The Future of Wet AMD Therapeutics

The pipeline is bursting with drug candidates that may one day provide more effective, durable, and cost-effective options.

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It's been an exciting year for AMD with new therapeutic options in the clinic. The traditional set of anti-VEGF options has expanded to include biosimilars, high-dose variations, and dual-action combination therapies. With all this innovation, we may soon have a doubling of available choices to treat wet AMD.

Nonetheless, the path to market can be challenging, and several promising candidates have been discontinued or paused in the last year. Kodiak discontinued and then reinitiated its tarcocimab program with the release of positive phase 3 GLOW data.[1] The FDA did not approve Outlook Therapeutic's ONS-5010/Lytenava, and the company is pursuing an additional phase 3 trial (NCT05112861) set to complete in March 2024.[2] The port delivery system with ranibizumab (Susvimo, Genentech/Roche) was voluntarily recalled due to issues with septum dislodgement, and the company hopes to introduce an updated version soon.[3]

Research continues for other therapeutics, and trials are underway that strive to offer more effective, durable, and cost-effective options for patients—some are exploring gene therapy, tyrosine kinase inhibition, and alternative methods of drug delivery beyond intravitreal injection (Table 1).

GENE THERAPY

Gene therapy is an exciting alternative to ongoing intravitreal injections. By using viral vectors to deliver anti-VEGF transgenes, these therapies may offer a one-and-done treatment regimen to provide sustained anti-VEGF protein expression after initial administration.

ABBV-RGX-314 (Regenxbio) is being tested as a subretinal injection during vitrectomy in two phase 3 trials, ASCENT (NCT05407636) and ATMOSPHERE (NCT04704921). The studies are comparing the drug candidate with intravitreal aflibercept (Eylea, Regeneron) and ranibizumab (Lucentis, Genentech/Roche), respectively. This gene therapy produces sustained expression of ranibizumab-like proteins.

ABBV-RGX-314 is also under investigation with a one-time in-clinic suprachoroidal delivery method in the phase 2 AAVIATE trial (NCT04514653). The 6-month interim safety results showed that the suprachoroidal delivery was well-tolerated in 85 patients. Mild intraocular inflammation was reported with an increase in incidence with the third dose level (cohort 4, $1x10^{12}$ GC/eye); all inflammation resolved with topical corticosteroids. There was an 85% reduction in the annualized injection rate, with 67% of patients (all previously treated with anti-VEGF therapy) remaining injection-free in the highest dose group.[4] ABBV-RGX-314 at the third dose level was also evaluated with a short course of prophylactic ocular steroids, which meaningfully reduced the occurrence of mild to moderate intraocular inflammation.[5]

Ixoberogene soroparvovec (Ixo-vec [formerly ADVM-022], Adverum Biotechnologies) is in the phase 2

AT A GLANCE

- Gene therapy may offer a one-time treatment regimen to provide sustained anti-VEGF protein expression after initial administration.
- Tyrosine kinase inhibitors bind to intracellular domains of tyrosine kinase receptors and target the downstream receptor signaling of VEGF receptors, platelet-derived growth factor signaling, and more.
- Several therapies incorporate dual targets, such as inhibition of VEGF-C and VEGF-D, VEGF and fibroblast growth factor, VEGF and Ang-2, VEGF and C3b/C4b, and VEGF with Tie2 promotion.

TABLE 1. WET AMD TREATMENT PIPELINE					
Drug (Company)	**Mechanism**	**NCT #**	**Estimated Completion**	**Recruitment Status**	**Last Update**
Phase 3					
ABBV-RGX-314 (Regenxbio)	Subretinal adeno-associated viral (AAV) vector with a gene encoding for a monoclonal antibody fragment	NCT04704921 NCT05407636	May 2025 December 2025	Recruiting	May 2023 August 2023
BAT5906 (Bio-thera)	Recombinant anti-VEGF intravitreal injection	NCT05439629	June 2025	Recruiting	February 2023
IBI302 (Innovent Biologics)	Intravitreal injection of a bispecific fusion protein	NCT05972473 NCT05403749	February 2027 June 2024	Not yet recruiting	August 2023 June 2022
OPT-302 (Opthea)	Biologic inhibitor of VEGF-C and VEGF-D	NCT04757610 NCT04757636	December 2024	Recruiting	September 2022
RC28-E (RemeGen)	VEGF/FGF dual decoy receptor fusion protein	NCT05727397	December 2025	Recruiting	August 2023
OTX-TKI (Axpaxli, Ocular Therapeutix)	Intravitreal tyrosine kinase inhibitor gel implant	Not posted (phase 3) NCT04989699 (phase 1)	February 2023	Not yet recruiting Active, not recruiting	September 2022
Tarcocimab (KSI-301, Kodiak Sciences)	Intravitreal injection of an antibody biopolymer conjugate	NCT04964089	Complete	Complete	May 2023
Phase 2					
4D-150 (4D Molecular Therapeutics)	Intravitreal AAV anti-VEGF transgene expressing aflibercept and VEGF-C inhibitory RNAi	NCT05197270	November 2025	Recruiting	August 2023
ABBV-RGX-314 (Regenexbio)	Suprachoroidal AAV with a gene encoding for a monoclonal antibody fragment	NCT04514653	January 2024	Recruiting	May 2023
AKST4290 (Alkahest)	Oral CCR3 inhibitor	NCT04331730	Complete	Complete	October 2022
AXT107 (Asclepix Therapeutics)	Suprachoroidal anti-VEGF and Tie2 activation	NCT05859776	April 2025	Not yet recruiting	May 2023
CLS-AX (Clearside Biomedical)	Suprachoroidal tyrosine kinase inhibitor	NCT04626128	Complete	Complete	September 2023
D-4517.2 (Ashvattha Therapeutics)	Subcutaneous VEGF-R tyrosine kinase inhibitor	NCT05387837	June 2023	Recruiting	February 2023
EYP-1901 (EyePoint Pharmaceuticals)	Tyrosine kinase inhibitor intravitreal implant	NCT05381948	April 2024	Active, not recruiting	July 2023
Ixoberogene soroparvovec (Ixo-vec, Adverum Biotechnologies)	Intravitreal AAV carrying an aflibercept coding sequence	NCT05536973	February 2024	Recruiting	May 2023
PAN-90806 (PanOptica)	Topical tyrosine kinase inhibitor	NCT03479372	Complete	Complete	July 2019
RBM-007 (Ribomic)	Anti-fibroblast growth factor 2 aptamer intravitreal injection	NCT04640272	Complete	Complete	June 2023
UBX1325 (Unity Biotechnology)	Intravitreal injection of a Bcl-xl inhibitor	NCT05275205	Complete	Complete	October 2023

TABLE 1. WET AMD TREATMENT PIPELINE (CONTINUED)

Drug (Company)	Mechanism	NCT #	Estimated Completion	Recruitment Status	Last Update
Phase 1					
AM712 (AffaMed)	Recombinant anti-VEGF humanized monoclonal antibody and Ang-2 antagonist peptide fusion protein	NCT05345769	June 2024	Recruiting	July 2023
AIV007 (AiViva Biopharma)	Periocular gel suspension broad-spectrum tyrosine kinase inhibitor	NCT05698329	April 2025	Recruiting	March 2023
Other Unique Trials					
Adjuvant doxycycline	Oral doxycycline, MMP-9 inhibition	NCT04504123	December 2023	Recruiting	March 2023
Episcleral brachytherapy (Salutaris Medical Devices)	Retrobulbar single brachytherapy treatment (fraction of 24 Gy Strontium90)	NCT02988895	May 2025	Active, not recruiting	August 2023
OCT angiography-directed photodynamic therapy triple therapy	Ranibizumab (Lucentis, Genentech/Roche), photodynamic therapy with verteporfin (Visudyne, Bausch + Lomb), and triamcinolone acetonide	NCT04075136	December 2024	Recruiting	May 2023

LUNA trial (NCT05536973) evaluating an intravitreal injection of one of two doses in conjunction with prophylactic steroids in patients with wet AMD. The 3-year data from the phase 1 OPTIC trial (NCT03748784) show that this aflibercept-encoding AAV.7m8 vector produced therapeutically active ranges of aflibercept protein; there was an 84% reduction in annualized anti-VEGF injections, with 53% of the participants at the 2E11 dose free of injections at 3 years.[6]

4D-150 (4D Molecular Therapeutics) is a dual anti-VEGF transgene that expresses aflibercept and VEGF-C inhibitory RNAi; the investigational therapy is dosed as a one-time intravitreal injection. The phase 1/2 trial (NCT05197270) consists of four cohorts: dose escalation (up to four dose levels), dose expansion (exploring two doses), steroid optimization, and population extension.

TYROSINE KINASE INHIBITORS

These small molecules bind to intracellular domains of tyrosine kinase receptors and target the downstream receptor signaling of VEGF receptors, platelet-derived growth factor signaling, and more.

Axitinib (CLS-AX, Clearside Biomedical) is in a phase 1/2a trial (NCT04626128) investigating one-time suprachoroidal delivery of the drug candidate. All four dose-escalating cohorts showed no serious safety signals, and cohorts three and four experienced a 73% reduction in treatment burden at 3 months.[7] The phase 2b ODYSSEY trial completed recruitment (NCT05891548).

EYP-1901 (EyePoint Pharmaceuticals) is an intravitreal sustained-release implant that is under investigation in the phase 2 DAVIO trial for patients with wet AMD (NCT05381948). Initial safety data suggest the therapy is well tolerated with no drug-related severe ocular adverse events. The company is expecting topline data in December.[8]

PAN-90806 (PanOptica) phase 1/2 clinical trial (NCT03479372) topline results showed safety and a biological response with this once-daily topical eye drop for the treatment of AMD. More than half of the treated patients completed the 12-week study without requiring rescue with an anti-VEGF injection, with 88% experiencing clinical improvement or disease stability.[9]

D-4517.2 (Ashvattha Therapeutics) is a monthly subcutaneous therapy in a phase 2 trial (NCT05387837) investigating the safety, tolerability, and pharmacokinetics of four different doses. In a mouse model, treatment with D-4517.2 led to an approximate two-fold decrease in choroidal neovascular lesion area compared with controls.[10]

OTX-TKI (Axpaxli, Ocular Therapeutix) is an investigational bioresorbable implant with axitinib. The company is initiating a phase 3 trial after the 12-month phase 1 (NCT04989699) data showed an 89% reduction in treatment burden for patients treated with the implant compared with those treated with aflibercept.[11] In the pivotal superiority trial, 300 patients will receive either a single OTX-TKI implant or one injection of aflibercept followed by as-needed anti-VEGF treatment.

DUAL TARGET THERAPY

OPT-302 (Opthea), is a Fc-fusion protein designed to inhibit VEGF-C and VEGF-D. The phase 3 trials (NCT04757610, NCT04757636) are investigating combination therapy with OPT-302 and either aflibercept or

TABLE 2. BIOSIMILARS IN PHASE 3 TRIALS					
Drug (Company)	Template Biologic	NCT #	Estimated Completion	Recruitment Status	Last Update
ABP-938 (Amgen)	Aflibercept	NCT04270747	Complete	Complete	May 2023
CKD-701 (Chong Kun Dang)	Ranibizumab	NCT04857177	Complete	Complete	April 2021
FYB203 (Formycon AG)	Aflibercept	NCT04522167	Complete	Complete	June 2023
ONS-5010 (Lytenava, Outlook Therapeutics)	Bevacizumab	NCT03834753	Complete	Complete	February 2022
SB15 (Samsung Bioepis)	Aflibercept	NCT04450329	Complete	Complete	April 2022
SOK583A19 (Sandoz)	Aflibercept	NCT04864834	Complete	Complete	July 2023
Xlucane (Xbrane Biopharma)	Ranibizumab	NCT03805100	Complete	Complete	March 2022
SCD-411 (Sam Chun Dang Pharmaceutical)	Aflibercept	NCT04480463	Complete	Complete	October 2023
LUBT010 (Lupin)	Ranibizumab	NCT04690556	October 2022	Unknown	March 2021
OT-702 (LY9004, Ocumension Therapeutics)	Aflibercept	NCT04572698	December 2023	Not yet recruiting	October 2020
TAB014 (TOT Biopharm)	Bevacizumab	NCT05461339	March 2024	Recruiting	March 2023
GNR-067 (Generium)	Ranibizumab	NCT04667039	September 2024	Recruiting	September 2023
HLX04-O (Shanghai Henlius)	Bevacizumab	NCT04740671	November 2024	Recruiting	August 2023
AVT06 (Alvotech)	Aflibercept	NCT05155293	December 2024	Recruiting	June 2023

ranibizumab, with a primary endpoint of change in BCVA at week 52. In phase 2, the mean visual acuity gain in the 2.0 mg OPT-302 group was significantly superior to sham.[12]

RC28-E (RemeGen) is a dual decoy receptor fusion protein targeting VEGF and fibroblast growth factor undergoing phase 3 testing (NCT05727397). The trial is investigating intravitreal injection of the study drug every 12 weeks after a loading dose of three monthly injections compared with aflibercept every 8 weeks after a loading dose of three monthly injections.

Efdamrofusp alfa (IBI302, Innovent Biologics) is a recombinant human anti-VEGF and anticomplement (C3b and C4b) bispecific fusion protein. The company announced the first patient dosed in the phase 3 STAR trial (NCT05972473) evaluating intravitreal injections of 8 mg efdamrofusp alfa compared with aflibercept.[13] The phase 2 trial (NCT05403749) is ongoing.

AXT107 (Asclepix Therapeutics) is a suprachoroidal injection of a suspension that self-assembles into a gel inside the eye and blocks VEGF and promotes Tie2 signaling. The phase 1/2 trial (NCT05859776) is investigating low, mid, and high doses of the study drug in 15 patients to assess safety up to 40 weeks.

AM712 (AffaMed) is a candidate fusion protein targeting VEGF and Ang-2, similar to faricimab-svoa (Vabysmo, Genentech/Roche). The phase 1 clinical trial (NCT05345769), set for completion in June 2024, is evaluating ascending doses of the study drug, followed by its safety, tolerability, pharmacokinetics, and efficacy.

ALTERNATIVE APPROACHES

UBX1325 (Unity Biotechnology) is a small molecule Bcl-xl inhibitor that increases apoptosis of diseased senescent cells in the retinal pigment epithelium, suppressing inflammation and neovascularization. At 48 weeks in the completed phase 2 ENVISION trial (NCT05275205), 40% of patients treated with the study drug did not require anti-VEGF treatment, and 64% achieved an anti-VEGF treatment-free interval of more than 24 weeks. However, the company indicated that it will be focusing on the diabetic macular edema program for UBX1325.[14]

RBM-007 (Ribomic) is an anti-fibroblast growth factor 2 aptamer that inhibits angiogenesis and scar formation. The company completed the phase 2 trial (NCT04895293), which suggested a clinical benefit in treatment-naïve patients.

Tarcocimab (KSI-301, Kodiak Sciences), an intravitreal antibody biopolymer conjugate, met its primary endpoint in the phase 3 DAYLIGHT study (NCT04964089) of noninferior visual acuity gains with monthly KSI-301 compared with aflibercept every 8 weeks. The company plans to pursue another phase 3 trial to support a single biologics licensing agreement submission for wet AMD, nonproliferative diabetic retinopathy, and retinal vein occlusion.[1]

Other unique approaches to wet AMD therapy include an oral CCR3 inhibitor (NCT04331730, AKST4290, Alkahest); episcleral brachytherapy (NCT02988895, Salutaris Medical Devices); OCT angiography-directed photodynamic therapy triple therapy with ranibizumab, photodynamic therapy with

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verteporfin (Visudyne, Bausch + Lomb), and triamcinolone acetonide (NCT04075136); and adjuvant doxycycline/MMP-9 inhibition (NCT04504123).

BIOSIMILARS

Many companies are rushing to introduce anti-VEGF biosimilars, and more than 10 drug candidates are in phase 3 clinical trials with biosimilars of bevacizumab (Avastin, Genentech/Roche), aflibercept, and ranibizumab (Table 2).

THE LANDSCAPE

Exciting therapies are on the horizon for wet AMD. We may soon be using gene therapy, tyrosine kinase inhibitors, or a variety of other approaches in the clinic; the future of wet AMD treatment, and the practice of retina, may look quite different in just a few years. ■

Editor's Note: Data are cited as of November 13, 2023.

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