria for Initial Authorization

Beovu (brolucizumab-dbll) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❑ Board-certified ophthalmologist or retinal specialist

2. Diagnosis/Indication [ALL]

- ❒ Definitive diagnosis of Neovascular (Wet) Age-Related Macular Degeneration (AMD)
  AND
- ❒ Baseline measurement of the best corrected visual acuity (BCVA)

3. Age/Gender/Other restrictions [ALL]

- ❑ 18 years of age or older
  The safety and effectiveness of aflibercept in pediatric patients have not been established.
  AND
- ❑ Females of reproductive potential: Evaluate pregnancy status prior to use in females of reproductive potential; consult/prescribe highly effective contraception (methods with pregnancy rates <1%) during therapy and for ≥1 month following the last brolucizumab dose
  Brolucizumab is a VEGF inhibitor; VEGF is required to achieve and maintain normal pregnancies (Peracha 2016). Based on findings in animal reproduction studies and on the mechanism of action, brolucizumab may cause fetal harm if administered to a pregnant female. Treatment should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.
  Highly effective contraception should be used during treatment and for at least one month after the last dose when discontinuing treatment.

4. Step/Conservative Therapy/Other condition Requirements [ALL]

- ❒ Inadequate response (defined as 1-2 injections with minimal to no improvement), clinically significant adverse effects, or contraindication to **Avastin (bevacizumab).** Prescriber submit documentation of contraindication, adverse events, or date(s) of failed therapy to Avastin (bevacizumab).
  AND
- ❒ Member does not have the following condition(s): [ANY]
  - ❍ Ocular and/or peri-ocular infections
  - ❍ Active intraocular inflammation

  AND
- ❒ Beovu (brolucizumab-dbll) will not be used with other ophthalmic VEGF inhibitors (i.e., aflibercept, ranibizumab, pegaptanib, bevacizumab, etc.)

5. Contraindications/Exclusions/Discontinuations to Beovu (brolucizumab-dbll) therapy
Authorization will <u>not</u> be granted if ANY of the following conditions apply [ANY]

- ❑ Non-FDA approved indications
- ❑ Hypersensitivity (e.g., rash, pruritus, urticaria, erythema, severe intraocular inflammation) to brolucizumab or any component of the formulation
- ❑ Ocular or periocular infections; active intraocular inflammation
- ❑ Less than 18 years of age
- ❑ Prescribed for use in combination with other VEGF inhibitors, including but not limited to bevacizumab (Avastin), pegaptanib (Macugen), and ranibizumab (Lucentis)

6. Labs/Reports/Documentation required [ALL]
All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP are included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

Reauthorization /Continuation of Therapy

Beovu (brolucizumab-dbll) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria

- ❑ Reauthorization request is for the **same eye** as initial authorization
  NOTE: The continuation of therapy criteria is only for the same previously treated eye. If member has developed condition in an untreated eye, Prescriber must submit new request with Initial Coverage criteria.
  AND
- ❑ Member currently meets ALL initial coverage criteria
  AND
- ❑ Subsequent authorizations will require the Member re-assessment for this condition to determine if continuation of treatment with requested medication is medically necessary. Clinical documentation indicating must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Labs/Reports/Documentation required [ALL]

Beovu (brolucizumab-dbll) maintenance therapy may be authorized when therapy has demonstrated efficacy as evidenced by an improvement in disease activity after initial therapy. Documentation of **disease stabilization or improvement** is required for continuation of therapy.

- ❒ Response to treatment (including disease progression or history of progressive visual loss or worsening of anatomic appearance) as determined by fluorescein angiography, Optical Coherence Tomography (OCT), optical coherence tomography angiography (OCTA) or Scanning Computerized Ophthalmic Diagnostic Imaging (SCODI) as documented of ONE (1) of the following compared to baseline: [ONE]
  - ❍ Detained neovascularization
  - ❍ Clinical improvement or stability with visual acuity
  - ❍ Maintenance of corrected visual acuity from prior treatment

  NOTE: For dosage change requests, refer to 'Administration, Quantity Limitations, and Authorization Period' section.

  Fluorescein angiography, OCT, and OCTA are useful diagnostic tests in clinical practice to detect new or recurrent neovascular disease activity and guide therapy. (AAO 2019).

  AND
- ❒ Examination identifying evidence of retinal cysts and/or subretinal fluid (hemorrhage by OCT or fluorescein angiography (as applicable). Prescriber submit documentation of exam/diagnostic test results if completed.
  AND
- ❒ Persistent evidence of lesion activity, however the lesion continues to respond to repeated treatment
  AND
- ❒ Administration of intravitreal therapy (*recorded in the procedure or post-procedure note following the completion of treatments*) for the previous authorization period with the following information: name of the medication, dose/amount of drug administered, and treated eye (Right eye, Left eye, or Both eyes)

3. Discontinuation of Treatment

Member should be assessed for discontinuation of therapy if **ANY** of the following are applicable: **[ANY]**

- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms following the initial authorization of coverage
  AND

- ❑ Absence of unacceptable toxicity from the drug (i.e. endophthalmitis and retinal detachments; increase in intraocular pressure; arterial thromboembolic events)
  AND
- ❒ Deterioration of eye visual acuity to less than 20/320 in the eye being treated after three or more injections
  AND
- ❒ Reduction of best corrected visual acuity (BCVA) in the treated eye to less than 15 letters (3 Snellen lines), on 2 consecutive visits in the treated eye, attributed to wet AMD in the absence of other pathology
  AND
- ❒ Deterioration of lesion morphology despite optimal treatment as evidenced by worsening of optical coherence tomography (OCT), increase of lesion size or other evidence of disease activity resulting from new hemorrhage or exudates over 3 consecutive visits
  AND
- ❒ Examination identifies a fluid free macula
  AND
- ❑ Contraindications/Exclusions to Beovu (brolucizumab-dbll) therapy
  Authorization will not be granted if ANY of the following conditions apply [ANY]
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity (e.g., rash, pruritus, urticaria, erythema, severe intraocular inflammation) to brolucizumab or any component of the formulation
  - ❍ Ocular or periocular infections; active intraocular inflammation
  - ❍ Less than 18 years of age
  - ❍ Prescribed for use in combination with other VEGF inhibitors, including but not limited to bevacizumab (Avastin), pegaptanib (Macugen), and ranibizumab (Lucentis)

Administration, Quantity Limitations, and Authorization Period

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosing Regimen [ALL]

Neovascular (wet) age-related macular degeneration **[ALL]**

- ❑ Initial dosage: 6 mg (0.05 mL of 120 mg/mL solution) by intravitreal injection once per month (approximately every 25 to 31 days) for 3 months (3 doses)
  AND
- ❑ Maintenance dosage: After three loading doses administered at 4 week intervals, a maintenance treatment regimen every 8 to 12 weeks; 6 mg by intravitreal injection once every 8 to 12 weeks.

  Dosing at the every 12-week frequency is sufficient for most patients; however, for some patients who show continued disease activity, increasing the frequency to every 8 weeks may be considered.
  Patients in the brolucizumab arms could be switched to every-8-week dosing if disease activity was observed according to protocol- defined changes in VA or intraretinal fluid.
  Subsequent follow-up and treatment intervals vary depending on the clinical findings and judgment of the treating ophthalmologist (AAO 2019).

  AND
- ❑ **For maintenance dosing at every 8-weeks:** Submit clinical documentation supporting maintenance dosage of every 8 weeks, instead of a 12-week dose. Documentation to include, but not limited to, fluorescein angiography, OCT, OCTA and any additional clinical findings used to guide therapy.
  - ◆ *Fluorescein angiography, OCT, and OCTA are useful diagnostic tests in clinical practice to detect new or recurrent neovascular disease activity and guide therapy. (AAO 2019) As-needed treatment may be based on the presence or absence of subretinal or intraretinal fluid.*

2. Dosage Change Requests [ALL]

- ❑ Requested dose is within the FDA-recommendations and does not exceed the recommended maximum dose for indication
  AND

- ❑ For requests from 12 weeks to 8 weeks frequency: Member has been titrated up from the less frequent dose of 12 weeks. Documentation required: Prescriber submit date(s) of dosage/duration and clinical documentation supporting increase in dose/frequency. Additional documentation may be requested for review
  NOTE: Members initiated on an 8-week maintenance dosage are not required to meet this criterion (clinical documentation supporting an initiation of an 8-week maintenance dosage required previously; in #1).

3. Authorization Limit [ALL]

- ❑ Quantity limit:
  - ❍ Initial: 6 mg intravitreally once a month per eye [6 mg injection; 6mg/0.05mL (single-dose vial)]
  - ❍ Maintenance dosage: 6 mg by intravitreal injection once every 8 to 12 weeks
- ❒ Duration of initial authorization: **3 months**
- ❒ Continuation of treatment: Re-authorization for continuation of treatment is required every **6 months** to determine continued need based on member meeting 'Continuation of Therapy' criteria

4. Route of Administration [ALL]

- ❑ Beovu (brolucizumab-dbll) is **provider-administered** via intravitreal injection by a retinal specialist
- ❑ Provider-administration will be authorized in a **physician office** setting only. Routine administration in a hospital or outpatient setting will not be authorized
- ❑ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.
- ❑ Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

Coverage Exclusions

This policy only addresses the indication of Beovu (brolucizumab-dbll) when appropriate criteria are met.

All other uses of Beovu (brolucizumab-dbll) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

**FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

Background/Summary

Age-Related Macular Degeneration (AMD)

AMD is a leading cause of vision loss globally, with adults > 50 years old most often affected. AMD is a progressive chronic retinal disease affecting the aging eye(s), characterized by drusen (focal yellowish deposits of acellular, polymorphous debris), geographic atrophy of retinal pigment epithelium, and neovascularization that can lead to visual impairment.

There are 2 forms of AMD: wet and dry. The dry form is the most common form and is characterized by yellow deposits in the retina, called "drusen." The dry form can progress to the wet form, which is more aggressive and severe. Wet or exudative AMD is caused by the growth of abnormal leaky blood vessels (choroidal neovascularization or CNV) that eventually damage the macula. The macula is the area of the eye responsible for central vision, which is essential for most visual activities, including reading, driving, and recognizing faces. CNV associated with wet AMD may include classic or occult neovascular leakage patterns. Classic CNV is distinct or well demarcated during fluorescein angiography whereas occult CNV is obscured or poorly demarcated on fluorescein angiography.

Clinical Efficacy

The efficacy of brolucizumab was evaluated in two double-masked, active-controlled, Phase III randomized multi-center studies studies (HAWK and HARRIER) in 1,817 untreated wet AMD patients. Both studies were designed to provide a head-to-head non-inferiority comparison of brolucizumab to aflibercept in the treatment of nAMD.

Patients were randomized to brolucizumab or aflibercept. The studies compared two different doses of brolucizumab, 6 mg and 3 mg, to a 2 mg dose of aflibercept. Brolucizumab was administered as a maintenance dose every 8 or 12 weeks (depending on disease activity) vs. every 8 weeks for Eylea.

All patients received study drug injections at weeks 0, 4, and 8 during a loading phase. Brolucizumab was then injected every 12 weeks; if disease activity was identified, the dosing interval was permanently changed to every 8 weeks. Aflibercept was injected every 8 weeks after the loading phase.

Brolucizumab was administered as an intravitreal injection. Patients received a loading dose of three monthly injections, followed by injections every 12 weeks. The interval could be adjusted to every 8 weeks if disease activity was present. The dosing interval for aflibercept was bi-monthly.

Study Endpoints

HAWK and HARRIER met their pre-specified primary and secondary endpoints.

The primary endpoint was non-inferiority in change in best-corrected visual acuity (BCVA) from baseline to week 48

Key secondary endpoints included the following:

- number of patients on 12-week dosing interval at 48 and 96 weeks
- change in BCVA from baseline at each visit up to 96 weeks
- change in central sub-field thickness (CST) at each visit up to 96 weeks
- presence of intra-retinal fluid (IRF) and/or sub-retinal fluid (SRF) from baseline at each visit up to 96 weeks
- presence of sub-retinal epithelium (sub-RPE) fluid from baseline at each visit up to 96 weeks

Brolucizumab demonstrated non-inferiority to aflibercept for the primary endpoint of mean BCVA change from baseline ($p < 0.001$) at year 1 (week 48) in both studies

Mean baseline BCVA was 60.6 in the HAWK study and 61.2 in the HARRIER study

Mean BCVA change from baseline to week 48 was non-inferior with brolucizumab 6 mg compared with aflibercept 2 mg in the 2-year randomized HAWK (N=1082; +6.6 vs +6.8 letters) and HARRIER (N=743; +6.9 vs +7.6 letters) studies; the HAWK study also included a brolucizumab 3 mg arm

The average change in BCVA from baseline to weeks 36 to 48 was 6.7 for both brolucizumab-dbll 6 mg and aflibercept in the HAWK study and 6.5 versus 7.7, respectively, in the HARRIER study; a 15 or more letter gain was achieved by 33.6% versus 25.4% in HAWK and 29.3% versus 29.9% in HARRIER.

With all treatments, gains in BCVA were achieved during the loading phase with slight increases to week 48.

In both trials patients on brolucizumab achieved vision gains that were non-inferior to aflibercept at year one with longer treatment intervals in a majority of patients. In both clinical trials, approximately 30% of patients gained at least 15 letters at year one.

During the first 16 weeks of treatment when all patients had at least 8 weeks until the next treatment after loading doses, brolucizumab-dbll 6 mg compared with aflibercept had significantly fewer patients with disease activity (HAWK, 24% vs 34.5%; HARRIER, 22.7% vs 32.2%), greater mean reductions in central subfield thickness (HAWK, -161.4 vs -133.6 mcm; HARRIER, -174.4 vs -134.2 mcm), and fewer eyes with intraretinal/subretinal fluid (HAWK, 33.9% vs 52.2%; HARRIER, 29.4% vs 45.1%).

Beovu also demonstrated superiority to aflibercept in several secondary endpoints including improvements in disease activity and other anatomical retinal fluid outcomes:

At week 16, fewer brolucizumab patients had disease activity vs. aflibercept in HAWK (24.0% vs. 34.5%; $p = 0.001$) and HARRIER (22.7% vs. 32.2%; $p = 0.002$).

Beovu showed greater reduction in central subfield thickness (CST) as early as week 16 and at year one, and fewer patients had intra-retinal (IRF) and/or sub-retinal fluid (SRF).

A reduction of CST is an important measure of abnormal fluid accumulation and edema that may result in reduced vision

Lower number of patients with retinal fluid (intraretinal and/or subretinal).

Retinal fluid is a key marker of disease activity and key markers used by providers to determine injection frequency

A reduction in disease activity

Results at week 96 with the 6 mg dose of brolucizumab have been consistent with the 48 week results in both primary and secondary endpoints.

In both trials eligible patients could be maintained on a three-month dosing interval immediately after the loading phase.

At year one, over half of patients were maintained on the three-month dosing interval (56% in HAWK and 51% in HARRIER). The remaining patients in the study were treated on a two-month dosing schedule.

Adverse events with brolucizumab-dbll 6 mg compared with aflibercept included conjunctival hemorrhage (HAWK, 6.4% vs 5.6%; HARRIER, 1.9% vs 3.3%), reduced visual acuity (HAWK, 5.3% vs 6.7%; HARRIER, 5.4% vs 5.4%), uveitis (HAWK, 2.2% vs 0.3%; HARRIER, 0.8% vs 0%), and iritis (HAWK, 2.2% vs 0%; HARRIER, 0% vs 0.3%).

Practice Guidelines and Position Statements

At the time of this writing in November 2019, no published guidelines were identified that recommend the use of Beovu (brolucizumab-dbll) for neovascular AMD.

American Academy of Ophthalmology (AAO): Age-Related Macular Degeneration Preferred Practice Patterns (2015; 2019)

The AAO guideline recommends the use of anti-VEGF agents (e.g., aflibercept, bevacizumab, ranibizumab) as a first-line therapy to effectively manage neovascular AMD.

The VEGF inhibitors have demonstrated improved visual and anatomic outcomes compared with other therapies.

Anti-VEGF therapies have become first-line therapy for treating and stabilizing most cases of neovascular AMD and a Cochrane systematic review demonstrates the effectiveness of these agents to maintain visual acuity. (I+, Good quality, Strong recommendation) (*Reference: Cochrane Review: Solomon SD, Lindsley K, et al. 2019*)

Definitions

Neovascularization: The formation of abnormal new blood vessels

Retinopathy: Damage to the retina

Vascular endothelial growth factor (VEGF): chemical signal produced by the body's cells that stimulates growth of new blood vessels

Coding Information: The codes listed in this clinical policy are for informational purposes only. listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered. coverage is determined by the benefit document. this list of codes may not be all inclusive and Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS	Description
J0179	Injection, brolucizumab-dbll, 1 mg

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Policy History	Approval
Policy Developed *Peer Review: AMR Peer Review Network. 12/4/2019. Practicing Physician. Board certified in Ophthalmology*	P&T Q12020

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