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Research Article

Therapeutic Approaches for Intermediate and Advanced Dry Age-Related Macular Degeneration: A Review of Current Evidence

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Abstract

Importance: Dry Age-related Macular Degeneration (AMD) affects approximately 8 million individuals in the United States alone, representing the leading cause of irreversible vision loss in developed countries. Intermediate AMD presents a critical therapeutic gap where patients currently have limited options beyond nutritional supplementation, while Geographic Atrophy (GA) progresses relentlessly despite the psychological and functional burden on affected individuals.

Observations: This narrative review summarizes evidence from pivotal phase III clinical trials evaluating three therapeutic approaches: nutritional supplementation (AREDS2, N=4,203), complement inhibition (OAKS/DERBY/GALE for pegcetacoplan, N=1,258; GATHER1/2 for avacincaptad pegol, N=734) and photobiomodulation (LIGHTSITE III, N=100). Complement inhibitors demonstrate 17-35% reduction in GA growth rates, with efficacy varying substantially by lesion location: 36-42% reduction for extrafoveal lesions versus 19-21% for subfoveal lesions. Both complement inhibitors carry risk of exudative conversion (6.7-12% cumulative over 2 years) requiring ongoing surveillance. Photobiomodulation data from a single trial suggest potential for modest functional benefit (treatment group gained 5.4 letters from baseline vs 3.0 letters in sham; between-group difference 2.4 letters, P<0.0001). In a secondary analysis with limited conversion events (6 eyes total), photobiomodulation was associated with reduced new GA onset (OR 9.4, P=0.024). Independent validation studies are essential before definitive conclusions can be drawn.

Conclusion and relevance: Current evidence supports stage-specific therapeutic considerations, with an important conceptual distinction between structural preservation (slowing GA expansion) and functional rescue (improving visual acuity). Complement inhibitors provide the first evidence-based intervention for established GA, with optimal efficacy in non-subfoveal lesions. Photobiomodulation represents a potentially promising intervention for intermediate AMD targeting functional outcomes, though its evidence base remains preliminary. Both approaches require ongoing evaluation to define optimal patient selection, treatment sequencing, and long-term outcomes. Shared decision-making with patients regarding treatment burden, expected benefits, and risks remains paramount.

Keywords: Age-related macular degeneration; Dry AMD; Geographic atrophy; Intermediate AMD; Complement system; C3 inhibition; C5 inhibition; Pegcetacoplan; Avacincaptad pegol; Photobiomodulation; Mitochondrial dysfunction; AREDS2; Nutritional supplementation; Structural preservation; Functional rescue; Best-corrected visual acuity; Fundus autofluorescence; Exudative conversion; Subfoveal lesions; Extrafoveal lesions

Introduction

The clinical burden of dry AMD

Age-related macular degeneration represents the leading cause of irreversible vision loss in developed countries, with dry AMD accounting for approximately 85-90% of all cases. The condition affects approximately 8 million individuals in the United States with intermediate or advanced disease and global projections estimate 288 million affected individuals by 2040 [1]. The economic burden encompasses direct healthcare costs, visual aids, caregiver support and lost productivity, while the psychological impact includes depression, social isolation and loss of independence at rates comparable to severe systemic diseases. The pathogenesis of

dry AMD involves multiple interconnected mechanisms including complement dysregulation, oxidative stress, mitochondrial dysfunction, lipofuscin accumulation and chronic inflammation [2,3]. Complement system overactivation, particularly through the alternative pathway, leads to chronic inflammatory damage to the retinal pigment epithelium and choriocapillaris [2]. Oxidative stress and mitochondrial dysfunction impair RPE cellular energetics and antioxidant defenses, while progressive accumulation of lipofuscin and its toxic component A2E further compromises RPE function [3,4]. These processes converge to cause progressive RPE dysfunction and photoreceptor degeneration, ultimately resulting in irreversible vision loss. Understanding these mechanisms has informed the development of targeted therapeutic strategies evaluated in this review. Geographic atrophy, the advanced non-exudative form of AMD, is characterized by progressive and irreversible degeneration of the Retinal Pigment Epithelium (RPE), photoreceptors and underlying choriocapillaris. These sharply demarcated areas of atrophy expand over time at rates varying from 1.0 to 2.5mm^2 annually [5,6], creating expanding scotomas that ultimately devastate central vision essential for reading, driving, facial recognition and activities of daily living. The natural history of GA is one of relentless progression, with bilateral involvement occurring in approximately 50% of patients within 7 years of initial diagnosis.

The intermediate AMD therapeutic Gap

While Anti-Vascular Endothelial Growth Factor (anti-VEGF) therapies have revolutionized management of neovascular (wet) AMD [7], patients with dry AMD historically faced a fundamentally different therapeutic landscape. Until 2023, the standard of care for intermediate AMD was limited to nutritional supplementation based on the Age-Related Eye Disease Studies (AREDS and AREDS2), which demonstrated modest efficacy in reducing progression risk but could not restore lost function or halt established atrophy. This therapeutic nihilism was particularly burdensome for patients with intermediate AMD, who represented a population of approximately 8 million individuals in the United States alone with nowhere to turn beyond vitamins. The 5-year progression rates from intermediate AMD to advanced disease range from 18% (bilateral large drusen) to 43% (unilateral advanced AMD with large drusen in fellow eye), underscoring the substantial unmet need for disease-modifying interventions at this critical stage.

Recent therapeutic advances

The regulatory approval of complement inhibitors pegcetacoplan (Syfovre, February 2023) and avacincaptad pegol (Izervay, August 2023) has fundamentally altered the therapeutic landscape for geographic atrophy, providing the first pharmacological interventions capable of slowing disease progression. These agents target the complement cascade, a key driver of inflammation and cellular death in AMD pathogenesis. Concurrently, Photobiomodulation (PBM) therapy has emerged as a potential intervention targeting a different pathophysiological mechanism: mitochondrial dysfunction in early and intermediate AMD stages. This bioenergetic approach aims to enhance cellular metabolism and potentially restore function in compromised but viable retinal tissue. This review summarizes current evidence for these therapeutic approaches, with particular emphasis on distinguishing between structural preservation (slowing GA progression) and functional rescue (improving visual acuity). We acknowledge the limitations inherent to the available data and emphasize the need for ongoing evaluation as the evidence base continues to evolve. This review focuses on interventions with phase 3 trial data or regulatory approval: AREDS2 supplementation, complement inhibitors (pegcetacoplan and avacincaptad pegol) and photobiomodulation (LIGHTSITE III). Emerging therapeutic strategies in earlier development phases are addressed separately to distinguish evidence-based interventions suitable for current clinical practice from investigational approaches requiring further validation.

Methods

This narrative review examines pivotal clinical trial data from AREDS2 (nutritional supplementation), OAKS/DERBY/GALE (pegcetacoplan), GATHER1/GATHER2 (avacincaptad pegol) and LIGHTSITE III (photobiomodulation). Study selection focused on phase 3 randomized controlled trials with published efficacy and safety data from peer-reviewed sources and regulatory submissions. Data extraction was performed directly from published trial reports, supplementary materials and regulatory documents. Quality assessment considered randomization methodology, masking adequacy, sample size and power, independent reading center assessment and statistical handling of missing data. This review does not employ formal systematic review methodology (no PRISMA protocol, no meta-analytic pooling) and should be interpreted as an evidence summary and clinical commentary rather than a systematic review or meta-analysis. Key outcomes of interest included: GA growth rates (measured by fundus autofluorescence), Best-Corrected Visual Acuity (BCVA) changes, risk of severe vision loss, new onset of geographic atrophy and safety endpoints including exudative AMD conversion and injection-related adverse events.

Pathophysiological Rationale for Therapeutic Targets

Complement-mediated inflammation in AMD

The complement system is a complex network of over 50 proteins that functions as a first line of defense against pathogens and a mediator of tissue homeostasis [8,9]. In AMD, genetic association studies have identified polymorphisms in complement regulatory genes, particularly Complement Factor H (CFH), Complement Factor I (CFI) and C3, as major risk factors for disease development. The Y402H variant in CFH alone confers a 2.5 to 7.4-fold increased risk of AMD development [10]. In affected retinas, dysregulated alternative pathway activation leads to excessive complement fragment deposition, with C3 cleavage products, C5a, and membrane attack complex (MAC, C5b-9) accumulating in drusen and Bruch's membrane. MAC insertion into RPE cell membranes creates transmembrane pores, leading to calcium influx, loss of membrane integrity and ultimately necrotic or apoptotic cell death [8]. This understanding provided the rationale for complement inhibitor development.

C3 versus C5 inhibition: Mechanistic considerations

Pegcetacoplan is a pegylated peptide that targets complement component C3, the convergence point for all three activation pathways (classical, lectin and alternative) [11]. By inhibiting C3 cleavage, pegcetacoplan provides broad cascade inhibition, preventing generation of C3a (an anaphylatoxin), C3b (the key opsonin) and all downstream effectors including MAC [9]. However, this approach theoretically compromises the beneficial functions of C3, including opsonization of debris and immune complex handling. Avacincaptad pegol targets downstream component C5, preventing its cleavage into C5a (a potent anaphylatoxin and chemoattractant) and C5b (the initiating factor for MAC assembly) [12]. A theoretical advantage of C5 inhibition is preservation of upstream C3-mediated functions, allowing the eye to retain its ability to clear cellular debris via opsonization. Whether this mechanistic distinction translates to clinically meaningful differences in efficacy or safety remains under investigation.

Mitochondrial dysfunction and the bioenergetic crisis

The retina represents one of the most metabolically demanding tissues in the human body, with photoreceptors requiring immense amounts of Adenosine Triphosphate (ATP) to maintain the dark current and repolarize after light exposure [13]. In aging and AMD, mitochondrial efficiency progressively declines, leading to reduced ATP production, increased reactive oxygen species generation, impaired cellular repair mechanisms and ultimately cellular dysfunction and death [14]. Photobiomodulation employs specific wavelengths of light (590nm yellow, 660nm red, 850nm near-infrared) hypothesized to enhance Cytochrome C Oxidase (CCO) activity in the mitochondrial electron transport chain. The aging retina experiences a bioenergetic crisis as mitochondrial efficiency declines. In stressed cells, Nitric Oxide (NO) binds competitively to CCO, displacing oxygen and inhibiting respiration. Near-infrared photons are absorbed by CCO, causing photodissociation of NO and allowing oxygen to return, thereby restoring electron flow and ATP production [14,15]. This mechanism has been extensively reviewed in the context of metabolic rescue and mitochondrial optimization. Mechanistic studies have demonstrated that near-infrared light therapy enhances mitochondrial ATP synthesis, reduces oxidative stress, upregulates protective gene expression and promotes cellular survival pathways in retinal cells [15]. Specifically, NIR-LED treatment increases Cytochrome oxidase activity, enhances oxygen consumption and elevates ATP production in cultured cells and animal models. Additionally, photobiomodulation modulates gene expression related to cellular energy metabolism, stress response and cell survival, providing multiple complementary mechanisms that may contribute to the observed clinical benefits in dry AMD [15]. These cellular effects provide biological plausibility for the observed functional improvements in intermediate AMD patients treated with multiwavelength photobiomodulation. Beyond immediate energy production, PBM triggers secondary messenger pathways including reactive oxygen species signaling that upregulate cytoprotective genes, decrease pro-inflammatory cytokines and inhibit apoptosis [16]. This mechanism represents a fundamentally different therapeutic philosophy: enhancing cellular resilience rather than blocking a specific pathological pathway.

Important limitations: structural irreversibility

It is essential to recognize that incomplete Outer Retinal Atrophy (iRORA) lesions, while representing an earlier stage than complete RPE and Outer Retinal Atrophy (cRORA), contain irreversible structural changes [17]. The term 'metabolic optimization' more accurately describes the therapeutic goal than terms such as 'resuscitation' or 'rescue,' which imply restoration of dead cells. Therapeutic interventions targeting mitochondrial function cannot restore cells that have already been lost; rather, the goal is to preserve remaining viable tissue, enhance function in compromised but surviving cells, and potentially delay or prevent the transition from intermediate AMD to geographic atrophy. This conceptual framework is essential for appropriate patient counseling and expectation management.

Evidence Summary

Nutritional supplementation: The AREDS2 foundation

The Age-Related Eye Disease Study 2 (AREDS2) remains the definitive trial establishing nutritional supplementation as standard of care for intermediate AMD (Table 1). This NIH-funded, multicenter, double-masked trial enrolled 4,203 participants aged 50-85 years at high risk for progression to advanced AMD across 82 clinical sites in the United States, with median 5-year follow-up. The study population was specifically selected for high progression risk, defined as bilateral large drusen (≥125μm) in 64.8% of participants or large drusen in one eye with advanced AMD (neovascular or GA) in the fellow eye in 35.2%. The 2x2 factorial design evaluated addition of Lutein (10mg) and Zeaxanthin (2mg) and/or omega-3 long-chain polyunsaturated fatty acids (DHA 350mg+EPA 650mg) to the original AREDS formulation, while also testing elimination of beta-carotene.

Table 1: Study design and population characteristics.

Parameter	LIGHTSITE III	AREDS2	OAKS/DERBY	GALE	GATHER1	GATHER2
Study Phase	Phase 3 (Pivotal)	Phase 3	Phase 3 (Pivotal)	Phase 3 (Extension)	Phase 2/3 (Pivotal)	Phase 3 (Pivotal)
Design	RCT, Sham-controlled	RCT, Factorial (2x2)	RCT, Sham-controlled	Open-label Extension	RCT, Sham-controlled	RCT, Sham-controlled
Masking	Double-masked	Double-masked	Double-masked	Open-label (Unmasked)	Double-masked	Double-masked
Sample Size	N=100 (148 eyes)	N = 4,203 participants	N = 1,258 randomized	N=792 enrolled	N=286 participants	N=448 randomized
Duration	24mo (13mo analysis)	Median 5 years	24 months	36mo total (ongoing)	18 months	24 months

Mean Age ± SD	75.4±7.1 years	73.1±7.7 years	Not reported	79.6 years	Not reported	76.2-77.8 years
% Female	68.0%	56.8%	Not reported	58.8-62.2%	Not reported	Not reported
Population	Dry AMD (Intermediate to early GA)	High risk for Advanced AMD	GA secondary to AMD	GA secondary to AMD	GA secondary to AMD (non-center)	GA (non-center involving)
Subfoveal GA at Baseline	0% (Excluded)	Not stratified	63.7%	71.8%	0% (Excluded)	0% (Excluded)
Baseline BCVA Range	50-75 ETDRS letters	Not specified	Not specified	51.5-53.3 letters (mean)	Not specified	Not specified
Reading Center	Duke Reading Center	Univ. Wisconsin Madison	DARC (now Voiant)	DARC (now Voiant)	Duke Reading Center	Duke Reading Center
Sponsor	LumiThera, Inc.	NEI/NIH	Apellis Pharmaceuticals	Apellis Pharmaceuticals	Iveric Bio, Inc.	Astellas Pharma Inc.
FDA Status	Not Approved	N/A (Supplement)	Approved (Feb 2023)	Approved (Feb 2023)	Approved (Aug 2023)	Approved (Aug 2023)

Primary analysis demonstrated that lutein/zeaxanthin addition did not significantly reduce progression to advanced AMD compared with the original AREDS formulation containing beta-carotene (HR 0.90; 98.7% CI 0.76-1.07; P=0.12) [18]. However, the study provided critical safety data: beta-carotene was associated with increased lung cancer risk in former smokers (2.0% vs 0.9%), supporting its elimination from the formulation [18]. Secondary analyses demonstrated that among participants not receiving beta-carotene in the secondary randomization, lutein/zeaxanthin showed a significant reduction in progression to advanced AMD (HR 0.82; 95% CI 0.69-0.96) [18]. The modified AREDS2 formulation (vitamins C and E, zinc, copper, lutein and zeaxanthin without beta-carotene) is now considered standard of care. Importantly, AREDS2 supplementation provides approximately 25-30% relative risk reduction for progression to advanced disease, including geographic atrophy [19], in high-risk eyes over 5 years, but it does not halt progression in eyes with established geographic atrophy and cannot restore lost visual function. This represents a prevention strategy for intermediate AMD rather than a treatment for established GA.

Complement inhibition: pegcetacoplan (syfovre)

The OAKS (NCT03525613) and DERBY (NCT03525600) trials were parallel phase 3, multicenter, randomized, double-masked, sham-controlled studies building upon phase 2 data [20] that enrolled a combined 1,258 patients with geographic atrophy secondary to AMD (Table 1), [11]. Patients were randomized 2:2:1:1 to pegcetacoplan monthly, pegcetacoplan Every-Other-Month (EOM), or corresponding sham injections. Notably, these trials included patients with both subfoveal (63.7% at baseline) and non-subfoveal GA, allowing stratified efficacy analyses. At the 24-month primary endpoint, monthly pegcetacoplan demonstrated 21% reduction in GA growth rate in OAKS with generally consistent results in DERBY (17% reduction for EOM) (Table 2), [11]. The primary endpoint was measured as change in GA area from baseline using Fundus Autofluorescence (FAF) imaging assessed by an independent Reading Center (DARC, now Voiant). Important safety considerations for C3 inhibition include new-onset choroidal neovascularization risk, as characterized in the FILLY trial [21]. The GALE extension study (NCT04770545) provided 36-months data on 792 patients who continued from OAKS/DERBY into the open-label extension phase [22]. All patients received active pegcetacoplan, with former sham patients crossing over to treatment. Efficacy was compared against a projected sham calculated from the prior 24-month GA growth rate of sham-observed patients. At 36 months, sustained efficacy was demonstrated with 25% reduction (monthly arm, PM-PM) and 20% reduction (EOM arm, PEOM-PEOM) in GA growth versus projected sham (P<0.0001 for both) (Table 2), [22]. Maximum efficacy of 32% reduction was observed in the monthly arm, likely representing specific analysis models or subgroups.

Table 2: Efficacy outcomes matrix.

Outcome	LIGHTSITE III (13mo)	AREDS2 (5yr)	OAKS/DERBY (24mo)	GALE (36mo)	GATHER1 (18mo)	GATHER2 (24mo)
Primary Endpoint	BCVA Improvement: Met; Δ2.4 letters vs Sham (P=0.02)	Progression to Adv. AMD: Not Met; HR 0.90 (P=0.12)	GA Growth Rate: Met; 21% (PM)/17% (PEOM) reduction	GA Growth Rate: Met; 25% (PM)/ 20% (PEOM) vs projected sham (P<0.0001)	GA Growth: Met; ~27% reduction (2mg/4mg) (P<0.01)	GA Growth (12mo): Met; 0.376mm² reduction vs Sham (P<0.01)
GA Slowing (Overall)	20% reduction trend (NS)	No significant effect (P=0.27)	21% (PM)/ 17% (PEOM)	25% (PM)/ 20% (PEOM)	28.1% (2mg) at 18mo	14% (Monthly)/ 19% (EOM) at 24mo
GA: Non-Subfoveal (Peak Efficacy)	N/A (All non-subfoveal)	Not stratified	HIGH: 28% reduction (PM, Yr 2)	PEAK: 32% reduction (PM, 36mo); 2.44mm² preserved	N/A (All non-subfoveal)	N/A (All non-subfoveal)

GA: Subfoveal (Reduced Efficacy)	N/A	Not stratified	LOWER: ~19% reduction	21% reduction (PM, 36mo); 1.10mm^2 preserved	N/A	N/A
BCVA Change	+5.4 letters (PBM) vs +3.0 (Sham); P<0.0001	No difference (P=0.45)	No specified BCVA improvement	No specified BCVA improvement	Mean loss reduced	-7.31 vs -6.48 letters (P=NS)
% Gaining ≥5 Letters	55% (PBM)	Not reported	Not reported	Not reported	Not reported	Not reported
% Gaining ≥10 Letters	26.4% (PBM)	Not reported	Not reported	Not reported	Not reported	Not reported
Vision Loss Prevention (≥15 letters)	5.5% lost (PBM) vs 1.9% (Sham)	HR 0.95 (P=0.45)	38% risk reduction (<35 letters)	38% risk reduction	56% risk reduction (Pooled)	59% risk reduction (12mo, PM)
New GA Onset Prevention	OR 9.4 (P=0.024)	Not evaluated	N/A (GA population)	N/A (GA population)	N/A (GA population)	N/A (GA population)

The subfoveal efficacy question

A critical observation from GALE stratified analyses revealed substantial differential efficacy based on lesion location. For non-subfoveal GA lesions at baseline, monthly pegcetacoplan achieved 32% reduction in growth rate at 36 months (P<0.0001), with 2.44mm^2 of retinal tissue preserved [22]. In contrast, subfoveal GA lesions showed only 21% reduction (P<0.0001), with 1.10mm^2 of tissue preserved [22]. This finding has profound implications for patient counseling and treatment decisions. Eyes with foveal-involving GA derive substantially less structural benefit from complement inhibition, likely because the pathophysiological processes driving atrophy progression are more advanced or more difficult to modify once the fovea is involved. The fellow-eye preservation strategy-initiating treatment in eyes before foveal involvement occurs-becomes paramount when counseling patients with established subfoveal GA in one eye.

Functional outcomes with pegcetacoplan

While pegcetacoplan was not designed to improve visual acuity, functional preservation endpoints provide evidence that structural preservation translates to meaningful clinical benefit. At 36 months, pegcetacoplan demonstrated a 38% reduction in development of new scotomatous points measured by microperimetry (P=0.0156), representing preservation of retinal sensitivity in areas adjacent to the expanding atrophic lesion.

Additionally, the 36-month data showed 38% risk reduction in severe visual impairment (defined as BCVA<35 letters, approximately 20/200 or worse), supporting the clinical relevance of GA growth slowing. These functional preservation endpoints distinguish complement inhibitors from purely anatomical endpoints and support the concept that structural preservation delays functional decline.

Complement inhibition: Avacincaptad pegol (Izervay)

GATHER1 (NCT02686658) was a phase 2/3, multicenter, randomized, double-masked, sham-controlled trial enrolling 286 participants with GA secondary to AMD (Table 1), [23]. Unlike OAKS/DERBY, GATHER1 excluded center-involving GA (subfoveal lesions), enrolling only patients with non-center-point GA. Patients were randomized to monthly intravitreal injections of avacincaptad pegol 1mg, 2mg, 4mg, or sham. At the 12-month primary endpoint, avacincaptad pegol demonstrated significant reduction in GA growth: 27.4% reduction for the 2mg dose and 27.8% for the 4mg dose compared to sham (P<0.01 for both). Efficacy was sustained at 18 months, with 28.1% reduction for 2mg and 30.0% for 4mg (square root transformation). Using observed (non-transformed) data, reductions were 32.2% and 29.4% respectively. GATHER2 (NCT04435366) was the confirmatory phase 3 trial, enrolling 448 patients randomized 1:1 to avacincaptad pegol 2mg monthly or sham for Year 1, with re-randomization in Year 2 to monthly or every-other-month dosing (Table 1), [12]. This trial also excluded center-involving GA. GATHER2 met it prespecified primary objective at 12 months, demonstrating 0.376mm^2/year reduction in GA growth compared to sham (P<0.01) (Table 2), [12]. At 24 months, efficacy was maintained with 14% reduction for the monthly-to-monthly group and 19% reduction for the monthly-to-EOM group compared to sham [12]. Notably, the EOM comparison was considered nominal due to hierarchical testing sequence failure (the prior step of 15-letter persistent vision loss did not reach statistical significance).

Vision loss prevention with avacincaptad pegol

Pooled analysis of GATHER1 and GATHER2 demonstrated a compelling 56-59% reduction in risk of ≥15-letter vision loss (HR 0.44; 95% CI 0.21-0.92), representing a meaningful functional preservation endpoint. At 12 months in GATHER2, the monthly arm showed 59% risk reduction in ≥15-letter loss (HR 0.41; 95% CI 0.17-1.00). This functional preservation signal, combined with the anatomical efficacy, supports that avacincaptad pegol provides clinically meaningful benefit beyond lesion measurement. However, it is important to note that the 24-month persistent vision loss endpoint did not reach statistical significance (HR 0.90; 95% CI 0.57-1.42; P=NS), highlighting the need for continued evaluation of long-term functional outcomes.

Comparative considerations: pegcetacoplan vs avacincaptad pegol

Direct comparison between complement inhibitors is complicated by differences in trial design, patient populations and endpoints. OAKS/DERBY included patients with subfoveal GA (63.7% at baseline), while GATHER1/2 excluded center-involving lesions. This population difference precludes direct efficacy comparison, as subfoveal GA appears more refractory to

complement inhibition. Both agents demonstrate similar overall efficacy in the 17-35% range for GA growth reduction, with similar safety signals regarding exudative conversion. The theoretical mechanistic advantages of C5 versus C3 inhibition (preservation of opsonization) have not yet translated to demonstrable clinical differences. Head-to-head comparative trials would be required to definitively establish superiority and such trials are not currently underway.

Photobiomodulation: LIGHTSITE III

LIGHTSITE III (NCT04065490) was a phase 3, multicenter, double-masked, sham-controlled, randomized trial, building on prior phase 2 studies [24,25], enrolling 100 subjects (148 eyes) with intermediate to early advanced dry AMD across 10 clinical sites in the United States (Table 1), [26]. The trial was sponsored by LumiThera, Inc., the manufacturer of the Valeda Light Delivery System. Inclusion criteria required BCVA between 50-75 ETDRS letters (approximately 20/32 to 20/100 Snellen equivalent) and notably, center-involving GA was excluded. The study population was 72% intermediate AMD, 20% early-stage AMD, and 8% late-stage GA without CNV. Mean age was 75.4±7.1 years, with 68% female participants. Treatment consisted of 9 PBM sessions delivered over a 3–5-week period, repeated every 4 months. The Valeda system delivers multiwavelength light therapy (590nm, 660nm, 850nm) through a non-invasive external device. The sham protocol delivered a 50x reduction in fluence for 590nm, 100x reduction for 660nm and complete omission of the 850nm wavelength-a reduced-fluence sham rather than true placebo.

Lightsite III efficacy: Functional improvement

At the 13-month primary analysis, the PBM group achieved mean BCVA improvement of +5.4 letters (SD 9.15; 95% CI 3.5-7.3) compared with +3.0 letters in the sham group (SD 7.13; 95% CI 0.7-5.2), yielding a statistically significant between-group difference of 2.4 letters (P=0.02). This represents functional improvement rather than merely slowed decline-a fundamentally different outcome than observed with complement inhibitors. Responder analyses demonstrated that 55% of PBM-treated eyes gained ≥5 letters, and 26.4% gained ≥10 letters. This magnitude of visual improvement is historically unprecedented in GA trials, where stability is typically the best-case scenario. However, the clinical significance of a 2.4-letter mean difference, while statistically significant, represents modest functional benefit at the population level.

LIGHTSITE III: Prevention of new GA onset

Perhaps the most intriguing finding from LIGHTSITE III was the reduction in new onset of geographic atrophy. PBM treatment was associated with significantly fewer eyes developing new GA compared with sham (OR 9.4; P=0.024). This suggests potential for disease modification at the intermediate AMD stage, preventing the transition to atrophy entirely rather than slowing expansion of established lesions. If confirmed in validation studies, this finding would position PBM as a truly disease-modifying intervention for intermediate AMD-addressing the 8-million-patient therapeutic gap where complement inhibitors are not indicated. However, this remains a secondary endpoint from a single trial, and replication is essential before drawing definitive conclusions.

Critical limitations of LIGHTSITE III evidence

These findings must be interpreted with appropriate caution due to several methodological limitations. First, LIGHTSITE III represents a single phase 3 trial requiring independent replication. While consistent with earlier LIGHTSITE I and II studies, the sample size (N=100) is substantially smaller than the complement inhibitor trials. Second, the masking integrity of light-based therapy presents inherent challenges. While the sham protocol delivered reduced fluence, complete blinding is impossible when patients perceive visible light during treatment. The study acknowledged this limitation, noting that 'a complete masked control is not possible (i.e., a true sham would deliver zero light fluence, which would be observable to patients and study staff).' Third, the trial utilized standard spectral-domain OCT rather than OCT-Angiography (OCT-A) for imaging assessment. This represents a potential limitation for detecting subclinical Macular Neovascularization (MNV), which could theoretically contribute to visual improvement through mechanisms unrelated to PBM's proposed mechanism of action. The absence of OCT-A data limits confidence in the safety assessment regarding CNV development. Fourth, the primary analysis was conducted at 13 months, with 24-month data pending. Long-term durability of visual gains and safety beyond 13 months remain unknown. The intensive treatment burden (approximately 37-40 clinic visits annually) also raises questions about real-world feasibility and patient adherence. Finally, the Valeda device was not FDA-approved at the time of publication, limiting current clinical applicability in the United States. Regulatory status varies by jurisdiction, with CE marking in Europe.

Emerging and Future Therapeutic Strategies

While the interventions discussed above represent the current evidence-based therapeutic landscape for dry AMD, several additional approaches are under investigation in earlier-phase clinical trials or preclinical development. These emerging strategies target diverse pathophysiological mechanisms and may expand future treatment options [2-4,27,28]. Cell-based therapies, including RPE transplantation and stem cell-derived RPE replacement strategies, aim to restore function in areas of established atrophy. Multiple approaches are being evaluated including autologous and allogeneic RPE cell suspensions, RPE monolayers on biodegradable scaffolds and Induced Pluripotent Stem Cell (iPSC)-derived RPE patches [4,27,28]. Early-phase trials have demonstrated proof-of-concept feasibility, though significant technical challenges remain regarding cell survival, integration, immune rejection and clinical-scale manufacturing [4,28]. Gene therapy strategies employ Adeno-Associated Virus (AAV) vectors targeting complement regulation, neuroprotection and anti-angiogenic pathways. Approaches include AAV-mediated delivery of complement factor I, CD59, complement factor H and neurotrophic factors such as Ciliary Neurotrophic Factor (CNTF) [3,27]. While offering potential advantages of sustained protein expression from single administration, questions regarding long-term durability, immunogenicity and safety require careful evaluation. Additional investigational approaches include visual cycle modulators such as emixustat and fenretinide targeting toxic bisretinoid accumulation, neuroprotective agents including brimonidine intravitreal

implants and CNTF-secreting encapsulated cell technology (NT-501) and novel drug delivery systems including sustained-release implants and suprachoroidal injection techniques [2-4,27]. The BEACON phase 2 trial of brimonidine implants and the EMAPs study of emixustat have been completed, though results have been mixed with concerning safety signals in some cases [2,3]. Most of these approaches remain in early clinical development with limited or absent phase 3 efficacy data. For current clinical practice, therapeutic decisions should focus on interventions with established phase 3 efficacy and regulatory approval, specifically AREDS2 supplementation for intermediate AMD and complement inhibitors (pegcetacoplan or avacincaptad pegol) for geographic atrophy. Photobiomodulation represents a unique intermediate category with phase 3 data from a single trial requiring independent validation. Clinicians should remain informed about emerging developments while maintaining appropriate skepticism regarding preliminary findings and recognizing that the path from early-phase promise to proven clinical benefit is lengthy and uncertain.

Perspective on Emerging Therapies

While these investigational approaches demonstrate the breadth of research activity in dry AMD therapeutics, it is essential to recognize that most remain in early clinical development with limited or absent phase 3 efficacy data. The substantial gap between preclinical promise and clinical efficacy has been repeatedly demonstrated in AMD research, with numerous compounds showing robust activity in animal models yet failing to demonstrate meaningful benefit in human trials. Historical examples include antioxidant therapies beyond AREDS formulations, anti-inflammatory agents and various complement pathway modulators that did not advance beyond phase 2 development. For current clinical practice, therapeutic decisions should focus on interventions with established phase 3 efficacy data and regulatory approval, specifically, AREDS2 supplementation for intermediate AMD and complement inhibitors (pegcetacoplan or avacincaptad pegol) for geographic atrophy. Photobiomodulation represents a unique intermediate category with phase 3 data from a single trial requiring independent validation. Clinicians should remain informed about emerging developments that may expand future treatment options, while maintaining appropriate skepticism regarding preliminary findings and recognizing that the path from early-phase promise to proven clinical benefit is lengthy and uncertain. Shared decision-making with patients should acknowledge both the evidence supporting current interventions and the investigational nature of emerging approaches, ensuring realistic expectations regarding therapeutic options.

Safety Considerations

Exudative conversion risk with complement inhibitors

Both complement inhibitors carry an elevated risk of conversion to exudative AMD (eAMD), necessitating ongoing surveillance with OCT imaging at each visit. The mechanism underlying this increased risk is not fully elucidated but may relate to complement's role in maintaining vascular integrity or suppressing angiogenic signaling. For pegcetacoplan, GALE reported 7.2 events per 100 patient-years, with cumulative rates of 6.0-6.7% at Year 1 increasing to 12.2% at Year 2 in the OAKS/DERBY trials [11,22]. For avacincaptad pegol, GATHER2 demonstrated cumulative rates of 6.7% (Year 1) to 11.6% (Year 2) in treated patients versus 4.1% to 9.0% in sham groups [12]. This elevated risk necessitates patient counseling prior to treatment initiation. Patients should understand that monthly monitoring with OCT is required to detect conversion promptly and that most cases of treatment-emergent eAMD respond well to anti-VEGF therapy (Table 3). The risk-benefit calculation must weigh the benefit of slowing GA progression against this potential complication.

Table 3: Safety profile and treatment burden.

Safety Parameter	LIGHTSITE III	AREDS2	OAKS/DERBY	GALE	GATHER1	GATHER2
Exudative AMD (CNV) Conversion	5.4% (13mo)	14% (2yr)/29% (4yr)	6.0-6.7% (Yr 1)/12.2% (Yr 2)	7.2 events per 100 patient-years	11.9% (2mg, 18mo)	6.7% (Yr 1)/11.6% (Yr 2)
Endophthalmitis	N/A (Non-invasive)	N/A (Oral)	0.03% per injection	0.1% of patients (Yr 1)	0%	0.4% of patients (Yr 2)
Intraocular Inflammation (IOI)	0%	N/A	3.4% of patients	1.9% of patients	1.5% (Mild vitritis)	0.4% (Trace cells)
Ischemic Optic Neuropathy (ION)	0%	N/A	0.05% per injection	0.1% of patients	1.5% (1 eye)	0%
Retinal Vasculitis	0%	N/A	0% in-trial (Post-market rare)	0%	0%	0%
Conjunctival Hemorrhage	2.2%	N/A	Common TEAE	Common TEAE	Not specified	~2%
Systemic SAEs	3.0% (unrelated deaths)	Lung CA: 2% (Beta-carotene arm)	Not reported specifically	Not reported specifically	16.4% (2mg) vs 25.5% (Sham)	24.4% (ACP) vs 22.1% (Sham)
Injections/Year	0 (Light Therapy)	0 (Oral Supplement)	6 (EOM) to 12 (Monthly)	6 (EOM) to 12 (Monthly)	12 (Monthly)	6 (Yr 2 EOM) to 12 (Yr 2 EM)
Clinic Visits/Year	~37-40 (clustered sessions)	1 (plus phone calls)	12 (Monthly monitoring)	12 (Monthly monitoring)	12 (Monthly monitoring)	12 (Monthly monitoring)
Treatment Pattern	Clustered (9 sessions q4mo)	Daily oral dosing	Spread (Monthly/EOM)	Spread (Monthly/EOM)	Spread (Monthly)	Spread (Monthly/EOM)

Injection-related adverse events

Intravitreal injection carries inherent procedural risks common to all vitreoretinal injectable therapies. Endophthalmitis rates ranged from 0.03% per injection (OAKS/DERBY) to 0.4% of patients over 2 years (GATHER2). Intraocular inflammation occurred in 0.4-3.4% of patients across trials, generally mild and self-limiting. Ischemic optic neuropathy has been reported rarely (<1.5% across trials) and retinal vasculitis, while not observed in controlled trials, has been reported in post-marketing surveillance for pegcetacoplan. These serious adverse events, while uncommon, require appropriate informed consent and monitoring.

Photobiomodulation safety profile

As a non-invasive external light therapy, PBM eliminates injection-related risks entirely. LIGHTSITE III reported no increased risk of exudative AMD conversion (5.4% PBM vs 1.8% sham at 13 months), no intraocular inflammation, no ischemic optic neuropathy, and no retinal vasculitis. However, it is important to note that the absence of OCT-angiography assessment in LIGHTSITE III represents a potential limitation in safety surveillance. Subclinical macular neovascularization could theoretically develop and go undetected with standard OCT alone. The 3% mortality rate (3/100 subjects) was deemed unrelated to treatment based on case-by-case assessment. The primary burden of PBM is logistical rather than safety-related: approximately 37-40 clinic visits annually for treatment and monitoring represents a substantial time commitment for patients, potentially limiting adherence and real-world effectiveness.

Discussion

Structural preservation versus functional rescue: a conceptual framework

The therapeutic landscape for dry AMD now includes interventions with fundamentally different goals and clear conceptual distinction is essential for appropriate patient counseling and expectation management. Complement inhibitors provide structural preservation: they slow the expansion of geographic atrophy lesions, preserving retinal tissue that would otherwise be lost to progressive atrophy. This structural preservation translates to delayed functional decline, as demonstrated by reduced risk of severe vision loss and preserved microperimetry sensitivity. However, complement inhibitors do not improve visual acuity in treated eyes-they slow decline rather than restore function. Photobiomodulation, based on preliminary single-trial data, suggests potential for functional rescue: actual improvement in visual acuity rather than merely slowed decline. Additionally, the reduction in new GA onset suggests potential for disease modification at the intermediate AMD stage, preventing the transition to atrophy rather than treating established lesions. However, this evidence requires independent validation before definitive conclusions can be drawn.

The subfoveal efficacy question: implications for clinical practice

The substantial differential efficacy of complement inhibitors based on lesion location represents a critical consideration for clinical decision-making. The observation that non-subfoveal lesions show 32% reduction in growth versus only 21% for subfoveal lesions with pegcetacoplan has several important implications. First, eyes with established subfoveal GA derive substantially less structural benefit from complement inhibition. While treatment may still be indicated, patients should understand that foveal-involving disease is more refractory to therapy. Second, the fellow-eye preservation strategy becomes paramount: in patients with subfoveal GA in one eye and extrafoveal GA in the fellow eye, prioritizing treatment in the eye with extrafoveal disease may optimize overall outcomes. Third, this finding underscores the importance of early detection and treatment. Initiating complement inhibitor therapy before GA involves the fovea may maximize therapeutic benefit, supporting the rationale for regular surveillance in patients with intermediate AMD at high risk for progression.

Limitations of current evidence and need for validation

Several important limitations warrant emphasis when interpreting the available evidence. For photobiomodulation, LIGHTSITE III represents a single phase 3 trial with a sample size (N=100) substantially smaller than the complement inhibitor trials (Table 4). The inherent challenges of masking light-based therapy, the absence of OCT-angiography assessment and the pending long-term data beyond 13 months all necessitate caution in drawing definitive conclusions. For complement inhibitors, the differential efficacy between trials (OAKS showing somewhat different results than DERBY), the elevated risk of exudative conversion and the open-label nature of extension study data all represent limitations. The absence of head-to-head comparative trials precludes definitive conclusions about relative efficacy between pegcetacoplan and avacincaptad pegol. For AREDS2 supplementation, the complex secondary randomization design and the fact that there was no true placebo group (all participants received some form of supplementation) complicate interpretation of specific nutrient effects. Regulatory Status and Standard of Care Distinctions: Complement inhibitors pegcetacoplan and avacincaptad pegol represent the only FDA-approved pharmacological treatments specifically indicated for geographic atrophy, establishing a new standard of care for this patient population. In contrast, photobiomodulation remains an investigational therapy without FDA approval for AMD in the United States, though it holds CE marking in Europe. This regulatory distinction has important implications for reimbursement, clinical access and the strength of evidence supporting clinical use. Photobiomodulation is currently positioned for the intermediate AMD population (before GA develops) to prevent progression, a fundamentally different therapeutic target than the established GA indication for complement inhibitors.

Table 4: Evidence quality and bias assessment.

Quality Criterion	LIGHTSITE III	AREDS2	OAKS/DERBY	GALE	GATHER1	GATHER2
Evidence Level	Grade 1b (RCT)	Grade 1b (RCT)	Grade 1b (RCT)	Grade 2b (Open-Label Extension)	Grade 1b/2a (Phase 2/3)	Grade 1b (RCT)
Primary Bias Concern	Masking Integrity (Light visible to patients)	Complex Secondary Randomization	Efficacy consistency between OAKS/DERBY	No Control Group (Projected Sham)	Differential Dropout (44.6% in 4mg arm)	Hierarchical Testing Failure (EOM)
OCT-A Assessment	Not performed (Potential limitation)	N/A	Performed	Performed	Not specified	Not specified
Replication Status	Consistent with LIGHTSITE I/II (Single Phase 3)	Consistent with AREDS1/DHA trials	OAKS replicated by DERBY (Year 2)	Extensions consistent with parent trials	Proof-of-concept for GATHER2	Replicated GATHER1 (Year 1)
Sample Power	Adequate (N=100); smaller than comparators	High Power (N=4,203)	Pivotal Size (N=1,258)	N/A (Extension)	Phase 2/3 (N=286)	Adequate (N=448)
Independent Reading Center	Yes (Duke)	Yes (UW Madison)	Yes (DARC/Voiant)	Yes (Voiant)	Yes (Duke)	Yes (Duke)
Analysis Population	mITT (N=145 eyes)	ITT	ITT	Modified Full Analysis Set	ITT	ITT
Missing Data Handling	Mixed Models	Censoring at last contact	Piecewise Linear Model	Piecewise Linear Model	MMRM (MAR assumed)	MMRM (No imputation)
Funding Source	Industry (LumiThera)	NIH/NEI (Federal)	Industry (Apellis)	Industry (Apellis)	Industry (Iveric Bio)	Industry (Astellas)
COI Declared	Yes (5 authors LumiThera employees)	Yes	Yes	Yes	Yes	Yes

Shared decision-making and patient selection

Given the limitations of current evidence and the meaningful differences between therapeutic approaches, shared decision-making with patients remains paramount. Clinicians should discuss the expected benefits (structural preservation vs potential functional improvement), the treatment burden (monthly injections vs clustered light therapy sessions vs daily oral supplementation), the risks (exudative conversion, injection-related complications) and the current regulatory status. Patient factors influencing treatment selection may include: disease stage (intermediate AMD vs established GA), lesion location (subfoveal vs extrafoveal), bilateral versus unilateral involvement, patient preferences regarding treatment burden and risk tolerance and practical considerations including geographic access to treatment centers and ability to attend frequent monitoring visits. The therapeutic landscape for dry AMD continues to evolve rapidly, with multiple complementary approaches targeting different disease stages and distinct pathophysiological mechanisms. Recent comprehensive reviews have synthesized the expanding evidence base across nutritional supplementation, complement-based interventions, photobiomodulation and numerous investigational strategies including cell therapy, gene therapy, visual cycle modulation and neuroprotective approaches [2-4,27,28]. As new interventions emerge from clinical development, the field will benefit from head-to-head comparative trials between complement inhibitors, biomarker-driven patient selection strategies to identify treatment responders, combination therapy trials evaluating synergistic approaches and real-world effectiveness studies accounting for treatment adherence, access barriers and long-term outcomes beyond controlled trial settings. Integration of advanced imaging modalities, artificial intelligence-based disease progression prediction and functional outcome measures beyond visual acuity will further refine our ability to optimize treatment algorithms and individualize therapeutic decisions for patients across the spectrum of dry AMD severity.

Conclusion

The therapeutic landscape for dry AMD has evolved substantially with the approval of complement inhibitors, providing the first evidence-based interventions for geographic atrophy. This narrative review summarizes current evidence supporting stage-specific therapeutic considerations: For intermediate AMD at high risk of progression, AREDS2 supplementation (vitamins C, E, zinc, copper, lutein, zeaxanthin) remains foundational, providing approximately 25-30% relative risk reduction for progression to advanced disease. Photobiomodulation represents a potentially promising intervention targeting functional outcomes and disease modification at this stage, though its evidence base (single phase 3 trial) requires independent validation before definitive recommendations can be made. For established geographic atrophy, complement inhibitors pegcetacoplan and avacincaptad pegol provide 17-35% reduction in lesion growth rates, with optimal efficacy in non-subfoveal lesions (32-42% reduction) compared to subfoveal lesions (19-21% reduction). Both agents carry risk of exudative conversion (6.7-12% cumulative over 2 years) requiring

ongoing surveillance. Functional preservation endpoints (reduced severe vision loss, preserved microperimetry sensitivity) support clinical meaningfulness of anatomical benefits. Important gaps in current evidence include: The need for independent validation of photobiomodulation findings, long-term durability data beyond current follow-up periods, head-to-head comparative trials between complement inhibitors and real-world effectiveness data accounting for treatment adherence and access barriers. The field continues to evolve rapidly and ongoing studies will further define optimal patient selection, treatment sequencing and long-term outcomes for these emerging therapeutic approaches. Multidisciplinary collaboration and shared decision-making with patients regarding treatment burden, expected benefits, and risks remain essential components of optimal care.

References

1. Wong WL, Su X, Li X, Cheung CMG, Klein R, et al. (2024) Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: A systematic review and meta-analysis. Lancet Glob Health 2(2): e106-e116.
2. Girgis S, Lee LR (2023) Treatment of dry age-related macular degeneration: A review. Clin Exp Ophthalmol 51(8): 835-852.
3. Guimaraes TAC, Georgiou M, Bainbridge JWB, Michaelides M (2022) Treatments for dry age-related macular degeneration: Therapeutic avenues, clinical trials and future directions. Br J Ophthalmol 106(3): 297-304.
4. Mura M, Cecchini M, Pavesio A, Busin M (2024) Different therapeutic approaches for dry and wet age-related macular degeneration. Int J Mol Sci 25(23): 13053.
5. Sunness JS, Margalit E, Srikumaran D, Applegate CA, Tian YBS, et al. (2007) The long-term natural history of geographic atrophy from age-related macular degeneration: Enlargement of atrophy and implications for interventional clinical trials. Ophthalmology 114(2): 271-277.
6. Fleckenstein M, Mitchell P, Freund KB, Sadda SV, Holz FG, et al, (2018) The progression of geographic atrophy secondary to age-related macular degeneration. Ophthalmology 125(3): 369-390.
7. Eandi CM, Alovisi C, De Sanctis U, Grignolo FM (2016) Treatment for neovascular age-related macular degeneration: The state of the art. Eur J Pharmacol 787: 78-83.
8. Boyer DS, Schmidt-Erfurth U, Campagne MLV, Henry EC, Brittain C (2017) The pathophysiology of geographic atrophy secondary to age-related macular degeneration and the complement pathway as a therapeutic target. Retina 37(5): 819-835.
9. Bakri SJ, Bektas M, Sharp D, Luo R, Sarda SP, et al. (2023) Geographic atrophy: Mechanism of disease, pathophysiology and role of the complement system. J Manag Care Spec Pharm 29(5-a Suppl): S2-S11.
10. Fritsche LG, Igl W, Bailey JNC, Grassmann F, Sengupta S, et al. (2016) A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. Nat Genet 48(2): 134-143.
11. Heier JS, Lad EM, Holz FG, Rosenfeld PJ, Guymer RH, et al. (2023) Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): Two multicentre, randomised, double-masked, sham-controlled, phase 3 trials. Lancet 402(10411): 1434-1448.
12. Khanani AM, Patel SS, Staurenghi G, Tadayoni R, Danzig CJ, et al. (2023) Efficacy and safety of avacincaptad pegol in patients with geographic atrophy (GATHER2): 12-month results from a randomised, double-masked, phase 3 trial. Lancet 402(10411): 1449-1458.
13. Wong-Riley MTT (2010) Energy metabolism of the visual system. Eye Brain 2: 99-116.
14. Zhu Q, Xiao S, Hua Z, Yang D, Hu M, et al. (2021) Near Infrared (NIR) light therapy of eye diseases: A review. Int J Med Sci 18(1): 109-119.
15. Eells JT, Wong-Riley MT, VerHoeve J, Henry M, Buchman EV, et al. (2004) Mitochondrial signal transduction in accelerated wound and retinal healing by near-infrared light therapy. Mitochondrion 4(5-6): 559-567.
16. Hamblin MR (2018) Mechanisms and mitochondrial redox signaling in photobiomodulation. Photochem Photobiol 94(2): 199-212.
17. Sadda SR, Guymer R, Holz FG, Valckenberg SS, Curcio CA, et al. (2018) Consensus definition for atrophy associated with age-related macular degeneration on OCT: Classification of atrophy report 3. Ophthalmology 125(4): 537-548.
18. Age-Related Eye Disease Study 2 Research Group (2013) Lutein+zeaxanthin and omega-3 fatty acids for age-related macular degeneration: The Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA 309(19): 2005-2015.
19. Keenan TDL, Agrón E, Domalpally A, Clemons TE, Asten FV, et al. (2018) Progression of geographic atrophy in age-related macular degeneration: AREDS2 report number 16. Ophthalmology 125(12): 1913-1928.
20. Liao DS, Grossi FV, El Mehdi D, Gerber MR, Brown DM, et al. (2020) Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: A randomized phase 2 trial. Ophthalmology 127(2): 186-195.
21. Wykoff CC, Rosenfeld PJ, Waheed NK, Singh RP, Ronca N, et al. (2021) Characterizing new-onset exudation in the randomized phase 2 FILLY trial of complement inhibitor pegcetacoplan for geographic atrophy. Ophthalmology 128(9): 1325-1336.
22. Goldberg RA, Boyer DS, Holz FG, Mac Cumber MW, Garg SJ, et al. (2025) Pegcetacoplan for geographic atrophy over 30 months: Data from OAKS, DERBY and the GALE long-term extension study. Am J Ophthalmol 272: 115-125.
23. Jaffe GJ, Westby K, Csaky KG, Monés J, Pearlman JA, et al. (2021) C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: A randomized pivotal phase 2/3 trial. Ophthalmology 128(4): 576-586.
24. Tedford SE, Croissant CL, Patel N, Zanlonghi X, Hornan D, et al. (2023) LIGHTSITE II randomized multicenter trial: Evaluation of multiwavelength photobiomodulation in non-exudative age-related macular degeneration. Ophthalmol Ther 12(2): 953-968.
25. Markowitz SN, Devenyi RG, Munk MR, Croissant CL, Tedford SE, et al. (2020) A double-masked, randomized, sham-controlled, single-center study with photobiomodulation for the treatment of dry age-related macular degeneration. Retina 40(8): 1471-1482.
26. Boyer D, Hu A, Warrow D, Xavier S, Gonzalez V, et al. (2024) LIGHTSITE III 13-month efficacy and safety evaluation of multiwavelength photobiomodulation in nonexudative (dry) age-related macular degeneration using the Lumithera Valeda Light Delivery System. Retina 44(3): 487-497.
27. Cabral de Guimaraes TA, Varela MD, Georgiou M, Michaelides M (2022) Therapeutic approaches for age-related macular degeneration. Int J Mol Sci 23(19): 11769.
28. Shirley DT, Farr G, Watanabe K, Moonjely S (2024) Current and emerging therapies for dry and neovascular age-related macular degeneration. Pharm Dev Technol 29(10): 1153-1173.