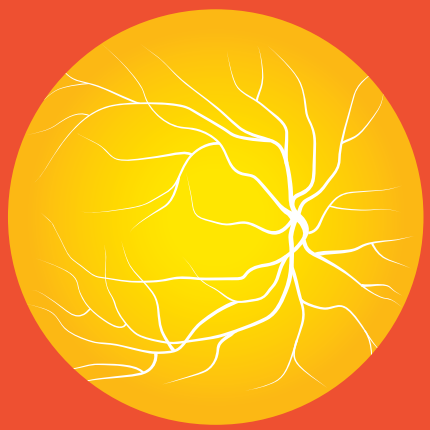

THE THERAPEUTIC LANDSCAPE FOR DIABETIC EYE DISEASE

Many novel approaches are chugging through the pipeline, with promising data from phase 2 and 3 trials.

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The treatment of diabetic retinopathy (DR) currently includes panretinal photocoagulation to prevent severe vision loss due to proliferative DR (PDR) and intravitreal anti-VEGF agents. Although these treatments have reduced the rate of vision loss from DR and its sequelae,[1,2] many patients have treatment-resistant disease or struggle with treatment burden. Thus, many advances are under investigation, not only in terms of treatment delivery but also for targeting pathways other than anti-VEGF. In this article, we highlight some of the latest therapeutic developments (Table).

INTRAVITREAL DELIVERY

Tarcocimab tedromer (KSI-301, Kodiak Sciences) is an anti-VEGF antibody biopolymer conjugate that blocks all VEGF-A isoforms. The phase 3 GLOW trial (NCT05066230) compared tarcocimab with sham in moderately severe to severe nonproliferative DR (NPDR). After receiving four injections of the study drug, a significantly higher proportion of patients had a 2-step or more DRSS improvement from baseline (41.1%) compared with sham (1.4%) at week 48.[3] The similarly designed phase 3 GLOW2 clinical trial (NCT06270836) is recruiting.

RC28-E (RemeGen), a fusion protein targeting FGF2 and VEGF, is in a phase 3 trial (NCT05885503) for the treatment of diabetic macular edema (DME). The trial is comparing 2 mg RC28-E with 2 mg aflibercept (Eylea, Regeneron) with the primary outcome being change in BCVA at week 52.

MK-3000 (restoret, EyeBio/Merck) is a tetravalent, trispecific antibody that acts as an agonist of the Wnt signaling pathway.[4] The phase 2b/3 BRUNELLO trial (NCT06571045) is investigating the safety and efficacy of two dosages of MK-3000 compared with ranibizumab (Lucentis, Genentech/Roche) in patients with DME.[4] Primary endpoints are safety and mean change in BCVA from baseline to week 52.

UBX1325 (foselutoclax, Unity Biotechnology) is a senolytic small-molecule inhibitor of antiapoptotic protein BCL-xL. In the phase 2 BEHOLD study (NCT04857996), one injection of UBX1325 led to an improvement of 6.2 letters from baseline, 5.6 more than sham, at 48 weeks.[5] Of UBX1325-treated patients, 53% did not require rescue injections before 48 weeks.[5] The phase 2b ASPIRE study (NCT06011798) is comparing the safety and efficacy of UBX1325 with 2 mg aflibercept for patients with NPDR and DME.[6]

AG-73305 (Allgenesis Biotherapeutics), a bispecific Fc-fusion protein designed to block VEGF and integrin pathways, showed positive preliminary results from the phase 2a trial (NCT05301751) for DME. The data for

22 patients treated with a single intravitreal injection showed a mean BCVA improvement of +6.4 ETDRS letters and central subfield thickness (CST) reduction of 100 µm at 4 weeks, which lasted between 12 and 24 weeks.[7]

RG6179 (vamikibart, Roche) is a monoclonal antibody that binds interleukin-6 cytokines. The phase 2 trial (NCT05151731) is evaluating the safety and efficacy of two dosages of RG6179 compared with ranibizumab for DME. A second phase 2 trial (NCT05151744), now complete, is evaluating the therapy in combination with ranibizumab.

OPT-302 (Opthea), an intravitreal anti-VEGF therapy that blocks VEGF-C and VEGF-D, is designed as a combination therapy with current anti-VEGF agents. In the completed phase 2 trial (NCT03397264), 52.8% of patients with DME treated with OPT-302 in combination with aflibercept achieved a visual gain of ≥ 5 ETDRS letters at 12 weeks compared with baseline.[8] The company has not announced plans to pursue further trials for DME.

BI 764524 (Boehringer Ingelheim) is a humanized monoclonal anti-semaphorin 3A antibody.[9] The tolerability of BI 764524 in patients with diabetic macular ischemia was evaluated in a phase 1/2 trial (NCT04424290), which met its primary safety endpoints. The study also showed early efficacy of foveal avascular zone area stabilization at week 16.[10]

SUPRACHOROIDAL INJECTION

OXU-001 (Oxular) consists of dexamethasone-containing microspheres that are delivered suprachoroidally for the treatment of DME. The phase 2 OXEYE study (NCT05697809) is comparing the safety, tolerability, efficacy, and durability of two dose levels of OXU-001 with the intravitreal dexamethasone implant (Ozurdex, Abbvie). Another phase 2 study (NCT05512962) evaluated the same delivery approach with triamcinolone acetonide suspension in patients with DME; the trial is complete with data pending.

IMPLANTS IN THE WORKS

The port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche) remains in the pipeline for DR/DME as the company awaits an FDA decision.[11] The supplemental biologics license application is based on the 1-year results of the phase 3 Pagoda (NCT04108156) and Pavilion (NCT04503551) trials, both of which met their primary endpoints. The 2-year data show that 95% and 98% of patients treated with the PDS in Pagoda and Pavilion, respectively, did not need supplemental injections at 2 years.[11]

IBE-814 IVT (Ripple Therapeutics) is an intravitreal dexamethasone implant that showed efficacy and safety in the phase 2 RIPPLE-1 trial (NCT04576689). At 6 months, patients treated with the high dose had a mean BCVA improvement of 8.7 ETDRS letters; at 9 months, treatment with the high dose led to an 82% reduction in treatment burden. Future studies will focus on the high dose.[12]

EYP-1901 (Duravyu, EyePoint Pharmaceuticals) delivers vorolanib, a selective tyrosine kinase inhibitor (TKI), in a bioerodible insert.[13] It is a pan-VEGF receptor inhibitor. The phase 2 VERONA clinical trial (NCT06099184) is comparing low and high doses of EYP-1901 with aflibercept for the treatment of DME. Interim 16-week data show improvements in BCVA and CST compared with baseline, and 82% of eyes in the 2.7 mg arm were supplement-free compared with 50% in the aflibercept control arm at 16 weeks.[14]

The phase 2 PAVIA trial (NCT05381948) for moderately severe to severe NPDR did not meet its primary endpoint.[15]

OTX-TKI (Axpaxli, Ocular Therapeutix) is an intravitreal implant containing the TKI axitinib. Interim phase 1 data (NCT05695417) showed that 23.1% of treated patients had a 2-step DRSS improvement at week 48; no patients in the treatment arm developed PDR or center-involving DME at week 48 compared with 37.5% in the sham arm.[16]

TOPICAL/SUBCUTANEOUS APPROACHES

OCS-01 (Oculis) is a topical dexamethasone suspension for the treatment of DME. There was a VA improvement of 2.6 ETDRS letters with OCS-01 drops three times daily for 12 weeks in the phase 2 study (NCT05066997), which was not statistically significant.[17] Preliminary results from the first stage of the phase 3 DIAMOND-1 trial (NCT05066997) showed statistically significant improvement in mean BCVA at 12 weeks.[18] There was also a significant decrease in CST at 6 and 12 weeks. The second stage of the trial is ongoing, and the phase 3 DIAMOND-2 trial (NCT06172257) is recruiting.

KHK4951 (tivozanib, Kyowa Kirin) is a VEGF-1, -2, and -3 TKI eye drop in a phase 2 trial (NCT06116916) for the treatment of DME. The topical medication is delivered in either high, medium, or low doses in conjunction with intravitreal aflibercept. The primary outcome is BCVA at 36 weeks.

D-4517.2 (Ashvattha Therapeutics) is a subcutaneous therapy consisting of a nanoparticle that inhibits VEGF receptors 1 and 2 tyrosine kinases. The phase 2 study (NCT05387837) is evaluating the safety, tolerability, pharmacokinetics, and efficacy of various dosages of D-4517.2 in patients with wet AMD or DME.

AT A GLANCE

- Many hopeful advances are under investigation for the treatment of diabetic eye disease in terms of therapy, delivery, and targeting pathways other than anti-VEGF.
- At least five therapies are in phase 3, one of which is an oral formulation.
- Seven therapies have completed phase 2, three of which are oral therapies, and one is suprachoroidal.

TABLE. NOVEL THERAPIES FOR THE TREATMENT OF DIABETIC EYE DISEASE

Study Drug (Company)	Condition	Target	Delivery	Trial NCT	Trial Status	Completion
Phase 3						
Port delivery system with ranibizumab (Susvimo, Genentech/Roche)	DR/DME	Anti-VEGF	Implant	NCT04108156 NCT04503551	Active, not recruiting	September 2022 October 2022
Fenofibrate (DRCR Retina Network)	DR	Peroxisome proliferator activated receptor alpha	Oral	NCT01320345 NCT04661358	Recruiting	December 2024 April 2029
KSI-301 (tarcocimab tedromer, Kodiak Sciences)	NPDR	Anti-VEGF antibody biopolymer conjugate	Intravitreal	NCT06270836	Recruiting	December 2025
OCS-01 (Oculis)	DME	Dexamethasone	Topical	NCT06172257 NCT05066997	Recruiting	December 2025 June 2026
RC28-E (RemeGen)	DME	Fusion protein targeting FGF2/VEGF	Intravitreal	NCT05885503	Recruiting	June 2026
MK-3000 (Restoret, EyeBio/Merck)	DME	Wnt signaling agonist	Intravitreal	NCT06571045	Recruiting	December 2027
Phase 2						
CU06 (Curacle)	DME	VEGF/angiopoietin-2 inhibitor	Oral	NCT05573100	Complete	
APX3330 (Opus [formerly Ocuphire])	NPDR	Ref-1 protein	Oral	NCT04692688	Complete	
Runcaciguat (Bayer)	NPDR	Guanylate cyclase activator	Oral	NCT04722991	Complete	
AG-73305 (Allgenesis Biotherapeutics)	DME	Bifunctional Fc-fusion protein	Intravitreal	NCT05301751	Complete	
IBE-814 IVT (Ripple Therapeutics)	DME	Dexamethasone	Implant	NCT04576689	Complete	
OPT-302 (Opthea)	DME	VEGF-C and VEGF-D inhibitor	Intravitreal	NCT03397264	Complete	
OXU-001 (Oxular)	DME	Dexamethasone	Suprachoroidal	NCT05512962 NCT05697809	Complete Active, not recruiting	November 2024
EYP-1901 (Duravyu, EyePoint Pharmaceuticals)	NPDR DME	TKI	Intravitreal	NCT05381948 NCT06099184	Complete Fully enrolled	January 2025
RG6179 (vamikibart, Roche)	DME	Interleukin-6 cytokine inhibitor	Intravitreal	NCT05151744 NCT05151731	Complete Active, not recruiting	November 2024
RZ402 (Rezolute)	DME	Plasma kallikrein inhibitor	Oral	NCT05712720	Active, not recruiting	May 2024
ABBV-RGX-314 (Regenxbio/Abbvie)	NPDR/mild PDR	Gene therapy	Suprachoroidal	NCT04567550	Recruiting	May 2024
OPL-0401 (Valo Health)	NPDR/PDR	Rho kinase signaling inhibitor	Oral	NCT05393284	Active, not recruiting	August 2024
D-4517.2 (Ashvattha Therapeutics)	DME	VEGF-1 and VEGF-2 TKI	Subcutaneous	NCT05387837	Active, not recruiting	November 2024
UBX1325 (foselutoclax, Unity Biotechnology)	DME	BCL-xL inhibitor	Intravitreal	NCT06011798	Active, not recruiting	March 2025
Tonabersat	DME	Connexin43 hemichannel inhibitor	Oral	NCT05727891	Recruiting	May 2025
KHK4951 (Tivozanib, Kyowa Kirin)	DME	VEGF-1, VEGF-2, and VEGF-3 TKI	Topical	NCT06116916	Recruiting	December 2025
4D-150 (4D Molecular Therapeutics)	DME	Gene therapy	Intravitreal	NCT05930561	Recruiting	February 2028
Phase 1, 1/2						
BI 764524 (Boehringer Ingelheim)	DMI	Semaphorin 3A inhibitor	Intravitreal	NCT04424290	Complete	
OTX-TKI (Axpaxli, Ocular Therapeutix)	NPDR	TKI	Implant	NCT05695417	Active, not recruiting	January 2024

Abbreviations: DME, diabetic macular edema; DMI, diabetic macular ischemia; DR, diabetic retinopathy; NPDR, nonproliferative DR; PDR, proliferative DR; TKI, tyrosine kinase inhibitor

ORAL OPTIONS

Fenofibrate activates peroxisome proliferator activated receptor alpha, altering systemic lipid synthesis. The phase 3 FAME 1 EYE trial (NCT01320345) is evaluating 145 mg of fenofibrate versus placebo in adults with type 1 diabetes. Patients are followed for 36 months to assess DR progression. Patient recruitment is occurring in Australia, New Zealand, Hong Kong, and the United Kingdom. In the United States, Diabetic Retinopathy Clinical Research (DRCR) Retina Network Protocol AF (NCT04661358) is evaluating the effect of 160 mg fenofibrate compared with placebo in eyes with mild to moderately severe NPDR and no center-involving DME at baseline with a follow-up of 6 years.

APX3330 (Opus [formerly Ocuphire]) is an oral drug

that targets the Ref-1 protein. Although the phase 2 trial (NCT04692688) failed to meet its primary endpoint, the company is planning a phase 2/3 trial in patients with NPDR.[19] The company recently acquired Opus Genetics and has discontinued internal development of APX3330.[20]

Tonabersat is an oral Connexin43 hemichannel inhibitor, which is a gap-junction modulator used in migraine treatment. It is being investigated in a phase 2 clinical trial (NCT05727891), DRCR Retina Network Protocol AN, comparing the efficacy of tonabersat versus placebo to reduce CST in eyes with center-involving DME and good visual acuity after 6 months.

Runcaciguat (Bayer) is a soluble guanylate cyclase activator under investigation as an oral therapy for the treatment of NPDR. The phase 2 NEON-NPDR trial (NCT04722991), now complete, evaluated the safety and efficacy of runcaciguat versus placebo in 104 patients, with a primary endpoint of a ≥ 2-step DRSS improvement at 24 weeks.

RZ402 (Rezolute) is an orally administered selective plasma kallikrein inhibitor designed to treat DME. The phase 2 trial (NCT05712720) met its primary endpoint of safety and a clinically significant reduction in CST from baseline.[21]

OPL-0401 (Valo Health) is an oral Rho kinase signaling inhibitor in phase 2 (NCT05393284) for NPDR and mild PDR. The trial is evaluating twice-daily dosing of OPL-0401 versus placebo in 114 patients for 24 weeks.[22] The primary endpoint is the proportion of patients with a ≥ 2-step DRSS improvement from baseline at 24 weeks.

CU06 (Curacle) is an oral anti-VEGF and angiopoietin-2 inhibitor. The phase 2a study (NCT05573100) evaluated once-daily 100 mg, 200 mg, or 300 mg CU06 versus placebo in patients with DME; the primary outcomes are change in CST at 12 weeks and determination of the optimal dose.[23]

GENE THERAPIES IN THE PIPELINE

ABBV-RGX-314 (Regenxbio/Abbvie) is a single-dose subretinal or suprachoroidal injection of an AAV gene vector that expresses an anti-VEGF-A antigen-binding fragment leading to sustained VEGF suppression. The phase 2 dose-escalation ALTITUDE study (NCT04567550) is assessing the efficacy, safety, and tolerability of suprachoroidal delivery of ABBV-RGX-314 in patients with NPDR or mild PDR. Preliminary 1-year data show that dosage levels 1 and 2 were well tolerated. At 1 year, dose level 2 in NPDR patients prevented disease progression and reduced the risk of developing vision-threatening events by 89%.[24]

4D-150 (4D Molecular Therapeutics) is a single-dose intravitreal retinotropic AAV vector that delivers two transgenes. These encode aflibercept and an miRNA sequence that inhibits VEGF-C.[25] 4D-150 is being investigated in the phase 2 SPECTRA study (NCT05930561) for the treatment of DME. This study is assessing the need for aflibercept rescue injections over 52 weeks, as well as BCVA and CST. ■

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