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How Next-Gen Therapies Will Reshape nAMD and DME Management

Introduction

There are currently multiple approved biologics and biosimilars indicated for the treatment of neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME), though real-world outcomes often fall short of clinical trial results.

Nearly half of nAMD and DME patients aren't well-managed, according to one-hundred-plus retinal specialists surveyed by Spherix. The burden of frequent intravitreal injections, payer-driven prescribing constraints, and persistent unmet needs, including more consistent, durable disease control across a broad patient population and reduced treatment burden, underscore the hurdles facing both patients and providers.

Breaking into this complex market is challenging. The landscape is crowded with established brands like Avastin (used off-label), Lucentis, Eylea, Vabysmo, and Eylea HD, all vying for share alongside emerging biosimilars and next-generation therapies in development, such as gene therapies, and sustained delivery platforms with tyrosine kinase inhibitors.

Payer influence is strong, and even highly effective new entrants must overcome entrenched prescribing habits, reimbursement hurdles, and the high bar set by current standards of care.

High ongoing patient flow into retina clinics and persistent, frequent retreatment needs will continue to sustain demand. Against this backdrop, payers, practice operations, and durability demands shape adoption.

This white paper leverages Spherix's proprietary data and market expertise to answer a critical question: What does it take for a new therapy to make a meaningful impact in nAMD and DME? We examine the current market size and dynamics, identify key weaknesses and unmet needs, and provide a detailed analysis of the late-stage pipeline, highlighting which agents are best positioned to address the evolving demands of retinal care.

Disease Background: nAMD and DME

Age-related macular degeneration (AMD) and diabetic macular edema (DME) are the leading causes of vision loss among older adults in the United States,[1,2] with significant implications for patient quality of life and healthcare resource utilization.

AMD affects over eighteen million Americans aged forty and older, with approximately 1.5 million progressing to late-stage, vision-threatening disease.[3] As AMD advances, some patients develop neovascular or "wet" AMD (nAMD), an advanced form characterized by choroidal-based abnormal blood vessel growth in the macula and rapid central vision loss. Without timely and sustained therapy, nAMD can result in irreversible vision impairment.

DME is a common complication of diabetic retinopathy (DR), affecting an estimated 746,000 adults in the U.S.[4] Chronic hyperglycemia leads to retinal blood vessel wall breakdown with leakage and swelling of the macula, blurring central vision. If untreated, it causes progressive vision loss that can be permanent. The risk of DME increases with longer diabetes duration, higher levels of DR, and suboptimal metabolic control.

nAMD and DME management is complicated by the need for frequent monitoring and intervention. While anti- anti-vascular endothelial growth factor (VEGF) therapies have transformed outcomes in clinical trials, real-world results are often less robust due to challenges with adherence, visit burden, and payer-imposed access barriers. There remains a clear need for therapies that offer greater efficacy and durability and reduced treatment burden, and are accessible to a broad patient population.

Market History: nAMD and DME

The mid-2000s saw the advent of first-generation intravitreal anti-VEGF agents. Off-label use of Avastin (bevacizumab) became widespread due to its cost-effectiveness, despite the lack of formal FDA approval for retinal indications.

Lucentis (ranibizumab) received FDA approval for nAMD in 2006 with the DME indication approved in 2012.[5] This was followed by Eylea (aflibercept) in 2011.[6] Both treatments set new standards for efficacy and safety in retinal disease management.

The anti-VEGF market has since become increasingly crowded, with multiple agents competing for share and driving innovation. Vabysmo (faricimab) and Eylea HD (aflibercept 8 mg) have emerged as leading options, offering improved durability with extended dosing intervals, and are now central to current treatment strategies.

Biosimilars have also entered the market, expanding lower-cost options for patients and payers. Ophthalmologists anticipate the top-ranked sources for Pavblu to be patients

switching from Avastin or Eylea (2 mg), as well as biologic-naive patients. If approved, Outlook Therapeutics' Lytenava (on-label bevacizumab) could further shift payer policies and reshape first-line, cost-based pathways.

These developments have created a crowded and highly competitive market, with established brands and new entrants continually raising the bar for efficacy, durability, and/or value.

Current State of the Market

The nAMD and DME markets remain concentrated around Regeneron and Genentech/Roche, with Eylea (2 mg), Eylea HD, Avastin, and Vabysmo anchoring current use.

Regeneron's portfolio of Eylea (2 mg) and Eylea HD and Genentech's Vabysmo are all ophthalmologists' top picks in AMD and DME if they were limited to one biologic to treat each condition. Regeneron's Eylea HD also earns strong satisfaction and efficacy scores from physicians, reflecting an emphasis on agents perceived to deliver better drying and/or longer dosing intervals. Eylea (2 mg) remains the most trusted option for biologic-naive patients, indicating that familiarity and predictability still matter in first-line choice. Vabysmo is most picked for its drying effect.

Physician preference is increasingly driven by durability with the ability to extend dosing intervals and drying efficacy, which may translate into better visually acuity outcomes in select patients. Vabysmo and Eylea HD are favored for their perceived ability to reduce treatment burden, while Eylea (2 mg) is often selected for its well-established strong safety and tolerability profile.

The Port Delivery System (PDS), marketed as Susvimo®, represents an FDA-approved sustained delivery platform for Lucentis, indicated for nAMD, DME, and DR. It is a surgically implanted intraocular reservoir device designed to provide continuous drug release, with office-based refills typically required every six months. Despite its potential to reduce treatment burden relative to frequent intravitreal injections, uptake in clinical practice has been extremely limited. This reflects both the surgical nature of the implant procedure and higher observed rates of certain adverse events compared to conventional, office-administered biologic injections.

Biosimilars are expanding lower-cost options, but disruption in the space overall is expected to be limited with an impact mainly on first-generation (e.g., Lucentis and Eylea) agent use.

Weaknesses of Current Treatment Options

Patient compliance is a key weakness for current treatments. While compliance is reportedly higher in nAMD (75% in a recent Spherix survey) than in DME (51%), the rate leaves ample opportunity for new competitors to improve on. Ophthalmologists also perceive that patient satisfaction with available treatments is mixed, again creating an opening for novel treatment options to break into the market.

Ophthalmologists identified better accessibility, improved efficacy, and optimized dosing as key unmet needs in nAMD treatment. In DME, extended dosing is a crucial unmet need.

Payer Influence on First-Choice Treatment

Payer dynamics amplify the burden on patients and clinics, with 84% of ophthalmologists surveyed noting they frequently/always or somewhat frequently need to utilize a different biologic because their first choice was denied.

Nearly 80% of respondents noted that they prescribe the agent that has the lowest threat of PA denials frequently/always or somewhat frequently.

There is a notable gap between the agents physicians would prefer to use and those they use most often, with physicians identifying higher initial denial risk for Eylea HD and Vabysmo relative to Eylea 2 mg (or biosimilar). While Vabysmo and Eylea HD are consistently top picks if ophthalmologists were to be limited to only one brand for nAMD or DME, the market share leaders remain Avastin and Eylea (2 mg) due to payer constraints.

Physicians further emphasize the need to maintain consistent outcomes in real-world settings where adherence is challenging, particularly in DME, which shows lower reported compliance than nAMD. There's also a need to reduce the risk associated with missed visits by enabling longer intervals between treatments.

Cost and access pressures remain pervasive and can drive suboptimal care. Most practices dedicate staff to prior authorizations, with Eylea HD and Vabysmo viewed as more prone to initial payer denial (vs. Eylea 2 mg or biosimilar).

A third of physicians report out-of-pocket costs remain high even after approval. Ophthalmologists estimate that 32% (nAMD) and 37% (DME) of patients receive suboptimal treatment due to insurance limitations with high patient out-of-pocket cost.

Pipeline Outlook in Retinal Vascular Disease

Current standard-of-care treatments for nAMD and DME have improved patient outcomes significantly. However, the necessity for frequent injections, often every four to eight weeks, presents a considerable burden on patients and healthcare systems alike.

Despite widespread adoption of anti-VEGF therapies for both conditions, there remains opportunity for new products to address unmet needs. While the majority of Phase 2 and 3 activity is concentrated in nAMD, several of these same technologies are also advancing in DME, and we have selected novel delivery platforms and gene therapies as the focal point for this white paper.

The following section highlights several emerging modalities, presented once but noted for their applicability to both nAMD and DME where relevant.

Sustained Delivery of Tyrosine Kinase Inhibitors (TKIs)

One emerging area of advancement is the development of tyrosine kinase inhibitors (TKIs) integrated into sustained delivery platforms, which represent a new class of therapies designed to prevent VEGF signaling through a distinct mechanism of action. TKI-based intravitreally injected bioerodible implants and suprachoroidal suspensions are currently being developed by several companies.

TKIs are positioned as maintenance phase sustained delivery therapies to alleviate several of the unmet needs that exist in the market. The reduction of injection frequency due to longer durability would alleviate treatment burden and improve overall adherence. However, unless TKIs are shown to be more efficacious than anti-VEGF options and/or offer substantial savings, causing payers to adjust their formularies, the retinal disease treatment algorithms would likely remain stable following the launch of these options. Competition for patients switching from early line choices Avastin and Eylea will be fierce, as longer-acting TKIs battle for share against longer-acting anti-VEGF options Vabysmo and Eylea HD.

Axpaxli (OTX-TKI) in Development by Ocular Therapeutix

Axpaxli is an intravitreal bioerodible hydrogel fiber implant delivering axitinib. The product demonstrated an 89% reduction in treatment burden in Phase 1 trials with sustained drug activity beyond six months. It has the potential to reduce the need for additional anti-VEGF injections. Ongoing Phase 3 trials (SOL-1 and SOL-R) are measuring its non-inferiority and possible superiority to existing standards of care.

According to Spherix's recent research, ophthalmologists view the product as offering a moderate enhancement (6.4 on a 10-point scale) to existing therapies and think it will have a definite role in their practice if approved.

Duravyu (EYP-1901) in Development by EyePoint Pharmaceuticals

Another TKI-based therapy utilizes vorolanib in an intravitreal biodegradable polyvinyl alcohol implant. Phase 1 studies reported a 73% reduction in injection frequency after twelve months of treatment, with sustained control of retinal fluid and well-maintained visual acuity. The product has ongoing Phase 2 DAVIO2 and Phase 3 LUCIA pivotal trials, which are anticipated to further validate these findings.

According to Spherix's recent research, ophthalmologists view Duravyu as similar to Axpaxli in terms of enhancement to existing therapies, but it is viewed as likely having a leading role in their practice among 20% of survey respondents (compared to 11% for Axpaxli).

CLS-AX by Clearside Biomedical

A third TKI-based therapy, CLS-AX, also utilizes axitinib delivered via a suprachoroidal suspension with Clearside's FDA-approved suprachoroidal space microinjector—a method that enables targeted delivery and minimizes systemic exposure. The Phase 2b ODYSSEY trial demonstrated an 84% reduction in treatment burden, underscoring the effectiveness of this minimally invasive, office-based approach. A Phase 3 trial has not yet been announced.

Long-Acting and Bispecific Antibodies

Kodiak Sciences is developing a portfolio of long-acting antibodies to treat retinal disorders.

Tarcocimab Tedromer (KSI-301)

Tarcocimab is an anti-VEGF antibody conjugated to a biopolymer to extend the agent's half-life. It is formulated as a mix of conjugated and unconjugated antibody, intended to deliver immediate potency via the unconjugated and extended durability with the conjugated portion. Initially, mixed Phase 3 results of tarcocimab led Kodiak to discontinue development of the agent; however, they modified the formulation of tarcocimab (reducing the amount of biopolymer) and initiated new Phase 3 trials in nAMD and DME with additional dosing intervals allowed. Ophthalmologists acknowledge the advance offered

by tarcocimab over existing options and in DME in particular are enthusiastic about the agent's potential.

Tabirafusp Tedromer (KSI-501)

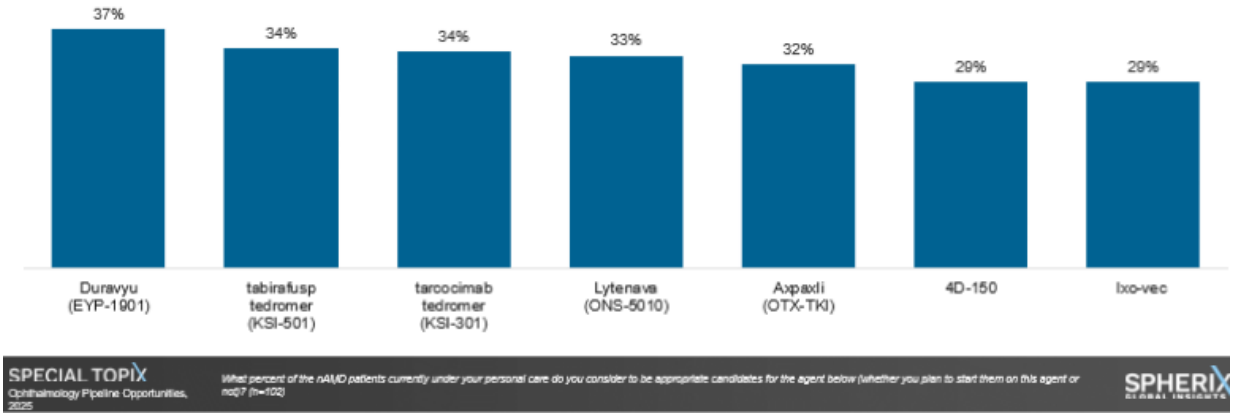
Kodiak is also developing a bispecific anti-IL-6/VEGF trap conjugated with a biopolymer intended to offer higher efficacy and higher durability. The agent would target both retinal inflammation via IL-6 inhibition and vascular permeability via the VEGF trap. The agent is currently being tested only in nAMD, and ophthalmologists have low familiarity with the agent. However, should it deliver on enhanced efficacy and durability, it could carve a niche in the market.

Gene Therapies

Looking to potentially disrupt the treatment landscape are several gene therapies in development. Gene therapy has emerged as a compelling approach that seeks to alter the disease course through sustained intraocular production of anti-VEGF proteins.

Gene therapies will likely be held in reserve as a later-line, maintenance phase treatment option, with ophthalmologists indicating that fewer than 30% of patients may be candidates for these treatments. Further, Spherix's research indicate that 72% of ophthalmologists characterize themselves as "wait and see" types with regard to new products, preferring to hear about their colleagues' experiences prior to prescribing for the first time.

Ophthalmologists see more patients as appropriate candidates for established VEGF-targeting therapies in nAMD, while fewer are viewed as suitable for newer approaches like gene therapy, which are met with cautious interest.



Despite being potentially curative, gene therapies may have a longer time horizon to expansive utilization than other emerging pipeline products and may ultimately see constrained use to a subset of patients.

Surabgene lomparvovec (ABBV-RGX-314, AbbVie/REGENXBIO)

Surabgene lomparvovec, or sura-vec, is delivered via subretinal or suprachoroidal injection using an AAV8 vector to deliver a gene encoding for an anti-VEGF monoclonal antibody fragment akin to ranibizumab. The therapy has demonstrated stable visual acuity outcomes over a four-year period in long-term follow-up studies. The treatment aims to reduce or even eliminate the need for ongoing injections, providing a potentially one-time treatment. Development is currently in nAMD (subretinal Phase 3 and suprachoroidal Phase 2) and DR (suprachoroidal Phase 2).

Spherix research indicates ophthalmologists view sura-vec as the most substantial advancement among all pipeline agents in nAMD (7.7 on a 10-point scale). However, results are mixed on where the product may be positioned, with 43% of respondents in the survey indicating a limited role, suggesting that the treatment will be reserved for select patients rather than broadly used.

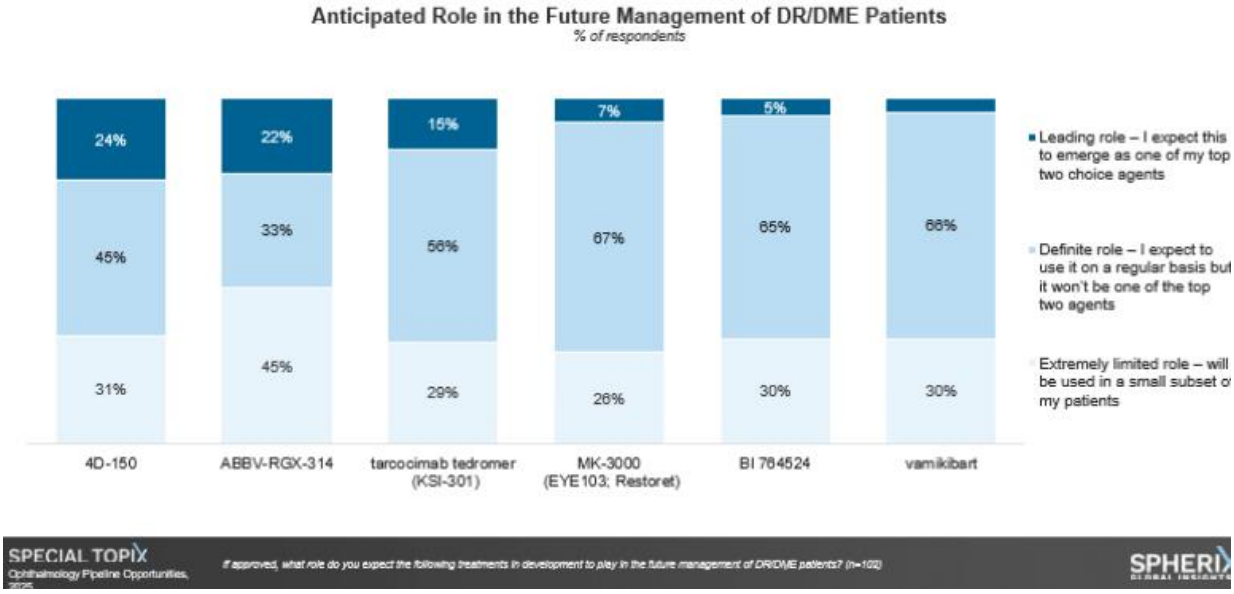
Ixo-vec (ixoberogene soroparvovec, ADVM-022, Adverum Biotechnologies)

Ixo-vec delivers aflibercept via an intravitreal AAV.7m8 vector. Early Phase 1 and 2 trial data suggest very good, sustained efficacy (up to four years), and physicians view it as an important potential late-line option, but there remain some concerns for possible long-term topical steroid use to suppress intraocular inflammation.

4D-150 (4D Molecular Therapeutics)

Molecular Theraputics' 4D-150 utilizes a dual-transgene vector encoding both aflibercept and a VEGF-C RNAi. It represents a next-generation gene therapy platform engineered for long-term, intravitreal control of neovascular and diabetic retinal diseases. This dual-mechanism approach of delivering a gene for aflibercept and for a VEGF-C targeting RNAi is tailored to address the complex, multifactorial drivers of diabetic macular edema, potentially improving durability and outcomes compared to existing agents. Physicians rate 4D-150 as the most innovative pipeline product for DME and anticipate it will have a leading role in treating the condition, according to Spherix research.

Ophthalmologists anticipate a stronger role for 4D-150 in managing DR with DME patients, with nearly one-quarter expecting it to become a top-choice agent, compared to ABBV-RGX-314, which is seen as having more limited use. KSI-301 is expected to have a consistent, though more modest, place in practice.



Expectations of Future Landscape

With so many treatment options in development that offer novel strategies to treat nAMD and DME, it is unsurprising that nearly three-quarters of ophthalmologists believe the treatment landscape of nAMD and DME will look very different five years from now. However, success for pipeline therapies will hinge not just on the innovations they offer but their ability to navigate the strict payer landscape to displace long-standing treatment paradigms.

Developers must be prepared to demonstrate not just clinically meaningful benefits for patients but also financial benefits to the healthcare system in order to win out against both entrenched and novel competition.

A therapy that can offer proof that overall costs of care are reduced while patients' clinical outcomes and quality of life are meaningfully improved, is the kind of treatment that will lead the next era of retinal diseases.

Connect with Spherix to gain a deeper understanding of market dynamics for DME and nAMD. Discover how our expertise can empower your strategic decisions in retinal care.

References

1. National Eye Institute. Age-related macular degeneration (AMD). National Institutes of Health; [updated 2021 Jun 22; cited 2025 Sep 25]. Available from: https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/age-related-macular-degeneration.

2. Prevent Blindness. Diabetic macular edema (DME). [cited 2025 Sep 25]. Available from: https://preventblindness.org/diabetic-macular-edema-dme.

3. Rein DB, Wittenborn JS, Burke-Conte Z, Gulia R, Robalik T, Ehrlich JR, Lundeen EA, Flaxman AD. Prevalence of age-related macular degeneration in the US in 2019. JAMA Opthamol. 2022 Nov 3; 140(12):1202-1208. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC9634594/.

4. Varma R, Bressler NM, Doan QV, Gleeson M, Danese M, Bower JK, Selvin E, Dolan C, Fine J, Colman S, Turpcu A. Prevalence of and risk factors for diabetic macular edema in the United States. JAMA Opthamol. 2015 Sep 21. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4576994/.

5. Ophthalmology Times. FDA approves ranibizumab injection, Lucentis. 2012 Aug 10. Available from: https://www.ophthalmologytimes.com/view/fda-approves-ranibizumab-injection-lucentis.

6. Stewart J. Eylea HD FDA approval history. Drugs.com; [updated 2023 Aug 22; cited 2025 Sep 25]. Available from: https://www.drugs.com/history/eylea-hd.html.