GEOGRAPHIC ATROPHY THERAPIES TO WATCH

An update on complement inhibitors, gene and cell therapies, and novel approaches.

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Patients with geographic atrophy (GA) are now presenting to US retina clinic to discuss their treatment options with one of two FDA approved therapies, pegcetacoplan (Syfovre, Apellis Pharmaceuticals) and avacincaptad pegol (Izervay, Astellas). While these complement inhibitors provide a much-needed option to slow lesion growth, they do not stop GA in its tracks, pushing researchers to find other novel approaches. Here are the many drugs in the pipeline that aim to slow GA lesion growth and, hopefully, preserve vision (Table).

PHASE 3 TRIALS

ALK-001 (gildeuretinol, Alkeus Pharmaceuticals) is an oral therapy designed to reduce the dimerization of vitamin A. Topline data from the phase 3 SAGA trial (NCT03845582) show a 13.4% reduction in GA lesion growth rate from baseline to 24 months ($P = .075$), which was not statistically significant. However, from 6 to 24 months, treatment reduced the lesion growth rate by 15.3% ($P = .047$) in a prespecified analysis.[1]

ANX007 (Annexon Biosciences) is an intravitreal C1q inhibitor. Although the phase 2 ARCHER trial (NCT04656561) did not meet its primary endpoint of statistically significant reduction in GA lesion growth at 12 months, 6% of patients treated with ANX007 lost 15 letters versus 21% of patients treated with sham ($P = .0021$).[2] The primary endpoint for the phase 3 ARCHER II trial (NCT06510816) is the proportion of patients experiencing a BCVA ≥ 15-letter loss from baseline through 18 months.

Elamipretide (Stealth Biotherapeutics) is a subcutaneous medication designed to normalize mitochondrial structure and function and improve cell viability in the setting of AMD. The phase 2 ReCLAIM-2 trial (NCT03891875) did not meet the primary endpoints of GA lesion progression and mean change in low-luminance visual acuity; however, patients treated with subcutaneous elamipretide had a 43% reduction in ellipsoid zone total attenuation at 48 weeks ($P = .003$) compared with those treated with placebo.[3] The primary endpoint of the phase 3 ReNEW trial (NCT06373731) is the rate of change in the macular area of photoreceptor loss at 48 weeks compared with baseline.[4] A second phase 3 trial, ReGAIN, is in the works.[4]

Tinlarebant (LBS-008, Belite Bio) is an oral agent in a clinical trial for the treatment of GA. This antagonist of retinol-binding protein is used to reduce the accumulation of vitamin A-based toxins (ie, bisretinoids). The phase 3 PHOENIX trial (NCT05949593) is investigating once-daily oral 5 mg tinlarebant versus placebo in approximately 430 patients with GA. The primary endpoint is the rate of change in GA lesion size, and the secondary endpoints include change in BCVA and changes in the inner/outer segment junction of photoreceptors.[5]

PHASE 2 INVESTIGATIONS

AVD-104 (Aviceda Therapeutics) is an intravitreal glycan-coated nanoparticle with a dual mechanism of action that is designed to repolarize activated microglia/macrophages to their healing state and inhibit complement cascade amplification. Results from part 1 of the phase 2 SIGLIC trial (NCT05839041) demonstrated a 48% reduction in lesion growth rate compared with the fellow eye at 3 months. Results of part 2 of the trial are expected in late 2025.[6]

CT1812 (Cognition Therapeutics) is an oral selective sigma-2 antagonist binding retinal pigment epithelium cells designed to regulate the damage-response processes impaired in GA. The phase 2 study (NCT05893537) is assessing the efficacy, safety, and tolerability of a single oral dose of CT1812 compared with placebo in approximately 246 patients. The primary endpoint is the change in GA lesion area from baseline at 104 weeks.[7]

Danicopan (ALXN2040, Alexion Pharmaceuticals/Astrazeneca), a complement factor D inhibitor, is under investigation as an oral therapy. The phase 2 trial (NCT05019521) is evaluating four treatment arms: 100 mg or 200 mg twice daily, 400 mg once daily, and matching placebo. The trial includes a 6-week screening period, a 104-week treatment period, and a 30-day follow-up period.

JNJ-1887 (Janssen) is an intravitreal gene therapy that expresses soluble CD59 and is designed to treat GA and wet AMD. The pooled phase 1 safety data showed that the therapy was well tolerated with no dose-limiting toxicities or serious or systemic adverse events.[8] The phase 2 trial (NCT05811351) is evaluating a high and low dose in combination with prophylactic steroids compared with sham.

ONL1204 (ONL Therapeutics) is an intravitreal therapy aimed at reducing Fas-mediated retinal cell apoptosis and inflammatory cytokines. The open label/dose escalation portion of the phase 1b trial (NCT04744662) found that a single injection of ONL1204 led to a 42% reduction in GA lesion growth at 24 weeks compared with the untreated fellow eye. The natural history/treatment component of the trial showed that treatment with 200 µg ONL1204 (two injections 12 weeks apart) led to an approximate 50% lower rate of lesion growth compared with sham-treated eyes at 24 weeks. The phase 2 trial (NCT06659445) is evaluating two dose levels of ONL1204 and two treatment frequencies in approximately 324 patients with GA.[9]

RG6501 (OpRegen, Lineage Cell Therapeutics and Genentech/Roche) is an allogeneic retinal pigment epithelial cell therapy that is delivered subretinally. In the phase 1/2a trial (NCT02286089), treatment led to a mean BCVA gain of 5.5 letters and improvements in the retinal pigment epithelium drusen complex in cohort 4 at 24 months.[10] The phase 2 trial (NCT05626114) is evaluating the success and safety of subretinal delivery and preliminary activity of the cell therapy in 60 patients with GA.

PROMISING PHASE 1 DRUG CANDIDATES

ASP7317 (Astellas) is a subretinal cell therapy derived from human embryonic stem cells. The phase 1b trial (NCT03178149) is evaluating three doses of ASP7317 with immunosuppressive therapy. The primary outcomes focus on safety and tolerability at 52 weeks, and secondary endpoints include change in GA lesion area and vision.

BI 771716 (Boehringer Ingelheim/CDR-Life) is an intravitreal antibody fragment designed to penetrate all retinal layers and target areas of GA. The phase 1 trial (NCT06006585) of single and multiple doses met its primary safety endpoint in 20 patients followed for up to 112 days. The company plans to launch a phase 2 trial in early 2025.[11]

OCU410 (AAV5-hRORA, Ocugen) is a gene therapy that delivers the *RORA* gene, which affects lipid metabolism, demonstrates an antiinflammatory role, and inhibits the complement system. Preliminary results from part 1 of the phase 1/2 trial (NCT06018558) showed a 21.4% slower lesion growth in treated eyes versus untreated eyes at 6 months, with no reported drug-related serious adverse events.[12]

SURGICAL APPROACHES TO RESTORING VISION IN GA

The PRIMA retinal implant (Science Corporation) is a visual prosthesis that incorporates a photovoltaic implant, glasses with a camera and a projection system, and a pocket processor. The preliminary results of the PRIMAvera trial (NCT04676854) of 38 patients with central visual field loss due to GA demonstrate a 23-letter (4.6 lines) mean improvement in vision at 12 months post-implantation compared with baseline. The most successful patient experienced a gain of 59 letters (11.8 lines).[13]

An intraocular lens implant, the Smaller-Incision New-Generation Implantable Miniature Telescope (SING IMT, Samsara Vision), remains under investigation in the United States with the CONCERTO study (NCT05438732) for patients with late-stage AMD. This trial is evaluating the safety and efficacy of the SING IMT implanted in approximately 125 patients. The device received a CE mark for the European Union in 2020.[14]

AT A GLANCE

- Four therapies are now in phase 3 investigations, two of which are oral agents targeting vitamin A and its role in the geographic atrophy disease process.
- Many therapies have novel delivery methods, including oral, subcutaneous, and subretinal.
- Retinal and intraocular implants are under investigation to restore vision in patients with late-state AMD.

TABLE. INVESTIGATIONAL THERAPIES FOR GEOGRAPHIC ATROPHY

Study Drug (Company)	Mechanism	Delivery	Trial NCT	Trial Status	Completion	Last Update
Phase 3						
ALK-001 (gildeuretinol, Alkeus Pharmaceuticals)	Visual cycle modulator	Oral	NCT03845582	Complete	July 2023	November 2024
Elamipretide (Stealth Biotherapeutics)	Mitochondrial enhancer	Subcutaneous	NCT06373731	Recruiting	August 2026	November 2024
ANX007 (Annexon Biosciences)	Immunomodulator	Intravitreal	NCT06510816	Recruiting	October 2026	November 2024
Tinlarebant (LBS-008, Belite Bio)	Visual cycle modulator	Oral	NCT05949593	Recruiting	August 2027	March 2024
Phase 2						
Danicopan (ALXN2040, Alexion Pharmaceuticals/AstraZeneca)	Immunomodulator	Oral	NCT05019521	Active, not recruiting	July 2024	November 2024
AVD-104 (Aviceda Therapeutics)	Immunomodulator	Intravitreal	NCT05839041	Active, not recruiting	June 2025	November 2024
JNJ-1887 (Janssen)	Gene therapy	Intravitreal	NCT05811351	Active, not recruiting	July 2025	October 2024
CT1812 (Cognition Therapeutics)	Immunomodulator	Oral	NCT05893537	Recruiting	July 2027	October 2024
ONL1204 (ONL Therapeutics)	Immunomodulator	Intravitreal	NCT06659445	Not yet recruiting	November 2027	October 2024
RG6501 (OpRegen, Lineage Cell Therapeutics/Genentech/Roche)	Cell therapy	Subretinal	NCT05626114	Recruiting	April 2029	October 2024
Phase 1, 1/2						
BI 771716 (Boehringer Ingelheim/CDR-Life)	Antibody fragment	Intravitreal	NCT06006585	Complete	May 2024	June 2024
OCU410 (AAV5-hRORA, Ocugen)	Gene therapy	Subretinal	NCT06018558	Recruiting	September 2025	October 2024
ASP7317 (Astellas)	Cell therapy	Subretinal	NCT03178149	Recruiting	June 2026	November 2024

THE ROAD AHEAD

This year has been marked by significant advances within the GA pipeline. We now have four therapies in phase 3, all of which offer alternative treatment approaches beyond complement C3 and C5—two of which are oral agents. Several gene and cell therapies are showing promise as potentially one-and-done treatments. We look forward to watching the clinical trial data develop in the hopes that we will one day have better, more durable therapies to offer patients with GA. ■

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 November 4, 2024. tinyurl.com/r72eyjnz
2. Annexon presents phase 2 vision preservation data with ANX007 in dry AMD patients with less advanced GA at the American Academy of Ophthalmology 2024 Meeting [press release]. Annexon. October 21, 2024. Accessed November 5, 2024. tinyurl.com/5x2kkwb7
3. Heier J. ReCLAIM-2 trial, a phase 2 trial of elamipretide in patients with non-central geographic atrophy. Presented at: American Society of Retina Specialists; July 14, 2022; New York, NY.
4. Stealth BioTherapeutics announces first patient enrolled in global phase 3 clinical program for elamipretide in patients with dry age-related macular degeneration [press release]. Stealth BioTherapeutics. June 5, 2024. Accessed November 5, 2024. tinyurl.com/ypwdpct8
5. Belite Bio. Company presentation: early intervention with an oral treatment for macular degeneration. October 2024. Accessed November 5, 2024. tinyurl.com/5n99vp7f
6. Singh RP. Results from phase 2/3 SIGLEC trial assessing AVD-104 for geographic atrophy: glyco-immunologic modulation of macrophage activity. Presented at AAO; October 18, 2024; Chicago.
7. Cognition Therapeutics. Age-related macular degeneration. Accessed November 5, 2024. bit.ly/47b058P
8. Lad EM, Chao DL, Pepio A, et al. Pooled safety analysis of a single intravitreal injection of JNJ-1887 (gene therapy, AAVCAG-sCD59) in patients with age-related macular degeneration (AMD). Presented at Euretina; October 5-8, 2023; Amsterdam.
9. Vajzovic L. Fas inhibition with ONL1204 for the treatment of geographic atrophy secondary to age-related macular degeneration: results from a phase 1b study. Presented at Euretina; September 19-22, 2024; Barcelona, Spain.
10. Telander D. OpRegen retinal pigment epithelium (RPE) cell therapy for patients with geographic atrophy (GA): month 24 results from the phase 1/2a trial. Presented at Retinal Cell and Gene Therapy Innovation Summit 2024; May 3, 2024; Seattle.
11. Boehringer Ingelheim announces plans to advance potential new treatment for geographic atrophy, following positive phase I results [press release]. Boehringer Ingelheim. September 5, 2024. Accessed November 6, 2024. tinyurl.com/4n6bn72y
12. Ocugen reports positive preliminary data from OCU410 trial for geographic atrophy [press release]. Eyewire+. November 19, 2024. Accessed November 20, 2024. tinyurl.com/yr755txh
13. Science announces positive preliminary results for vision restoration in pivotal clinical trial [press release]. Science Corporation. October 21, 2024. Accessed November 6, 2024. science.xyz/news/primavera-trial-preliminary-results
14. Samsara Vision. New Technology. Accessed November 6, 2024. tinyurl.com/4nzvzs5e

OUT OF THE PIPELINE AND INTO PRACTICE

LumiThera received FDA authorization to market its Valeda Light Delivery System, the first therapy to use photobiomodulation (PBM) to improve visual acuity in patients with intermediate AMD. The approval is based on LIGHTSITE III trial (NCT04065490) data, which demonstrated durable BCVA improvements of more than 5 letters that were maintained over 24 months.[1] This noninvasive treatment approach delivers PBM to the eye at wavelengths of 590 nm, 660 nm, and 850 nm. Each treatment cycle includes nine PBM treatment sessions delivered over 3 to 5 weeks, with each treatment lasting less than 5 minutes per eye (without the need for dilation). The LIGHTSITE III data were the result of six PBM treatment cycles (every 4 months) over 2 years.[2]

1. LumiThera obtains FDA authorization of Valeda treatment for dry AMD patients to improve vision [press release]. LumiThera. November 4, 2024. Accessed November 6, 2024. tinyurl.com/4t63naca
2. Do D. Photobiomodulation for dry AMD (phase 3 LIGHTSITE III study). Presented at AAO; October 20, 2024; Chicago.