

# Evolving Therapies in Neovascular Age-Related Macular Degeneration

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## ABSTRACT

Neovascular age-related macular degeneration (nAMD) continues to represent a major cause of irreversible central vision loss despite substantial therapeutic progress over the past two decades. The advent of intravitreal anti-vascular endothelial growth factor (VEGF) therapy fundamentally altered the natural course of the disease, enabling sustained visual stabilization and, in many patients, meaningful visual improvement. However, long-term management remains dependent on repeated injections and continuous monitoring, imposing a considerable burden on both patients and healthcare systems. Contemporary therapeutic development has therefore shifted from maximizing short-term efficacy toward enhancing durability and reducing injection frequency. High-dose formulations, such as aflibercept 8 mg, aim to intensify VEGF suppression, whereas dual-pathway inhibitors such as faricimab target both VEGF-A and angiopoietin-2, addressing complementary pathways implicated in vascular destabilization. Agents designed to optimize pharmacokinetics, including antibody–biopolymer conjugates, represent an alternative strategy aimed at prolonging intraocular residence time through pharmacokinetic optimization. In parallel, biosimilars are expanding treatment accessibility through regulatory frameworks based on analytical and clinical comparability. Sustained drug delivery systems and gene-based strategies further attempt to provide prolonged intraocular anti-angiogenic activity while minimizing injection burden. This review summarizes current and emerging treatment strategies in nAMD, with emphasis on mechanistic diversity, durability optimization, safety considerations, and real-world applicability. As the field evolves, the central challenge lies not only in suppressing VEGF effectively but in achieving sustainable, individualized disease control over years of treatment.

**Keywords:** Neovascular Age-Related Macular Degeneration, Anti-VEGF Therapy, Angiogenesis Inhibitors, Drug Delivery Systems, Gene Therapy

## 1. INTRODUCTION

Age-related macular degeneration (AMD) remains one of the leading causes of irreversible central vision loss among individuals older than 50 years worldwide.<sup>1,2</sup> In developed countries, it remains a leading cause of legal blindness in the elderly population.<sup>1</sup> The neovascular form accounts for the majority of severe vision loss associated with the disease.<sup>1</sup> With the progressive aging of the global population, the prevalence of AMD is expected to

increase significantly.<sup>2</sup> This growing burden has important socioeconomic implications due to prolonged treatment requirements.<sup>2</sup>

Neovascular AMD (nAMD) is characterized by the development of pathologic choroidal neovascularization (CNV) originating from the choriocapillaris.<sup>3</sup> Within this pathologic cascade, vascular endothelial growth factor (VEGF) plays an important role in promoting angiogenesis and increasing vascular permeability.<sup>3,4</sup> However,

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angiopoietin-2 (Ang-2) signaling and inflammatory mediators also contribute to vascular instability.<sup>5</sup> These newly formed vessels are fragile and prone to leakage or hemorrhage, disrupting normal retinal architecture. Persistent exudation and chronic inflammation may lead to subretinal fibrosis and irreversible photoreceptor damage.<sup>3</sup>

The introduction of intravitreal anti-VEGF treatments in the mid-2000s marked a turning point in the management of AMD.<sup>6,7</sup> Pivotal clinical trials demonstrated not only disease stabilization but meaningful visual improvement in a significant proportion of patients.<sup>6,7</sup> Since then, anti-VEGF injections have become the standard of care and have substantially altered the natural history of the disease.<sup>8</sup>

Nevertheless, the need for repeated intravitreal injections and close follow-up remains a major limitation of current treatment paradigms.<sup>9</sup> Persistent or recurrent fluid in some patients further highlights the necessity for more durable and optimized therapeutic approaches.<sup>9</sup> Recent advances include extended-durability agents, dual-pathway inhibition strategies, high-dose VEGF formulations, biosimilars, sustained drug delivery systems, and gene-based therapies. The conceptual evolution of these durability-oriented strategies is illustrated in Figure 1.

This review focuses on current and emerging treatment strategies in neovascular AMD, emphasizing innovations aimed at improving durability, maintaining visual outcomes, and reducing treatment burden.

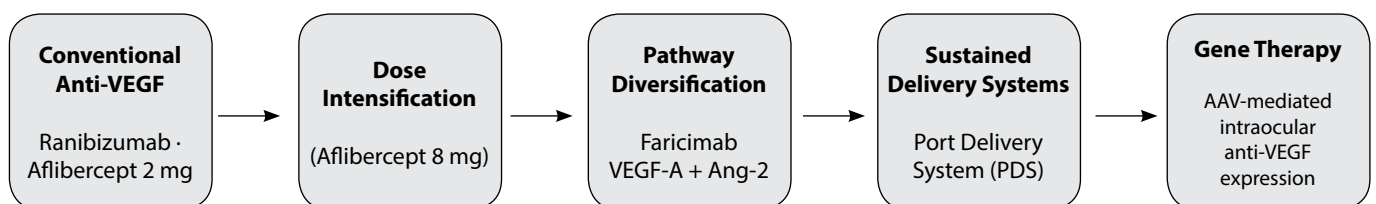
## 2. INTRAVITREAL PHARMACOTHERAPY

### 2.1 ESTABLISHED ANTI-VEGF AGENTS (BEVACIZUMAB, RANIBIZUMAB, AFLIBERCEPT)

Intravitreal VEGF inhibition has reshaped the management of neovascular age-related macular degeneration (nAMD). Before its widespread adoption, progressive central vision loss was common despite available therapies. The introduction of bevacizumab, ranibizumab, and aflibercept changed the clinical course of the disease, allowing sustained visual stabilization and in many cases meaningful improvement under regular treatment. Landmark phase 3 randomized controlled trials established anti-VEGF therapy as the standard of care in neovascular AMD.<sup>6,8</sup> Although these agents share VEGF-A as their primary molecular target, they differ substantially in molecular structure, regulatory pathways, and clinical development trajectories.<sup>10</sup> Ranibizumab, developed specifically for intraocular use, was introduced as an antibody fragment optimized for retinal delivery.<sup>6,7</sup> Aflibercept, designed as a recombinant fusion protein, provides high-affinity binding within standard injection volumes.<sup>8</sup> In practice, however, visual outcomes across these agents are generally comparable when treatment is administered consistently and according to evidence-based protocols.<sup>11,12</sup>

Over time, fixed monthly dosing evolved toward individualized regimens, particularly treat-and-extend

#### Evolution of Durability-Oriented Therapeutic Strategies in Neovascular AMD



**Figure 1.** Evolution of durability-oriented therapeutic strategies in neovascular age-related macular degeneration (nAMD).

Therapeutic paradigms have progressively shifted from conventional intravitreal vascular endothelial growth factor (VEGF) inhibition toward durability-enhancing approaches, including dose intensification, pathway diversification, sustained drug delivery systems, and gene-based therapies. Each strategy is grounded in a distinct biological and pharmacologic rationale aimed at extending treatment intervals while preserving long-term visual and anatomic outcomes.

Abbreviations: VEGF, vascular endothelial growth factor; Ang-2, angiopoietin-2; PDS, port delivery system; AAV, adeno-associated virus.

approaches aimed at balancing disease control with injection burden.<sup>9,13</sup> While these strategies reduced visit frequency for selected patients, they did not eliminate the need for ongoing therapy. Many eyes continue to demonstrate recurrent or persistent fluid, and long-term management remains resource-intensive.<sup>13</sup>

In contemporary retinal practice, therapeutic innovation is no longer primarily focused on improving short-term efficacy, but on extending durability and reducing cumulative treatment burden. In this context, the primary limitation of current therapy is not short-term efficacy but the durability of response and the cumulative burden of repeated intravitreal injections.<sup>9,13</sup>

## 2.2 NEXT-GENERATION ANTI-VEGF STRATEGIES AND DURABILITY OPTIMIZATION

### 2.2.1 Brolucizumab: High-Molar-Dose VEGF Suppression

Brolucizumab is a humanized single-chain antibody fragment targeting VEGF-A and is approved for the treatment of neovascular age-related macular degeneration.<sup>14</sup> Its relatively small molecular size permits delivery of a high molar dose within a standard injection volume, facilitating effective intraocular VEGF suppression.<sup>14</sup> The approved dosing regimen includes three monthly injections of 6 mg/0.05 mL, followed by maintenance dosing every 8 to 12 weeks according to clinical activity.<sup>14</sup> The development strategy aimed to enhance treatment durability while maintaining visual outcomes comparable to established anti-VEGF agents.

In the pivotal HAWK and HARRIER trials, brolucizumab was compared with aflibercept in treatment-naïve neovascular AMD. At one year, brolucizumab demonstrated non-inferior BCVA gains compared with aflibercept. A greater proportion of brolucizumab-treated eyes achieved complete retinal fluid resolution, and many patients were maintained on 12-week intervals after the loading phase.<sup>14</sup>

Subsequent post-approval analyses, including data from the MERLIN study, highlight the importance of dosing interval selection.<sup>15</sup> Shorter dosing intervals were associated with enhanced anatomic drying but a higher incidence of intraocular inflammation, including retinal

vasculitis and vascular occlusion. Accordingly, dosing at intervals shorter than eight weeks after the loading phase is not recommended.<sup>15</sup> In routine practice, careful patient selection and early recognition of inflammatory symptoms remain essential when considering brolucizumab therapy.<sup>16</sup>

### 2.2.2 Faricimab (Vabysmo): Dual VEGF-A and Angiopoietin-2 Inhibition

Faricimab is a bispecific monoclonal antibody targeting both vascular endothelial growth factor-A (VEGF-A) and angiopoietin-2 (Ang-2), thereby addressing complementary drivers of neovascularization and vascular destabilization.<sup>17,18</sup>

The approved dose is 6 mg administered intravitreally following four initial loading injections, after which interval extension is guided by disease activity assessment. In phase 3 protocols, dosing intervals extended up to 16 weeks in the absence of disease activity.<sup>19</sup>

Although VEGF inhibition remains the core strategy in neovascular age-related macular degeneration (nAMD), Ang-2 is increasingly recognized as a complementary mediator of endothelial dysfunction, pericyte loss, inflammatory activation, and leakage.<sup>20</sup> In this framework, dual inhibition is conceptually positioned to enhance vascular stabilization, improve anatomic control, and support longer retreatment intervals in suitable patients.

In the pivotal phase 3, multicenter, randomized TENAYA and LUCERNE trials, faricimab was evaluated against aflibercept 2 mg in treatment-naïve nAMD.<sup>19</sup> Following four initial monthly injections, patients assigned to faricimab were managed according to a protocol-defined treat-and-extend algorithm permitting extension to 12- or 16-week intervals based on prespecified disease activity criteria, whereas aflibercept was administered every 8 weeks after loading. Across both trials, faricimab demonstrated non-inferior best-corrected visual acuity (BCVA) gains compared with aflibercept at one year, with a substantial proportion of patients maintained on extended dosing intervals.<sup>19</sup>

Beyond visual acuity outcomes, durability and anatomic control represent key determinants of long-term treatment strategy in nAMD. In TENAYA and LUCERNE, a substantial proportion of patients treated with faricimab

were maintained on  $\geq 12$ -week dosing intervals, supporting the durability potential of dual-pathway inhibition.<sup>19</sup>

Anatomic outcomes paralleled functional efficacy. Faricimab demonstrated marked reductions in central subfield thickness and high rates of intraretinal and subretinal fluid resolution. These findings support the premise that dual VEGF-A/Ang-2 inhibition may enhance vascular stabilization without compromising visual outcomes.<sup>19</sup> A representative optical coherence tomography (OCT) example demonstrating anatomical response following faricimab therapy is shown in Figure 2.

The overall safety profile was comparable to established anti-VEGF therapies. Rates of intraocular inflammation were low, and no consistent signal of retinal vasculitis or occlusive events was observed in pivotal trial populations. Ongoing post-marketing surveillance remains important as broader real-world populations are incorporated into clinical practice.<sup>19,21</sup>

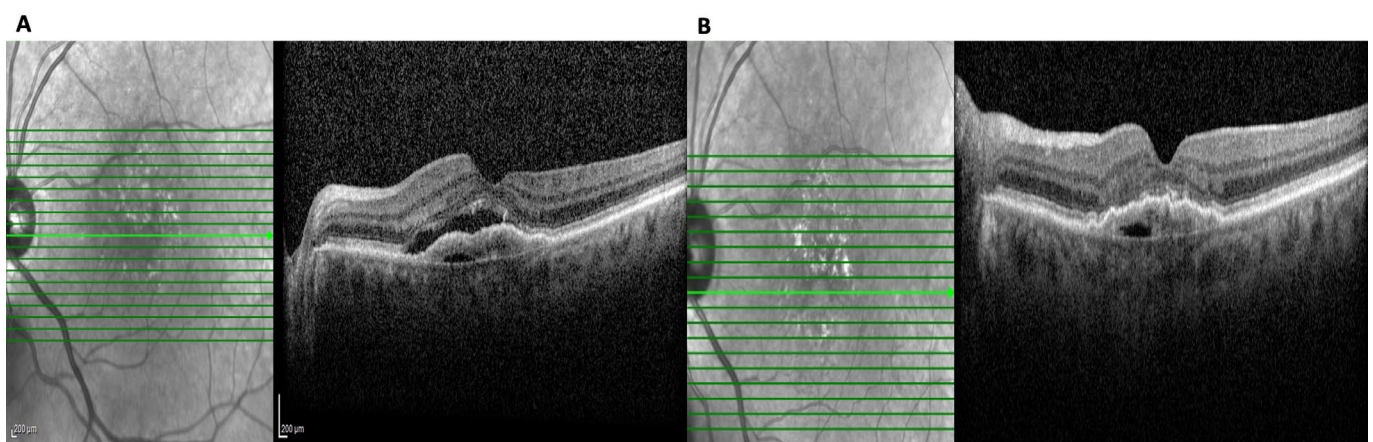
From a pragmatic perspective, faricimab is commonly considered in three clinical contexts: (i) treatment-naïve eyes where durability is an early priority, (ii) eyes with recurrent fluid on conventional treat-and-extend schedules that struggle to maintain longer intervals, and (iii) patients for whom reducing visit frequency has substantial logistical value.

Nonetheless, response heterogeneity remains a defining feature of nAMD management; some eyes may require shorter intervals despite dual-pathway inhibition, and clinicians should remain attentive to individualized disease kinetics, OCT biomarkers, and retreatment thresholds.

### 2.2.3 Aflibercept 8 mg (Eylea HD): Dose Intensification to Extend Durability

Aflibercept 8 mg (Eylea HD) received FDA approval in 2023 for the treatment of nAMD.<sup>22</sup>

Aflibercept 8 mg represents a dose-intensification strategy within the established VEGF-A blockade framework, designed to extend treatment intervals up to 16 weeks while preserving visual and anatomic outcomes.<sup>22</sup> Unlike pathway-diversifying approaches, the 8 mg formulation retains the same molecular mechanism as standard-dose aflibercept but increases intraocular drug availability, with the objective of sustaining VEGF suppression for longer durations. The conceptual shift is pragmatic rather than mechanistic, reflecting the unmet need for durability and reduced treatment burden rather than incremental short-term efficacy gains. Aflibercept is a recombinant fusion protein that functions as a high-affinity decoy receptor for VEGF-A.<sup>23</sup> By increasing the administered dose within the same injection volume, the 8 mg formulation aims to prolong pharmacodynamic coverage over time.



**Figure 2.** Optical coherence tomography (OCT) response following faricimab therapy in neovascular age-related macular degeneration (nAMD). (A) Baseline spectral-domain OCT demonstrating intraretinal and/or subretinal fluid consistent with active choroidal neovascularization. (B) Post-treatment OCT image showing resolution of fluid and reduction in central retinal thickness following intravitreal faricimab therapy. Representative case.

Abbreviations: OCT, optical coherence tomography; nAMD, neovascular age-related macular degeneration.

The pivotal phase 3 PULSAR trial evaluated aflibercept 8 mg in treatment-naïve nAMD.<sup>22</sup> Following loading, patients in the 8 mg arms were assigned to extended dosing intervals, with the protocol-defined interval adjustments permitted based on prespecified disease activity criteria. The control arm received standard-dose aflibercept 2 mg at fixed 8-week intervals following loading.

At one year, aflibercept 8 mg met non-inferiority criteria for best-corrected visual acuity (BCVA) compared with the 2 mg regimen. A substantial proportion of patients were maintained on extended dosing intervals, including regimens up to 16 weeks, without loss of visual efficacy.<sup>22</sup>

Anatomic improvements such as reductions in central retinal thickness and control of intraretinal and subretinal fluid were broadly consistent with effective VEGF suppression and aligned with the durability objective.<sup>22</sup> Extended intervals were achievable in a substantial subset of patients, although individualized monitoring remains essential.<sup>22</sup> A representative optical coherence tomography (OCT) example demonstrating anatomical response following aflibercept 8 mg therapy is illustrated in Figure 3.

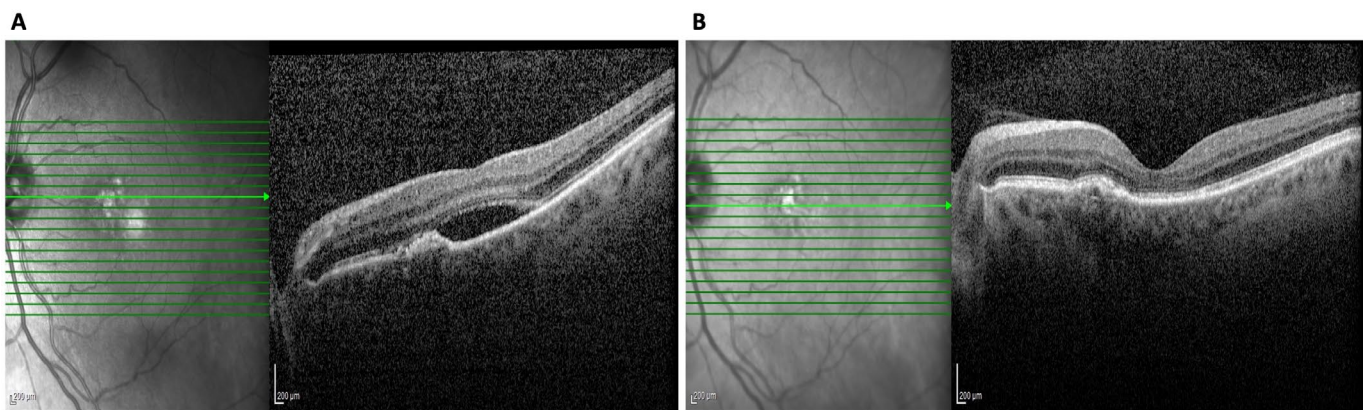
The durability concept was also evaluated in the phase 3 PHOTON trial in diabetic macular edema. Although DME differs pathophysiologically from AMD, the overarching goal of extending dosing intervals up to 16 weeks while

maintaining efficacy was similarly explored.<sup>24</sup> For a review focused on nAMD, a brief acknowledgment of the broader program reinforces that the high-dose strategy is positioned as a cross-indication durability platform rather than a niche reformulation.

In the pivotal programs, the overall safety profile of aflibercept 8 mg appeared broadly comparable to that of standard-dose aflibercept. Rates of intraocular inflammation and other ocular adverse events did not reveal a consistent new safety signal in trial populations.<sup>22,24</sup>

However, as with any intravitreal biologic, ongoing pharmacovigilance remains essential.<sup>22</sup> Real-world practice encompasses more heterogeneous lesion types, prior-treatment histories, and comorbid conditions that may not be fully represented in controlled trials.<sup>25</sup> Extended fixed intervals up to 16 weeks should therefore be implemented with appropriate OCT monitoring and readiness to shorten intervals when disease activity recurs.

Aflibercept 8 mg may be particularly relevant in scenarios where reducing injection frequency is a priority and where disease behavior suggests a VEGF-dominant phenotype responsive to intensified blockade.<sup>22</sup> Typical clinical contexts include: (i) Treatment-naïve eyes demonstrating strong early anatomic response, in which transition to extended fixed intervals up to 16 weeks may be feasible.



**Figure 3.** *Optical coherence tomography (OCT) response following aflibercept 8 mg therapy in neovascular age-related macular degeneration (nAMD). (A) Baseline spectral-domain OCT demonstrating intraretinal and/or subretinal fluid associated with active choroidal neovascularization. (B) Follow-up OCT image after intravitreal aflibercept 8 mg therapy showing anatomical improvement with reduction of retinal fluid and stabilization of central retinal thickness. Representative case.*

*Abbreviations: OCT, optical coherence tomography; nAMD, neovascular age-related macular degeneration.*

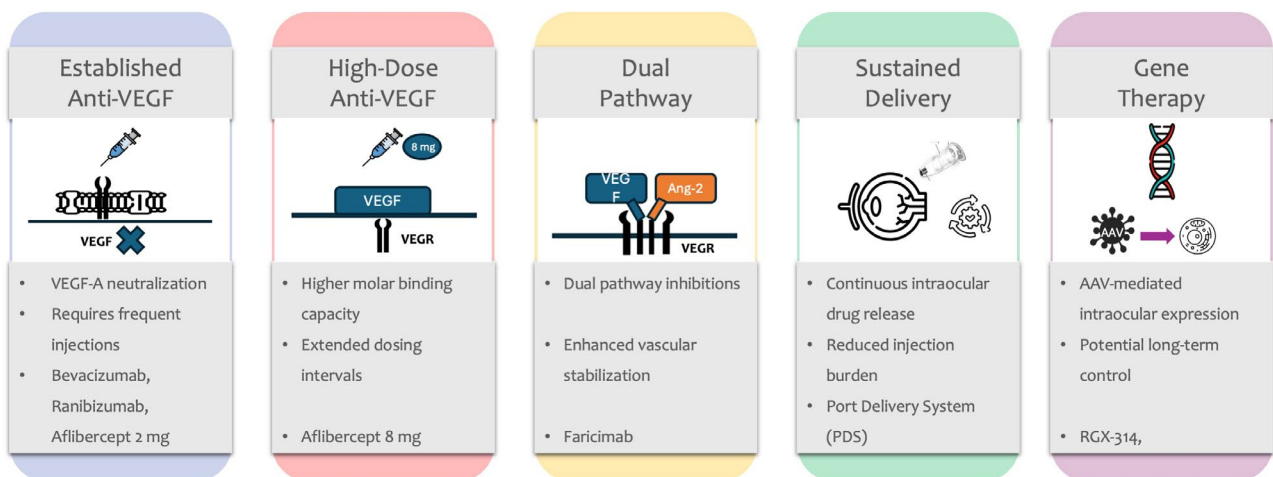
(ii) Patients stabilized on standard-dose therapy who experience recurrence before their next scheduled visit; dose intensification may enable longer spacing without sacrificing control. (iii) Individuals for whom visit burden poses significant logistical or quality-of-life challenges.

The availability of aflibercept 8 mg and faricimab illustrates two distinct contemporary strategies in retinal pharmacotherapy: intensifying VEGF blockade versus diversifying angiogenic pathway inhibition.<sup>5,22</sup> A conceptual

comparison of durability-oriented strategies is illustrated in Figure 4.

Whether one approach will demonstrate superior long-term sustainability remains to be determined, and clinical decision-making continues to rely on individualized response patterns. A structured comparison of their mechanisms, durability paradigms, clinical outcomes, and safety profiles is presented in Table 1.

#### Therapeutic Strategies for Enhancing Durability in Neovascular AMD: A Mechanistic Overview



**Figure 4.** Therapeutic strategies for enhancing durability in neovascular age-related macular degeneration (nAMD): mechanistic overview.

Contemporary treatment strategies in nAMD aim to extend treatment intervals while maintaining functional and anatomic stability. Established anti-VEGF therapy neutralizes VEGF-A but typically requires frequent intravitreal injections. High-dose VEGF inhibition (aflibercept 8 mg) increases intraocular drug exposure to prolong dosing intervals within the same molecular target framework. Dual-pathway inhibition (faricimab) simultaneously targets VEGF-A and angiopoietin-2 (Ang-2), addressing complementary mechanisms of vascular destabilization. Sustained delivery systems provide continuous intraocular drug release to reduce injection burden, whereas gene therapy approaches utilize adeno-associated viral (AAV) vectors to enable sustained intraocular anti-VEGF expression.

Abbreviations: VEGF, vascular endothelial growth factor; Ang-2, angiopoietin-2; PDS, port delivery system; AAV, adeno-associated virus.

**Table 1.** Comparative Clinical and Strategic Features of High-Dose and Dual-Pathway Anti-VEGF Strategies in nAMD

Parameter	Faricimab (TENAYA/ LUCERNE)	Aflibercept 8mg (PULSAR)
Mechanism	Bispecific antibody targeting VEGF-A and Ang-2	High-dose VEGF-A ligand trap (VEGFR-1/2 fusion protein)
1-year visual outcome	Met primary non-inferiority endpoint versus aflibercept 2mg (BCVA)	Non-inferior to aflibercept 2 mg
Durability Strategy	Treat-and-extend protocol allowing up to 16-week intervals	Fixed 12 -or 16- week dosing after loading phase
Year-2 Data	Maintenance of visual gains with flexible dosing	Sustained efficacy with extended intervals
Safety signals	Comparable to aflibercept; no increased incidence of intraocular inflammation versus aflibercept 2mg in phase 3 trials	Comparable to aflibercept 2mg; no new safety concerns identified
Inflammation risk	Low; similar to standard anti-VEGF therapy	Low; similar to standard-dose aflibercept
Approved dosing interval	Up to 16 weeks	Up to 16 weeks
Conceptual Approach	Pathway diversification	Dose intensification

### 2.3 BIOSIMILARS AND INTERCHANGEABILITY IN NAMD (YESAFILI/ OPUFIZ/ ENZEEVU/ PAVBLU)

#### 2.3.1 Aflibercept Biosimilar

The emergence of aflibercept biosimilars marks a relevant shift in the therapeutic landscape of neovascular age-related macular degeneration (nAMD), particularly in the context of long-term treatment burden and healthcare sustainability. YESAFILI (aflibercept-jbvf; Biocon Biologics) received FDA approval in 2024 as a biosimilar to aflibercept for the treatment of nAMD and other retinal vascular diseases.<sup>26</sup>

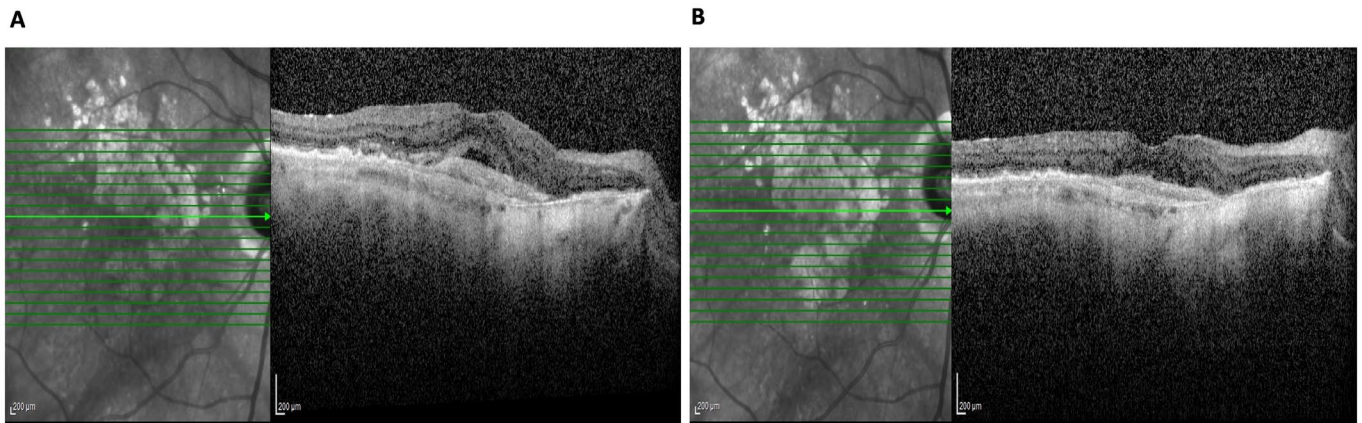
As a recombinant fusion protein, aflibercept-jbvf shares the same molecular target and mechanism of action as reference aflibercept, binding vascular endothelial growth factor-A (VEGF-A) to inhibit pathologic angiogenesis and vascular permeability. Biosimilar approval does not rely solely on clinical efficacy trials but on a totality-of-evidence framework, in which extensive analytical characterization and pharmacokinetic comparability form the foundation of regulatory assessment.<sup>27</sup> Clinical studies are primarily

designed to confirm the absence of clinically meaningful differences rather than to demonstrate superiority.

Available data indicate comparable visual and anatomical outcomes to reference aflibercept within predefined equivalence margins. In a phase 3 randomized clinical trial, aflibercept-jbvf demonstrated non-inferior improvement in BCVA and central retinal thickness, with a comparable safety and immunogenicity profile.<sup>26</sup> An illustrative OCT example following treatment with aflibercept-jbvf (YESAFILI) is presented in Figure 5.

While such findings support therapeutic similarity, long-term real-world experience and switching data will continue to inform clinician confidence and prescribing behavior in routine practice.

From a systems perspective, the introduction of aflibercept biosimilars such as aflibercept-jbvf may improve treatment accessibility and contribute to cost containment in settings where repeated anti-VEGF therapy represents a substantial economic burden.<sup>28</sup> Ultimately, the role of biosimilars in retinal practice extends beyond molecular equivalence,



**Figure 5.** Optical coherence tomography (OCT) response following treatment with aflibercept-jbyf (YESAFILI) in neovascular age-related macular degeneration (nAMD).

(A) Baseline OCT demonstrating exudative activity associated with choroidal neovascularization. (B) Follow-up OCT after intravitreal aflibercept-jbyf therapy showing anatomical improvement with reduction of intraretinal and/or subretinal fluid. Representative case.

Abbreviations: OCT, optical coherence tomography; nAMD, neovascular age-related macular degeneration.

encompassing considerations of interchangeability policies, institutional adoption, and real-world implementation. Physician confidence, pharmacovigilance data, interchangeability policies, and real-world switching outcomes play decisive roles in adoption. As cumulative experience expands, biosimilars may progressively reshape cost structures without altering therapeutic principles.

## 2.4 INVESTIGATIONAL BIOLOGIC STRATEGIES (KSI-301, EFDAMROFUSP ALFA, OPT-302)

### 2.4.1 Pharmacokinetic Extension Platforms (KSI-301)

KSI-301 (tarcocimab tedromer) is an investigational anti-VEGF biologic developed with the aim of improving intraocular durability. The molecule consists of an anti-VEGF antibody conjugated to a high-molecular weight biopolymer designed to prolong retinal tissue exposure and reduce intraocular clearance. This platform focuses on pharmacokinetic optimization rather than target diversification.<sup>29</sup>

Early-phase studies indicated the feasibility of extended dosing intervals. In subsequent phase 2-3 trials evaluating

KSI-301 in neovascular AMD, visual acuity outcomes were generally comparable to standard anti-VEGF therapy.<sup>30</sup> However, consistent superiority in durability was not uniformly demonstrated across study populations.<sup>31</sup> Ongoing analyses continue to explore patient selection and dosing strategies to better define the clinical role of this antibody–biopolymer conjugate approach.

### 2.4.2 Dual-Pathway Inhibition (Efdamrofusp alfa)

Efdamrofusp alfa is a bispecific investigational biologic targeting both vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2), pathways implicated in angiogenesis and vascular instability in neovascular AMD.<sup>31</sup>

In phase 2 studies, efdamrofusp alfa achieved visual acuity outcomes comparable to aflibercept 2 mg and met non-inferiority criteria in improvements of best-corrected visual acuity. Both 2 mg and 4 mg doses demonstrated an acceptable safety profile without unexpected inflammatory signals. Ongoing phase 3 trials aim to further define long-term efficacy, durability, and safety in larger patient populations with extended follow-up.<sup>31</sup>

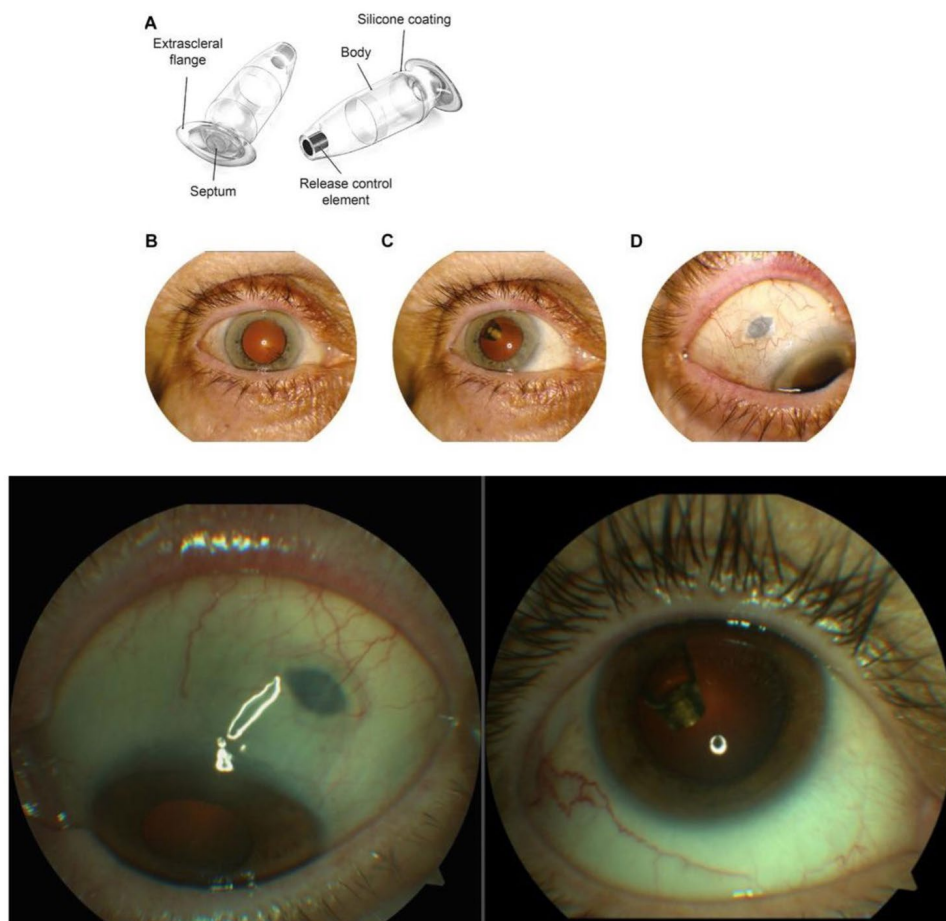
### 3. SUSTAINED INTRAOCULAR DRUG DELIVERY STRATEGIES

Sustained drug delivery systems have emerged as a strategy to address one of the principal limitations of intravitreal anti-VEGF therapy: treatment burden. Although anti-VEGF agents have substantially improved visual outcomes in nAMD, the requirement for frequent injections and close monitoring remains a substantial challenge for patients and healthcare systems. Long-acting delivery platforms are designed to maintain therapeutic intraocular drug concentrations over extended periods, thereby reducing injection frequency while preserving visual and anatomical outcomes.

The Port Delivery System (PDS) with ranibizumab is the first refillable intraocular implant developed for chronic retinal vascular disorders and received FDA approval in

2021. In the phase 2 LADDER trial, higher-concentration ranibizumab formulations within the implant prolonged time to first refill compared with monthly intravitreal ranibizumab, supporting further development of the system.<sup>32</sup>

The pivotal phase 3 ARCHWAY trial evaluated the PDS refilled every 24 weeks versus monthly ranibizumab in previously treated nAMD. At one year, visual acuity outcomes were non-inferior between treatment arms, demonstrating that scheduled refill intervals of approximately six months could maintain functional stability in appropriately selected patients.<sup>33</sup> A representative clinical image demonstrating the Port Delivery System (PDS) implant structure and postoperative slit-lamp appearance is shown in Figure 6.



**Figure 6.** Port Delivery System (PDS) with ranibizumab: device structure and clinical appearance. (A) Schematic representation of the PDS implant, including the extracleral flange, septum, body, silicone coating, and release control element. (B–D) Representative postoperative slit-lamp photographs demonstrating implant positioning and subconjunctival appearance following implantation.

Abbreviation: PDS, port delivery system.

The clinical appeal of the PDS lies primarily in its potential to substantially reduce treatment frequency. However, unlike injection-based strategies, the system introduces a surgical component. Device-related complications, including conjunctival erosion, endophthalmitis, vitreous hemorrhage, and implant dislocation, were reported in clinical trials. Although procedural refinements and increased surgical experience have reduced complication rates, the requirement for implantation alters the risk-benefit profile compared with standard intravitreal therapy.<sup>32,33</sup>

In practice, the PDS may be most suitable for patients with stable disease control on ranibizumab who face significant injection burden or adherence challenges.<sup>33</sup> Careful patient selection, surgical technique, and continued OCT-based monitoring remain essential.

Sustained delivery does not eliminate the need for surveillance; rather, it shifts durability from repeated injections to continuous intraocular drug exposure.<sup>32,33</sup>

Within the broader durability landscape, the PDS represents a third conceptual strategy alongside dose intensification and pathway diversification. Whether long-term implant-based delivery provides superior sustainability compared with extended-interval injections remains an evolving question, and real-world evidence will ultimately clarify its position within routine retinal practice.

#### 4. GENE THERAPY APPROACHES

Gene-based approaches in neovascular AMD aim to shift therapy from repeated pharmacologic suppression toward sustained intraocular expression of anti-angiogenic proteins. Platforms such as RGX-314 and ADVM-022 utilize adeno-associated viral vectors to enable continuous production of anti-VEGF molecules following a single surgical or intravitreal administration.<sup>34,35</sup>

Early-phase studies have demonstrated dose-dependent transgene expression and a reduction in rescue injection frequency in selected cohorts. However, variability in expression levels, intraocular inflammation, vector-related immune responses, and long-term durability of protein production remain active areas of investigation. Unlike conventional anti-VEGF agents, gene therapy introduces surgical complexity and immunologic considerations that may influence patient selection and real-world applicability.

Although preliminary data are encouraging, gene therapy has yet to establish consistent, predictable long-term efficacy across diverse patient populations. Ongoing randomized trials and extended follow-up will determine whether these strategies can meaningfully reduce treatment burden without introducing new safety concerns.

#### 5. FUTURE DIRECTIONS

Despite substantial therapeutic advances, the management of neovascular age-related macular degeneration remains a paradigm of chronic disease suppression rather than definitive control. While anti-VEGF therapy has transformed visual prognosis, the cumulative burden of repeated treatment, variable durability, and heterogeneous patient response continue to define clinical reality. Future innovation will therefore be measured not solely by incremental gains in visual acuity, but by sustainable disease control with reduced intervention frequency.

Emerging strategies are increasingly converging on three principal axes: pharmacologic optimization, pathway diversification, and biologic re-engineering. High-dose formulations seek to intensify VEGF suppression, whereas dual-pathway inhibitors aim to stabilize vascular architecture beyond angiogenesis alone. Sustained delivery platforms attempt to decouple therapeutic efficacy from injection frequency, while gene-based approaches explore the possibility of continuous intraocular protein expression following a single intervention. Each strategy reflects a shift from short-term response metrics toward durability and system-level efficiency. However, long-term success will depend on more than molecular design. Personalized retreatment algorithms, improved imaging biomarkers, and deeper understanding of inflammatory and fibrotic pathways may refine patient selection and optimize therapeutic sequencing. The integration of real-world evidence with randomized trial data will also play a critical role in determining which innovations translate into durable clinical benefit across diverse patient populations. Ultimately, the future of nAMD management will depend not on suppressing angiogenesis more aggressively, but on achieving biologically durable, patient-tailored disease control within sustainable healthcare frameworks.

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