Equity Research

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Healthcare, Biotechnology

Non-Proliferative Diabetic Retinopathy and Diabetic Macular Edema: A Primer

Summary

Next week (Sept. 30th), Ocular Therapeutix (OCUL: BUY, $18 PT) will host an Investor Day which will cover, among other things, plans to study lead asset AXPAXLI in non-proliferative diabetic retinopathy (NPDR) and diabetic macular edema (DME). Based on sheer patient population, the market appears large and untapped. However, drugs that have gained approval in the indication have failed to capture more than a sliver of the market. In this report we discuss the disease, the existing treatments, and the next wave of therapeutics in development aiming to finally become a blockbuster in the indication.

The NPDR Market is Huge and Within Reach

The CDC estimates ~1.8M Americans have vision-threatening DR. Ocular estimates 9M US DR patients total. Yet the treated patient population remains tiny due to the slow progression of the disease, low healthcare-seeking habits of the patients, cost, and frequent injection burden. Still, anti-VEGF inhibition has been shown to work, and we believe that solving the issue of administration burden is the key to unlocking the market.

AXPAXLI Has Proof-of-Concept and Durability

In a Ph1 in patients with moderate to severe NPDR, Ocular's AXPAXLI (OTX-TKI) improved by DRSS ≥1 step in 46% of patients (0% in control) at week 48 after a single injection, eliminating vision-threatening complications (37.5% of control experienced VTCs). If these results are replicated and a 1-yr dosing frequency is achieved, this should expand the market. We are looking forward to more details on the upcoming pivotal program at their Investor Day, which includes an undisclosed novel endpoint for NPDR developed alongside the FDA. Given Ocular's track record creating a highly favorable design of pivotal studies for wAMD in terms of likelihood of success and claims on a potential label, we expect the NPDR endpoint to offer the same advantages.

Gene Therapy Could Offer a One-time Lifetime Solution

Competitors, including Regenxbio/AbbVie (RGNX: Buy, $50 PT/ ABBV: not covered), are developing gene therapies that intend to offer continuous anti-VEGF antibody production after one treatment, which would solve the administration burden. We see additional clinical risk due to the added complexity of the therapy, and even if successful commercially, we expect that enough of the market would remain available for periodic anti-VEGF products to remain successful. Regenx is initiating a Ph2b trial for their product candidate this year.

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Please see analyst certification and important disclosures information on pages 14 - 16 of this report.

Diabetic Retinopathy

Epidemiology and Pathophysiology

Diabetic retinopathy (DR) is the leading cause of vision loss and blindness in working-age adults, estimated to affect nearly 10M US adults and more than 100M people worldwide. It is primarily driven by chronic hyperglycemia causing damage to blood vessels in the retina, which then leads to a cascade of pathogenic effects including vessel leakage, inflammation, retinal ischemia and neoangiogenesis.

Classification

DR is a progressive disease beginning with the nonproliferative (NPDR) stage (subclassified as mild/moderate/severe), which is generally asymptomatic, and then progresses to proliferative DR (PDR), which is characterized by abnormal blood vessel growth in the retina and carries higher risk of vision loss.

Diabetic Macular Edema (DME), defined as thickening of the retina, is the most common cause of vision loss in DR and is estimated to affect 1.7M people in the US. It can occur at any stage of DR but is more common in advanced stages. Thickening in the center of the macula, termed center-involved (CI)-DME, is associated with a higher risk of vision loss as compared to noncenter-involved DME.

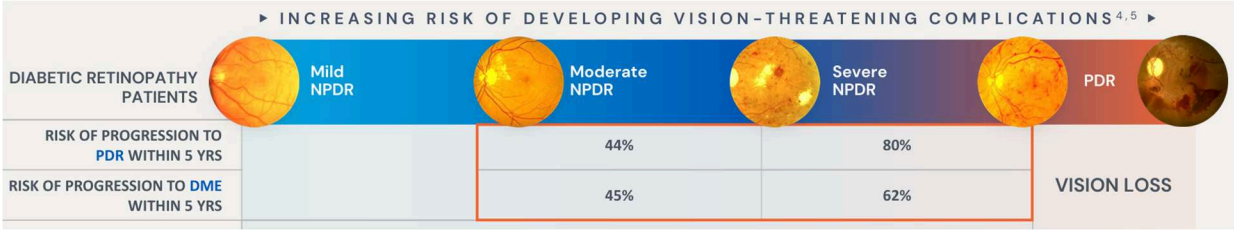
Detection

Early detection and intervention can reduce the risk of blindness in DR by over 90%. As the early stages of DR are asymptomatic, it is usually diagnosed prior to vision loss through a comprehensive eye exam. It is estimated that within 1-year, 5-10% of diabetes patients will develop DR, however, only ~50% of diabetes patients receive recommended annual screenings, indicating that many cases of DR are undiagnosed.

Risk Factors

Duration of diabetes is one of the biggest risk factors for developing DR, and once diagnosed, the overall risk of developing vision-threatening complications (PDR or DME) is estimated to be roughly 20-30% year over year, with increased risk at each progressive stage (Figure 1).

Figure 1. Risk of Developing Vision-Threatening Complications in DR



Source: Regenxbio ALTITUDE Study Presentation, November 2023

Treatment

Treatment depends on disease severity and presence of DME. Intravitreal anti-VEGF injections are the established first-line therapy for CI-DME and high-risk PDR, often combined with laser therapy. Corticosteroid implants or injections (dexamethasone or fluocinolone) are also effective but carry risks of elevated intraocular pressure and cataract progression, so are used as second line therapies.

For patients with NPDR or early PDR and without DME, the recommended intervention is management of healthy blood glucose levels and regular follow-up examinations (every 6-12 months for mild-moderate NPDR and every 2-4 months for severe NPDR and early PDR). The Diabetes Control and Complications Trial demonstrated that maintenance of healthy blood glucose levels (A1C<7%) reduced the development of PDR or severe NPDR by ~50%, and according to the National Diabetes Statistics Report, ~47% of US adults diagnosed with diabetes had an A1C value of 7% or higher in 2017-2020.

Anti-VEGF therapies have shown efficacy in improving DR severity and preventing development of PDR and DME, and several anti-VEGFs (Lucentis, Eylea, and Eylea HD) are now approved for the treatment of all stages of DR. However, the American Academy of Ophthalmology Preferred Practice Pattern recommends anti-VEGFs only in severe NPDR and according to a 2023 survey by the American Society of Retina Specialists, the majority of specialists treating severe NPDR without DME would not recommend anti-VEGF therapy.

Anti-VEGF Intravitreal Injections

Excessive production of VEGF (vascular endothelial growth factor) plays a central role in many retinal diseases by promoting angiogenesis and vascular permeability. Several anti-VEGF agents delivered by intravitreal injection are now approved for retinal diseases, most prominently wet age-related macular degeneration (wAMD), but also including DME and DR, macular edema following retinal vein occlusion (RVO), retinopathy of prematurity (ROP), myopic choroidal neovascularization (mCNV).

LUCENTIS (ranibizumab)

LUCENTIS (ranibizumab) is an anti-VEGF-A mAb that was first approved for DME in 2012, and in 2015, its approval was extended to treat DR in patients with DME. The approvals were based on results from two parallel sham-controlled Phase 3 trials, RIDE and RISE, which showed that monthly injections of ranibizumab improved macular edema, visual acuity and reduced the risk of further vision loss. In 2017, Lucentis was approved for all stages of DR based on the Diabetic Retinopathy Clinical Research Network's (DCR.net) Protocol S study, which compared Lucentis to panretinal laser therapy in DR patients with and without DME and showed that patients in the Lucentis group had greater improvements in DR severity. The US patent on Lucentis expired in June 2020 and at least two biosimilars are now marketed, after first launching in 2022.

AVASTIN (bevacizumab)

Bevacizumab is an anti-VEGF-A antibody approved for oncology indications. Its use in ophthalmologic indications followed the approval of ranibizumab and is still considered off-label. However, several studies have demonstrated bevacizumab to be safe and as effective in the

treatment of DME as ranibizumab. Intravitreal injections of bevacizumab are typically given every 4-6 weeks. Due to its considerably lower cost-per-treatment, it is usually the first-line anti-VEGF agent employed, with many insurers requiring that patients show disease progression on bevacizumab before another anti-VEGF agent will be covered (Global Trends in Retina Survey, 2022).

EYLEA (aflibercept 2 mg)

Aflibercept is a recombinant fusion protein, known as VEGF trap, consisting of an IgG backbone fused to the extracellular domains of the VEGF receptors, VEGFR1 and VEGFR2. Aflibercept has high affinity for VEGF-A and additionally binds VEGF-B and PIGF, which are also associated with angiogenesis.

EYLEA was first approved for the treatment of DME in 2014 and in 2015, its approval was extended for the treatment of DR in patients with DME. Those approvals followed the Phase 3 VIVID-DME and VISTA-DME trials, which compared EYLEA (given monthly or every 2 months after five initial monthly injections) to laser therapy. In 2019, EYLEA was approved for all stages of DR based on the PANORAMA trial, which showed that, in patients with moderately severe to severe NPDR without CI-DME, 20% of those treated with a sham (placebo) developed PDR after one year, while EYLEA reduced this risk by 85%. Regulatory exclusivity for EYLEA expired in May 2024, with the first biosimilars launching soon after.

EYLEA HD (aflibercept 8 mg)

In 2023, a high dose formulation of aflibercept, EYLEA HD (aflibercept 8 mg), was approved with an extended dosing interval of up to every 16 weeks in patients with DME, or up to 12 weeks in patients with DR, after demonstrating noninferiority to EYLEA Q8W in the Phase 2/3 PHOTON trial.

VABYSMO (faricimab)

VABYSMO is a bispecific antibody targeting VEGF-A and Ang-2 that was first approved in January 2022 for the treatment of wAMD and DME, with a dosing interval of every 16 weeks. Ang-2 is overexpressed in some patients with wAMD and DME, and its inhibition is thought to promote vascular stability and desensitize blood vessels to the effects of VEGF.

VABYSMO's approval in DME was based on results from two Phase 3 trials, YOSEMITE and RHINE, which compared VABYSMO to aflibercept in ~1900 patients with CI-DME over two years. The trials compared three treatment arms: aflibercept 2mg Q8W, faricimab 6 mg Q8W, and faricimab 6 mg administered according to a personalized treatment interval (PTI). Patients in the PTI arm were administered faricimab every 4 weeks for at least 4 doses and until the central subfield thickness (CST) of the macula, as measured by optical coherence tomography, was less than 325 microns (indicating resolution of edema). Then the interval of dosing was extended or reduced based on CST and visual acuity evaluations.

In both studies, both dosing regimens of faricimab demonstrated non-inferiority to aflibercept at the primary endpoint measuring visual acuity. In the PTI arm of both studies, more than 70% of patients were on a ≥12-week dosing interval at one year, and ~50% of patients were on a 16-week dosing interval.

SUSVIMO (Port Delivery System with ranibizumab)

SUSVIMO, developed by Roche/Genentech, is an implant (called the Port Delivery System, PDS) that is surgically installed in the eye and delivers ranibizumab continuously over time, requiring refilling every 6 to 9 months. It was first approved for wAMD in October 2021, however was pulled from the market in 2022 due to manufacturing problems with the seal of the port delivery device, which meant that the drug could leak from the device following refill. The device re-entered the wAMD market in July 2024, and in 2025 was approved for DME and DR with refills every 6 or 9 months, respectively.

The approval in DME was based on 1-year results from the Phase 3 PAGODA trial, which showed that SUSVIMO refilled every six months was non-inferior to monthly ranibizumab injections.

While the Phase 3 PAVILLION trial evaluated SUSVIMO in patients with moderately severe to severe NPDR without CI-DME. SUSVIMO refilled every 9 months (Q36W) produced a 2-step or greater improvement in DRSS score in 80% of patients, compared to 9% of patients in the observational arm, at 1-year (primary endpoint), which was also maintained at 2-years.

BEOVU (brolucizumab)

BEOVU, developed by Novartis, was approved to treat wAMD and DME in 2019 and 2022, respectively, with injection frequency of every 8-12 weeks following an initial loading phase. In Phase 3 trials, BEOVU demonstrated non-inferiority to aflibercept 2 mg in terms of change in visual acuity and was better at reducing retinal fluid. However, post-marketing reports and subsequent trials identified several safety risks, including increased rates of intraocular inflammation and vision loss, leading to the drug's commercial failure.

Figure 2. Anti-VEGF Intravitreal Injections for DR and DME

Company	Drug	Mechanism	Approved Indications	Injection Frequency	2024 sales	1st Approval Year
Genentech (OTC: RHHBY, not rated)	AVASTIN (bevacizumab)	anti-VEGF mAb	off-label	Q4-6W	n/a	2004
	LUCENTIS (ranibizumab)	anti-VEGF Fab	wAMD, DME, DR, RVO, mCNV	Q4W	$1.2B	2006
	SUSVIMO (ranibizumab PDS)	anti-VEGF Fab	wAMD, DME, DR	Q24-36W	n/a	2021
	VABYSMO (faricimab)	anti-VEGF/Ang-2 bsAb	wAMD, DME, RVO	Q8-16W	$4.7B	2022
Regeneron (REGN, not rated)	EYLEA (aflibercept 2 mg)	VEGF trap fusion protein	wAMD, DME, DR, RVO, ROP	Q8W	$8.1B	2011
	EYLEA HD (aflibercept 8 mg)	VEGF trap fusion protein	wAMD, DME, DR	Q8-16W	$1.5B	2023
Novartis (NVS, not rated)	BEOVU (brolucizumab)	anti-VEGF scFv	wAMD, DME	Q8-12W	n/a	2019

Source: Clear Street research

Anti-VEGFs in NPDR

Anti-VEGF intravitreal injections have now replaced laser as the frontline therapy in PDR and CI-DME, however uptake in patients with NPDR is less than 1%. The most obvious reason for this is that NPDR

patients are often asymptomatic and of working age, making routine injections every 1-2 months unfeasible. Additionally, it is unclear whether preventative treatment delivers long-term benefit to vision vs. close monitoring with treatment upon development of vision threatening complications.

The effectiveness of anti-VEGFs in the treatment of moderately severe to severe NPDR without CI-DME was evaluated in the PANORAMA and DRCR.net Protocol W trials. In Protocol W, 399 eyes were randomized to receive aflibercept 2 mg or sham injection every 3 months for 4 years. Patients in either arm were treated with aflibercept if they developed PDR or CI-DME during the study. The study found that aflibercept significantly reduced the proportion of eyes that developed PDR or CI-DME with vision loss at 4-years (34% vs. 57%). However, patients receiving preventative aflibercept, or sham with aflibercept only after development of PDR or vision-reducing CI-DME, had similar visual acuity outcomes (-2.7 vs. -2.4 letters from baseline).

Although the Protocol W study administered aflibercept at longer dosing intervals than is recommended on the label (every 4 months vs. every 2 months on-label), similar results were observed with aflibercept every 2 months in the PANORAMA trial, which was the basis for the approval of EYLEA in all stages of DR. Patients treated with aflibercept (Q16W or Q8W) showed greater improvement in DRSS score and less frequent development of PDR or CI-DME as compared to sham injections. However, no differences in visual acuity were observed at 48 or 100 weeks. These results indicate that preventative aflibercept treatment may not be worthwhile in NPDR, and close monitoring with treatment of vision threatening complications after they develop, as is generally practiced, may be adequate.

However, once PDR has developed, damage to the retina is irreversible in most patients, even with sustained treatment. For example, in the DRCR.net Protocol S trial, 65% of PDR eyes treated with ranibizumab did not improve to NPDR after 2 years of treatment. Without intervention, proliferative disease can rapidly lead to vision loss. As demonstrated in the Diabetic Retinopathy Study, 37% of untreated eyes with PDR will have severe vision loss at 72 months. Preventative intervention may therefore be beneficial in NPDR, however many patients and doctors do not deem it worthwhile when taking into account the treatment burden of currently approved anti-VEGFs, leaving unmet need that may be addressable with longer acting agents.

Precedent for Regulatory Approval

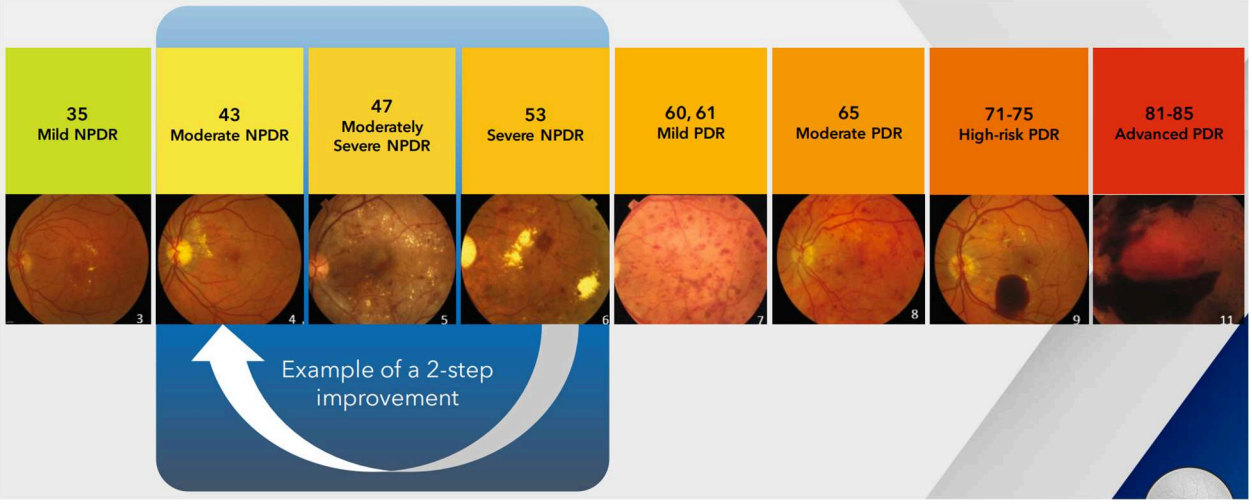
DR

FDA-approvals of anti-VEGF agents in the treatment of DR have been based on the use of the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS), with primary endpoints typically measuring the proportion of patients with a 2-step or greater improvement in DRSS score from baseline at 1-year (Figure 4).

The approval of EYLEA for all stages of DR was based on the PANORAMA trial in patients with moderately-severe to severe NPDR without CI-DME, where EYLEA (administered Q8W or Q16W) demonstrated superiority to sham injection in that primary endpoint. While EYLEA HD (Q12W) was approved based on non-inferiority to EYLEA in patients with CI-DME (PHOTON study).

While the proportion of patients with a 2-step or greater improvement in DRSS score has traditionally served as the benchmark for success in DR, this may not be the most appropriate endpoint for all stages. Particularly in NPDR, the desired outcome is to slow or halt the progression of DR and thereby reduce the risk of developing vision-threatening complications. In December 2024, Opus Genetics (IRD, not rated) received a Special Protocol Assessment (SPA) from the FDA for a Phase 3 trial evaluating oral APX3330 for the treatment of moderate to severe NPDR, with the agreed primary endpoint being a reduction in 3-step or greater worsening in DRSS score, compared to placebo. This SPA reflects that the FDA may be amenable to new therapies for NPDR achieving a lower bar for success as compared to previous approvals.

Figure 3. Diabetic Retinopathy Severity Scale (DRSS)



Source: Presentation by Dr. Dhoot on behalf of HELIOS Investigators at Clinical Trials Summit, June 2024

DME

FDA-approvals of anti-VEGF agents in the treatment of DME have been based on mean change from baseline in Best Corrected Visual Acuity (BCVA), typically at one year, as measured by ETDRS letter score. The earlier approvals of Eylea and Lucentis were based on those treatments demonstrating superiority to sham injection, while the more recent approvals of Eylea HD and Vabysmo with extended treatment intervals were based on demonstrations of noninferiority to aflibercept administered Q8W.

Figure 4. Efficacy of FDA-Approved Anti-VEGF Agents in DR and DME Endpoints

Drug	Trial	Patient Population	Timepoint	Arm	n	(DR) ≥2-step improvement in DRSS from baseline, % of pts	(DME) BCVA change from baseline, mean
LUCENTIS	RIDE	DR with DME	1-yr	Lucentis Q4W	117	35%	10.9
				Sham	124	3%	2.3
	Protocol S	DR with/without DME	2-yrs	Lucentis Q4W	191	48%	2.8
EYLEA	VISTA-DME	CI-DME	1-yr	Eylea Q8W	151	44%	10.7
				Eylea Q4W	154	52%	12.5
				Laser	154	22%	0.2
	PANORAMA	NPDR without CI-DME	1-yr	Eylea Q16W	135	65%	
				Eylea Q8W	134	80%	
				Sham	133	15%	
EYLEA HD	PHOTON	CI-DME	48-wks	Eylea HD Q12W	328	29%	8.8
				Eylea HD Q16W	163	20%	7.9
				Eylea Q8W	167	27%	9.2
VABYSMO	YOSEMITE	CI-DME	1-yr	Vabysmo Q8W	315	46%	10.7
				Vabysmo PTI	313	43%	11.6
				Aflibercept Q8W	312	36%	10.9
SUSVIMO	PAVILLION	NPDR without CI-DME	1-yr	PDS Q36W	106	80%	1.4
				Control	68	9%	-2.6
	PAGODA	CI-DME	60-64-wks	PDS Q24W	381	39%	9.6
				Ranibizumab Q4W	253	42%	9.4
BEOVU	KESTREL	DME	1-yr	Beovu Q12W	189	30%	9.2
				Aflibercept Q8W	187	22%	10.5

Source: Clear Street research

AXPAXLI, Sustained Release Anti-VEGF

AXPAXLI

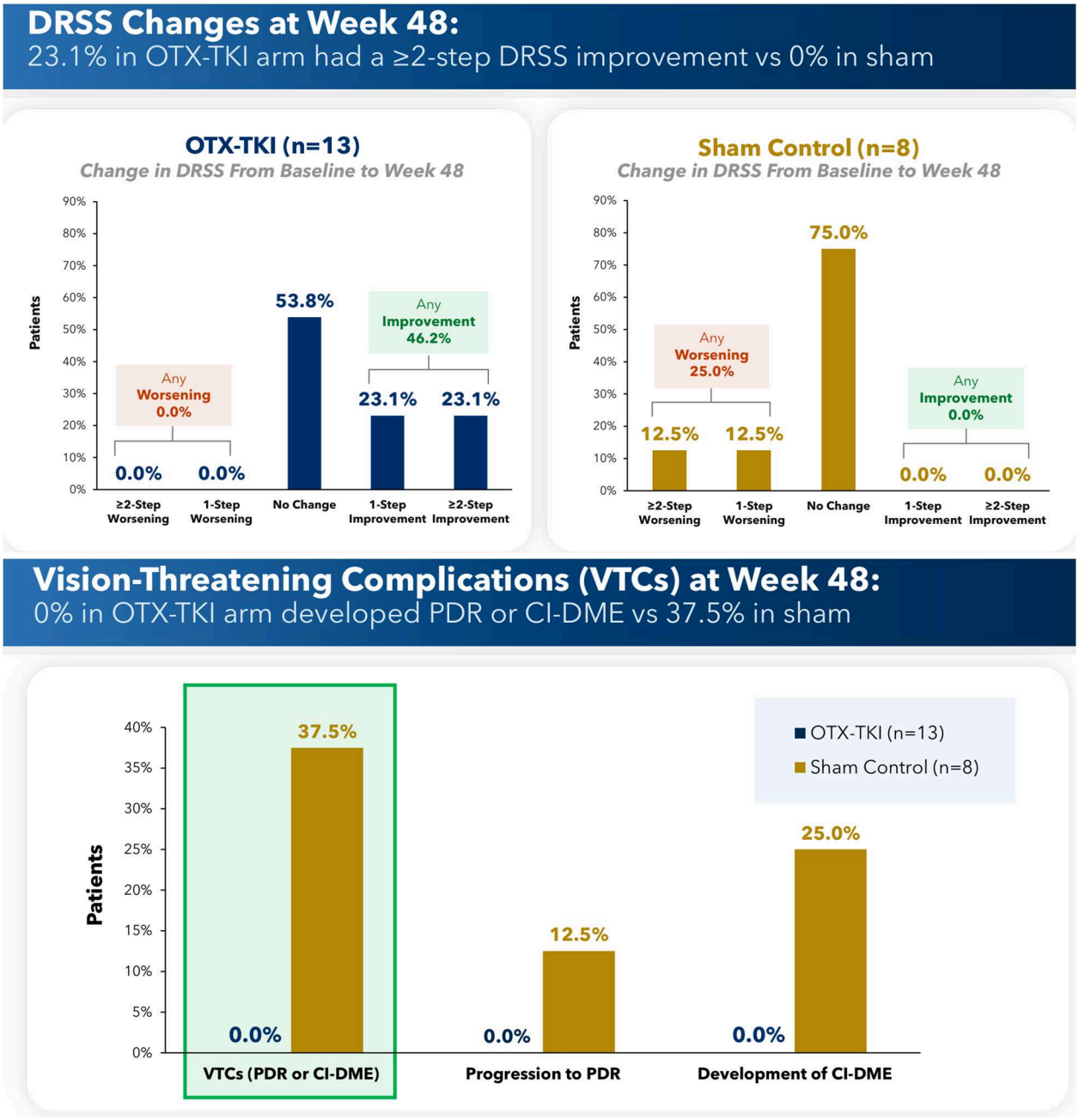
Ocular Therapeutix (OCUL, Buy, $18 PT) is currently developing AXPAXLI (axitinib intravitreal injection) for retinal diseases, primarily wAMD and DR. The active ingredient in AXPAXLI is a small molecule tyrosine kinase inhibitor (TKI), axitinib, that blocks VEGF signaling by inhibiting VEGFR2. Axitinib is embedded in Ocular's proprietary ELUTYX technology, a bioresorbable hydrogel that is injected into the vitreous cavity and facilitates sustained drug release over time. Phase 1/2 trials in wAMD and DR have established the safety and proof of concept of AXPAXLI, and its efficacy in wAMD with 6-12 month dosing is being evaluated in two Phase 3 trials in wAMD, with topline readouts anticipated in 1Q26 and 1H27, respectively. After which, the company plans to file an NDA under the 505(b)(2) pathway, given that both axitinib and Ocular's ELUTYX hydrogel have been previously approved by the FDA (axitinib in non-ophthalmic indications and ELUTYX in DEXTENZA), which is expected to shorten the review timeline by two months as compared to the traditional review pathway for new molecular entities.

HELIOS Phase 1 Study of AXPAXLI in NPDR

The safety and efficacy of AXPAXLI in NPDR patients was evaluated in the Phase I HELIOS study. The study enrolled participants with moderately severe to severe NPDR without CI-DME, and participants

were randomized 2:1 to receive a single injection of AXPAXLI (n=13) or sham (n=8). AXPAXLI was reported as well tolerated with no reported incidence of intraocular inflammation, and no subjects in either arm required rescue injections. At week 48, 46% of patients treated with AXPAXLI had at least a 1-step improvement in DRSS from baseline, and no patients had worsening, while no patients in the sham arm demonstrated improvement, and 25% had worsening on the DRSS scale. Additionally, no patients treated with AXPAXLI developed vision threatening complications (VTCs, CI-DME or PDR), vs 37.5% of patients in the sham arm (Figure 5).

Figure 5. Efficacy of AXPAXLI (OTX-TKI) in Patients with NPDR in the Phase 1 HELIOS Study



Source: Presentation by Dr Marcus on behalf of HELIOS Investigators, Retina Society Annual Meeting, Sep 2024

Development Plans for AXPAXLI in DR

In August 2025, Ocular received written agreement from the FDA on a Special Protocol Assessment (SPA) for a registrational trial of AXPAXLI in NPDR, and the company plans to share details on trial design, including a novel primary endpoint, and development strategy at their upcoming Investor Day on September 30, along with updated estimates of market size and opportunity. The company had previously estimated the total market opportunity in the US for NPDR and DME to be 4.4 million patients. The dosing frequency for AXPAXLI in NPDR/DME is likely to be once every 6-12 months and could therefore be incorporated into regular 6-12 month eye examinations recommended for DR patients without the need for additional appointments.

Sura-vec, Anti-VEGF Gene Therapy

Surabgene lomparvovec (sura-vec, formerly ABBV-RGX-314) is a gene therapy in development by Regenxbio (RGNX, Buy, $50 PT) in partnership AbbVie (ABBV, not rated), as a potential one-time treatment for wAMD and DR/DME. It consists of Regenxbio's proprietary NAV AAV8 vector containing a gene encoding for an anti-VEGF mAb. The therapy is currently in two Phase 3 pivotal trials in wAMD, with topline data due in 2026, and a Phase 2 study in DR and DME.

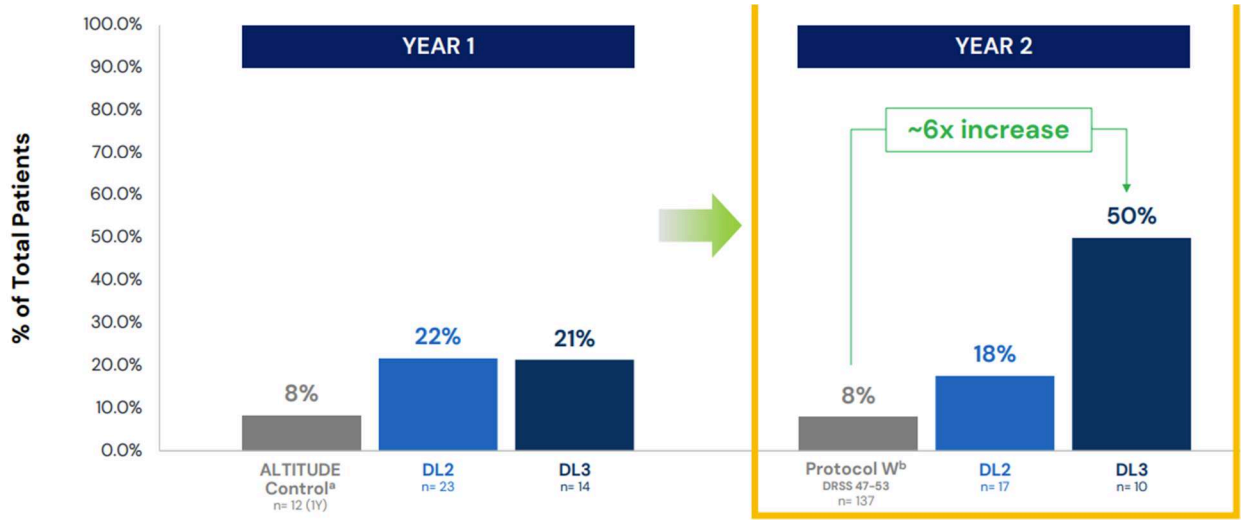
Phase 2 ALTITUDE Study

The Phase 2 ALTITUDE study in DR patients evaluated sura-vec administered by suprachoroidal injection, which is an in-office procedure suitable for delivering gene therapy to retinal cells. The study enrolled ~100 patients with severe NPDR or mild PDR across three dose levels, and was later expanded to include 30 CI-DME patients who received '314 at dose-level 4.

With two years of follow-up in NPDR patients (n=45), sura-vec has reportedly been well tolerated, with no cases of intraocular inflammation at DL3 (n=15), where patients also received short-course prophylactic topical steroids.

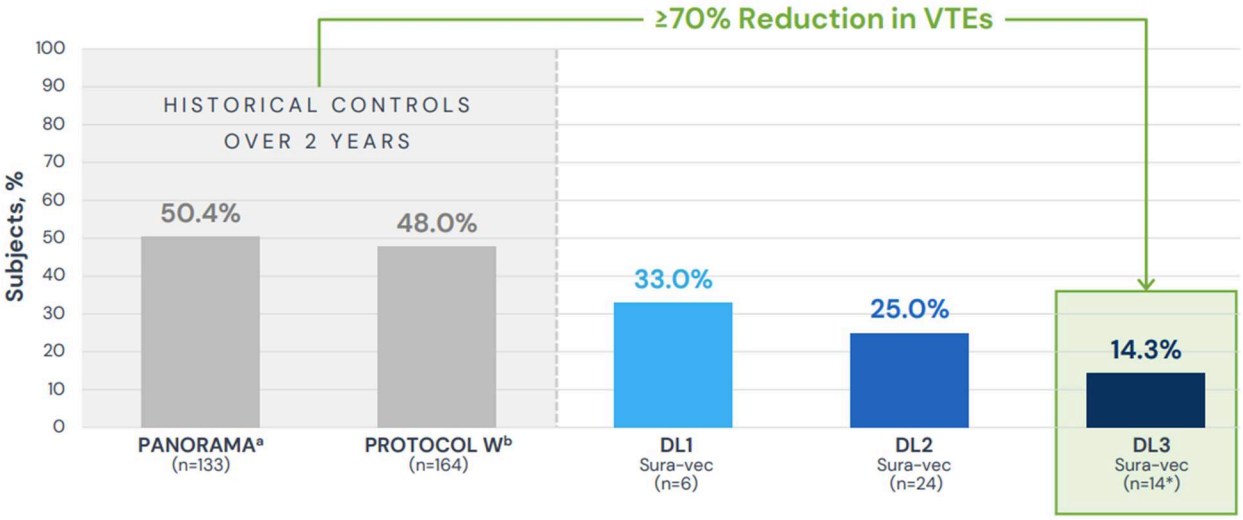
In patients who received DL3 (n=10), 50% had a ≥2-step DRSS improvement without additional DR treatment at 2 years, compared to 8% of control subjects and 18% of patients who received sura-vec at DL2 (Figure 6). Additionally, DL3 patients (n=14) had a 70% reduction in vision threatening events (VTEs) over 2 years, as compared to historical controls (Figure 7). Detailed results will be presented at a future medical meeting.

Figure 6. ALTITUDE: ≥2-Step DRSS Improvement Through 2-years



Source: Regenxbio Corporate Presentation, September 2025

Figure 7. ALTITUDE: Vision-Threatening Events (VTEs) Through 2-years



Source: Regenxbio Corporate Presentation, September 2025

Development Plans for Sura-vec

Following a successful end of Phase 2 meeting with the FDA in 4Q24, Regenxbio is planning a pivotal program for sura-vec in DR, which will begin with a Phase 2b/3 trial. Under the company's agreement with AbbVie, Regenx will receive a $100M milestone payment upon the first patient dosed in the Phase 2b/3 trial (expected 1H26), and an additional $100M upon the first patient dosed in a second Phase 3 trial. The primary endpoint for the trial will be ≥2-step DRSS improvement at 1 year.

Based on RGNX's estimates and market research, 20-25% of DR patients would consider a gene therapy.

Competitive Landscape

Figure 8. Candidates in Development for DR and DME

Company	Candidate	Mechanism	Dosing	Stage
Ocular Therapeutix, (OCUL, Buy, $18 PT)	AXPAXLI	Axitinib (TKI) in sustained-release bioresorbable hydrogel	Intravitreal injection Q6-12M	Ph3 in wAMD, planning pivotal in DR/DME
Regenxbio (RGNX, Buy, $50 PT)	Sura-vec	AAV gene therapy, anti-VEGF Fab transgene	Suprachorodial injection	Ph3 in wAMD; planning pivotal Ph2b/3 in DR
Kodiak Sciences (KOD, not rated)	Tarcocimab tedromer	anti-VEGF antibody biopolymer conjugate	Intravitreal injection Q1-6M	Ph3 in wAMD, DR, & RVO; BLA 3Q26
EyePoint Pharma (EYPT, not rated)	DURAVYU	Vorolanib (TKI) in sustained-release bioerodable insert	Intravitreal injection Q6M	Ph3 in wAMD; planning Ph3 in DME
4D Molecular Tx (FDMT, not rated)	4D-150	AAV gene therapy, aflibercept transgene and VEGF-C RNAi	Intravitreal injection	Ph3 in wAMD; Ph2 in DME
Opus Genetics (IRD, not rated)	APX3330	Small molecule Ref-1 inhibitor	Oral BID	Ph2/3 ready in DR

Source: Clear Street research

Figure 9. Efficacy Comparison in NPDR without CI-DME

Moderately-severe to severe NPDR without CI-DME										
					Change in DRSS from baseline, % of pts					
Drug	Trial	Time	Arm	n	Worsening	No change	≥1-step improvement	≥2-step improvement	VTCs	# of injections
EYLEA	PANORAMA (Ph3)	1-yr	Eylea Q16W	135				65	10	5.5
			Eylea Q8W	134				80	11	8.6
			Sham	133				15	41	
AXPAXLI	HELIOS (Ph1)	48-wks	Axpaxli	13	0	54	46	23	0	1
			Sham	8	25	75	0	0	38	
sura-vec	ALTITUDE (Ph2)	1-yr	RGX-314	24	0	29	71	21	4	1
			Control	8	38	38	25	13	38	
Tarcocimab	GLOW1 (Ph3)	48-wks	Tarcocimab	128	2.4	27	70	41	2.3	4
			Sham	125	12	78	11	1.4	21	
SUSVIMO	PAVILION (Ph3)	1-yr	PDS Q36W	106	≥3-step: 3%			80	7	2
			Control	68	≥3-step: 45%			9	47	
APX3330	ZETA-1 (Ph2)	24-wks	APX3330 BID	29	≥3-step: 3%			8	7	N/A
			Placebo	30	≥3-step: 20%			8	27	

Source: Clear Street research

A Note on Modeling

The CDC (via its Vision and Eye Health Surveillance System, VEHSS) estimates 9.6M Americans with DR, of which 1.84M are estimated to have vision-threatening DR (severe NPDR, PDR, or DME). We do not currently model standalone value for OCUL or RGNX for DR, as development plans and market potential until recently have been murky. However, with multiple competitive programs moving into pivotal studies, we expect more information on the market potential to become available soon, and potentially lead to upside to our estimates for these respective programs.

Important Disclosures

Analyst Certification

I, Bill Maughan, PhD and Jessica Bridgford, PhD, certify that the views I have expressed in this research report accurately reflect my personal views about the subject security(ies) and subject company(ies). I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the specific recommendations or views expressed in this research report.

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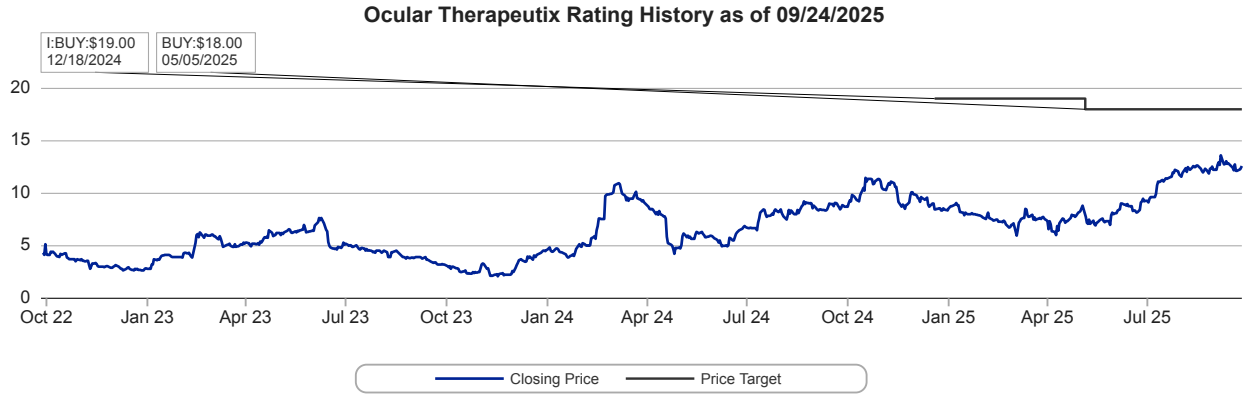

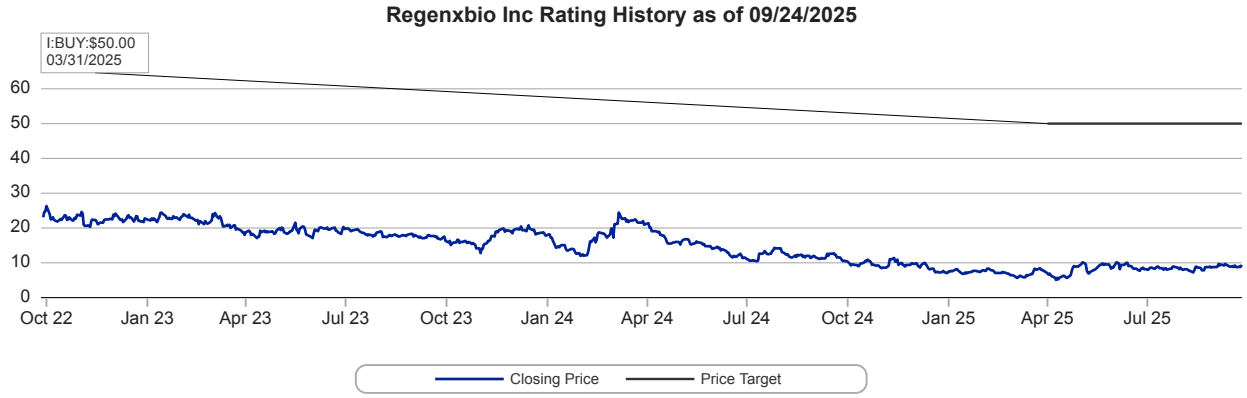

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Distribution of Ratings Table

Distribution of Ratings Table as of September 25, 2025				
			IB Service/Past 12 Months	
Ratings	Count	Percent	Count	Percent
BUY	59	78.67%	14	23.73%
HOLD	16	21.33%	0	0.00%
SELL	0	0.00%	0	0.00%
NOT RATED	0	0.00%	0	0.00%

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