TRIALS AND INNOVATIONS IN GEOGRAPHIC ATROPHY THERAPY

Novel mechanisms of action and delivery methods hold promise for patients with dry AMD.

By James M. Harris, MD, PhD, and Eleonora M. Lad, MD, PhD


This year has been busy for the geographic atrophy (GA) pipeline. The Valeda light delivery system (LumiThera/Alcon) gained approval for the treatment of early and intermediate dry AMD, joining the two complement inhibitors, pegcetacoplan (Syfovre, Apellis Pharmaceuticals) and avacincaptad pegol (Izervay, Astellas), as FDA-approved treatments for dry AMD. Additionally, post-hoc analysis of the AREDS and AREDS2 studies showed a 33% and 30% slower progression of noncentral GA to the foveal center point, respectively, for patients taking supplements compared with placebo for a mean follow-up period of 3 years.[1]

However, these therapies and supplements are just the tip of the iceberg when it comes to potential treatments for dry AMD. The current pipeline, some of which is highlighted below, contains many exciting therapies that target a diverse range of mechanisms with novel delivery strategies (Table).

PHASE 3 TRIALS

Elamipretide (Stealth Biotherapeutics) targets mitochondrial dysfunction by blocking cardiolipin from interacting with cytochrome c, preventing its conversion from an electron carrier into a peroxidase, which has been shown to reduce reactive oxygen species generation while boosting ATP generation.[2] ReNEW (NCT06373731) is investigating the effect of a once-daily subcutaneous injection of 40 mg elamipretide on the change in macular photoreceptor loss area after 48 weeks.[3] While the ReCLAIM-2 phase 2 trial (NCT03891875) failed to meet its primary endpoints of change in low-luminance BCVA (LLBCVA) and change in GA area growth, it did reduce

AT A GLANCE

- Four investigational therapies are in phase 3 trials for the treatment of geographic atrophy: elamipretide (Stealth Biotherapeutics), tinlarebant (LBS-008, Belite Bio), vonaprument (ANX007, Annexon), and Cemdisiran (Regeneron).
- Novel approaches such as sialic acid-coated nanoparticles, phospholipid modulators, Fas inhibitors, and gene and stem cell therapies are in phase 2 trials.
- At least two retinal implants hold promise for restoring some vision in patients with late-stage disease.

TABLE. INVESTIGATIONAL THERAPIES FOR DRY AMD

Study Drug (Company)	Mechanism	Delivery	Trial NCT	Trial Status	Completion	Last Update
Phase 3						
Vonaprument (ANX007, Annexon)	C1q inhibitor	Intravitreal	NCT06510816	Active, not recruiting	October 2026	November 2025
Elamipretide (Stealth Biotherapeutics)	Mitochondrial enhancer/ cardiolipin blocker	Subcutaneous	NCT06373731	Active, not recruiting	August 2027	November 2025
Tinlarebant (LBS-008, Belite Bio)	RBP4 antagonist	Oral	NCT05949593	Recruiting	August 2027	February 2025
Cemdisiran (Regeneron)	siRNA/C5 inhibitor	Subcutaneous	NCT06541704	Recruiting	November 2027	November 2025
Phase 2						
Eyecyte-RPE (Eyestem Research)	RPE cell replacement	Subretinal	NCT06394232	Recruiting	April 2025	September 2024
AVD-104 (Aviceda Therapeutics)	Siglec binding	Intravitreal	NCT05839041	Active, not recruiting	September 2025	December 2024
JNJ-1887 (JNJ-81201887; AAVCAGsCD59; Janssen)	sCD59 overexpression/ membrane attack complex inhibition	Intravitreal	NCT05811351	Active, not recruiting	February 2026	November 2025
OCU-410 (Ocugen)	Gene therapy (*RORA* overexpression)	Subretinal	NCT06018558	Active, not recruiting	February 2026	June 2025
BI 771716 (Boehringer Ingelheim/CDR-Life)	Proprietary antibody fragment	Oral	NCT06722157	Active, not recruiting	October 2026	October 2025
RPESC-RPE-4W (Luxa Biotechnology)	RPE cell replacement	Subretinal	NCT04627428	Recruiting	December 2026	October 2025
BI 1584862 (Boehringer Ingelheim)	Phospholipid modulator	Oral	NCT06769048	Recruiting	February 2027	October 2025
GAL-101 (Galimedix Therapeutics/Théa Open Innovation)	Amyloid-beta aggregation inhibitor	Topical	NCT06659549	Recruiting	March 2027	June 2025
CPCB-RPE1 (Regenerative Patch Technologies)	RPE cell replacement	Subretinal	NCT06557460	Recruiting	December 2027	August 2025
ONL1204 (ONL Therapeutics)	FasR inhibitor	Intravitreal	NCT06659445	Recruiting	November 2028	October 2025
OpRegen (RG6501, Lineage Cell Therapeutics, Genentech/Roche)	RPE cell replacement	Subretinal	NCT05626114	Recruiting	March 2031	October 2025
Iptacopan (LNP023, Novartis)	Complement factor B inhibitor	Oral	NCT05230537	Active, not recruiting	October 2026	July 2025
Phase 1 and 1/2						
VOY-101 (Perceive Biotherapeutics)	Gene therapy (complement factor H)	Intravitreal	NCT05380492 NCT06087458	Active, not recruiting Recruiting	November 2025 June 2027	April 2024 October 2025
PST-611 (Eyevensys)	Gene therapy (transferrin)	Ciliary muscle injection	NCT07024732	Not yet recruiting	December 2025	June 2025
ASP7317 (Astellas)	RPE cell replacement	Subretinal	NCT03178149	Recruiting	June 2026	October 2025
K8 (Inflammasome Therapeutics)	Inflammasome inhibition	Intraocular implant	NCT06164587	Recruiting	August 2026	August 2025
KRIYA-825 (Kriya Therapeutics)	Gene therapy (anti-C3 and C5)	Suprachoroidal	NCT06765980	Recruiting	December 2027	September 2025
National Eye Institute	RPE cell replacement	Subretinal	NCT04339764	Recruiting	May 2029	September 2025

Abbreviation: RPE, retinal pigment epithelium.

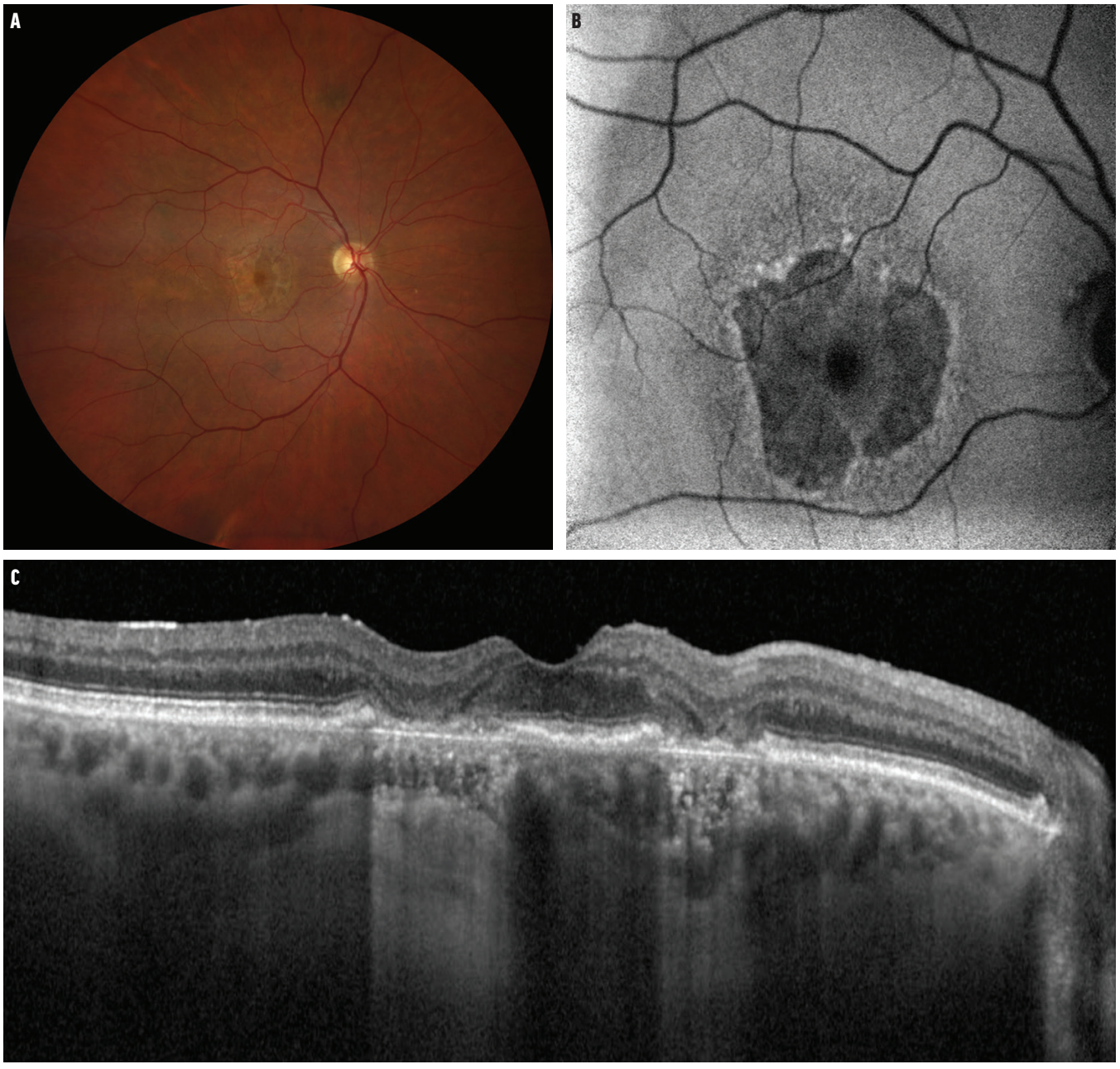

Figure. Fundus photography of a patient with GA that is threatening, but not yet involving, the fovea (A). The color photograph shows RPE loss with a central island. Fundus autofluoresence reveals hypoautofluoresence corresponding to the areas of RPE atrophy with a border of hyperautofluoresence and sparing of the foveal island (B). OCT confirms perifoveal loss of outer retinal layers (EZ and RPE), while the central foveal island's outer retinal layers are preserved (C).

progression of total ellipsoid zone (EZ) attenuation by 43% compared with baseline (P = .0034) and partial EZ attenuation by 47% compared with placebo (P = .0034) after 48 weeks (n = 176).[4]

Tinlarebant (LBS-008, Belite Bio) is a small molecule aimed at reducing the accumulation of the visual cycle pathway metabolite A2E, a toxic component of lipofuscin, by inhibiting retinal binding protein 4. The PHOENIX trial (NCT05949593) is investigating the effect of 5 mg daily oral tinlarebant with a primary endpoint of the rate of change in GA lesion size after promising phase 2 results in Stargardt disease.[5]

Vonaprument (ANX007, Annexon) is a Fab antibody fragment targeting C1q dosed monthly or every other month via intravitreal injection. The fully-enrolled ARCHER II study (NCT06510816) has a primary endpoint of prevention of ≥ 15-letter loss.[6] The phase 2 ARCHER study did not meet its primary endpoint of GA area reduction but found that treatment reduced the rates of ≥ 15-letter loss in BCVA to 5.6% and 9.8% in patients treated monthly

STALLED PROGRAM

ALK-001 (gildeuretinol, Alkeus Pharmaceuticals), an oral therapy designed to reduce the dimerization of vitamin A, did not meet its primary endpoint in the phase 3 SAGA trial, although treatment led to a 15.3% reduction in GA lesion growth rate from 6 to 24 months.[1] ALK-001 is currently under investigation for the treatment of Stargardt disease in the phase 2 TEASE trial (NCT02402660).

1. Topline results from Alkeus Pharmaceuticals' study of oral gildeuretinol demonstrate significant trend in slowing GA progression and visual function improvement [press release]. Alkeus Pharmaceuticals. October 23, 2024. Accessed September 24, 2024. tinyurl.com/r72eyjnz

and every other month, respectively, compared with 21.3% in sham patients.[7] Pooled analysis showed reduced EZ loss in the central 2.0 mm by 48% and central 1.5 mm by 50% after 1 year.[8]

Cemdisiran (Regeneron), an siRNA that reduces complement factor 5 (C5), is under investigation in the SIENNA phase 3 trial as a subcutaneous monotherapy or in combination with pozelimab, a C5 antibody, to treat GA (NCT06541704) with a primary endpoint of GA lesion area growth on fundus autofluorescence. In a phase 3 trial for myasthenia gravis, treatment with the combination therapy led to nearly 99% inhibition of complement activity.[9]

PHASE 2 STUDIES

AVD-104 (Aviceda Therapeutics) is a sialic acid-coated nanoparticle that helps recruit complement factor H to cell membranes and binds siglec receptors on macrophages, which is believed to reduce phagocytic and inflammatory activity.[10] The phase 2 SIGLEC trial (NCT05839041) is measuring the rate of GA area growth after monthly intravitreal injections of low- or high-dose AVD-104 compared with 2 mg avacincaptad pegol over 1 year. Preliminary results from part 1 of the trial (n = 30) showed a 48% reduction in GA lesion growth rate compared with fellow eyes and a 4.8- to 6.5-letter dose-dependent improvement compared with baseline at 3 months following a single injection.[11]

BI 1584862 (Boehringer Ingelheim) is a phospholipid modulator with daily oral dosing that is being studied in the dose-escalation JADE study (NCT06769048) comparing this drug with placebo, measuring the rate of change in GA area after 50 weeks.[12]

BI 771716 (Boehringer Ingelheim/CDR-Life) is an antibody fragment under investigation in the VERDANT study (NCT06722157) comparing the rate of change in GA area after 56 weeks of intravitreal BI 771716 versus pegcetacoplan. Safety endpoints were met in a prior phase 1 study (NCT06006585).[12]

Gal-101 (Galimedix Therapeutics/Théa Open Innovation) is a small-molecule inhibitor of toxic amyloid beta monomer aggregation under investigation for the treatment of Alzheimer disease, GA, and glaucoma. Following a successful phase 1 safety trial,[13] the eDREAM trial (NCT06659549) is testing GAL-101 eye drops versus placebo over 48 to 96 weeks, with a primary outcome of change in GA area.

ONL1204 (ONL Therapeutics) inhibits the Fas receptor, which triggers cells to undergo apoptosis. The GALAXY trial (NCT06659445) is comparing a dose escalation of every 12- or 24-week intravitreal dosing with placebo or monthly avacincaptad pegol, with a primary endpoint of GA lesion area change. Preliminary phase 1b data showed a 42% to 50% reduction in this metric after two injections 3 months apart.[14]

Iptacopan (LNP023, Novartis) is an oral complement factor B inhibitor under investigation to potentially prevent conversion from early or intermediate AMD to late-stage disease. The phase 2 trial (NCT05230537) enrolled 170 patients who were randomly assigned oral iptacopan or placebo and are being followed for 2 years.

Gene Therapies

JNJ-1887 (AAVCAGsCD59, Janssen) is an intravitreal gene therapy overexpressing soluble CD59, an endogenous protein that inhibits the formation of the membrane attack complex. The PARASOL study (NCT05811351) is comparing high and low doses administered with prophylactic steroids in 305 patients, with a primary outcome of the difference in GA lesion area after 18 months.[15]

OCU-410 (AAV-hRORA, Ocugen), a one-time gene therapy overexpressing the *RORA* gene delivered through subretinal injection, showed a 2-line improvement in LLBCVA and a 44% decrease in GA lesion growth at 9 months compared with controls in part 1 of the ArMaDa trial (NCT06018558).[16] *RORA* is a nuclear hormone receptor believed to regulate lipid metabolism, oxidative stress, and inflammation, including complement signaling.[17]

Stem Cell Therapies

CPCB-RPE1 (Regenerative Patch Technologies) is a subretinal implant consisting of 100,000 human embryonic stem cell-derived retinal pigment epithelium (RPE) cells grown on a synthetic Bruch membrane. In the phase 1 study, several patients showed improved BCVA after 1 year.[18] A phase 2b trial (NCT06557460) is comparing CPCB-RPE1 with sham using the change in retinal sensitivity by microperimetry after 1 year as the primary endpoint.

OpRegen (RG6501, Lineage Cell Therapeutics/Genentech/Roche) is a suspension of 200,000 allogeneic RPE cells delivered subretinally. In phase 1 of the GAlette trial (NCT02286089), 10 patients had a mean increase of

6.2 letters in BVCA after 36 months and durable increases in the external limiting membrane and RPE drusen complex on OCT. Phase 2a of the trial (NCT05626114) is investigating successful surgical delivery of OpRegen to the subretinal space and adverse events 3 months after treatment, with a secondary outcome measure of qualitative improvement in retinal structure by OCT.[19]

RPESC-RPE-4W (Luxa Biotechnology) is a single subretinal dose of 50,000, 150,00, or 250,000 RPE cells derived from human RPE stem cells. Preliminary data from six patients treated with 50,000 cells showed a good safety profile and a BCVA gain of 21.67 letters in a worse-seeing group after 1 year and a more modest 3.3 letter gain after 3 months in a better-seeing group (NCT04627428).[20]

RETINAL PROSTHETICS

The PRIMA implant (Science Corporation) is designed to mimic photoreceptor function by sending visual information and power from a pair of glasses to a subretinal implant that electrically activates inner retinal neurons. The PRIMAvera European study (NCT04676854) showed a mean improvement of 23 letters after 12 months of device implantation in 38 patients, with a feasibility study ongoing in the United States.[21]

The Smaller-Incision New-Generation Implantable Miniature Telescope (SING IMT, Samsara Vision) is under investigation in the CONCERTO study (NCT05438732) for patients with late-stage AMD.[22] Intermediate-term visual and safety outcomes 6 months postoperatively showed that 97.1%, 68.6%, and 51.4% of operated eyes achieved at least 1, 2, and 3 lines in best-corrected distance VA, respectively. In addition, 97.1% of patients were able to read at near distance compared with 28.6% at baseline.[23] The device received a CE mark for the European Union in 2020.[22]

LOOKING AHEAD

In addition to the therapies discussed here, several other phase 1 and phase 1/2 drug candidates use induced pluripotent stem cell-derived RPE; gene therapies targeting complement factor H, C3, and C5; an intraocular implant that elutes kamuvudines, which inhibit inflammasomes; and others. See the Table for more information.

We are excited by the diverse mechanisms of action under investigation. The underlying pathobiology driving GA is likely multifactorial, and therapies targeting multiple mechanisms may be required to fully control the disease (Figure). We are also encouraged by the advances in stem cell and gene therapy technologies and novel delivery systems, which hold great potential as future GA treatments. ■

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