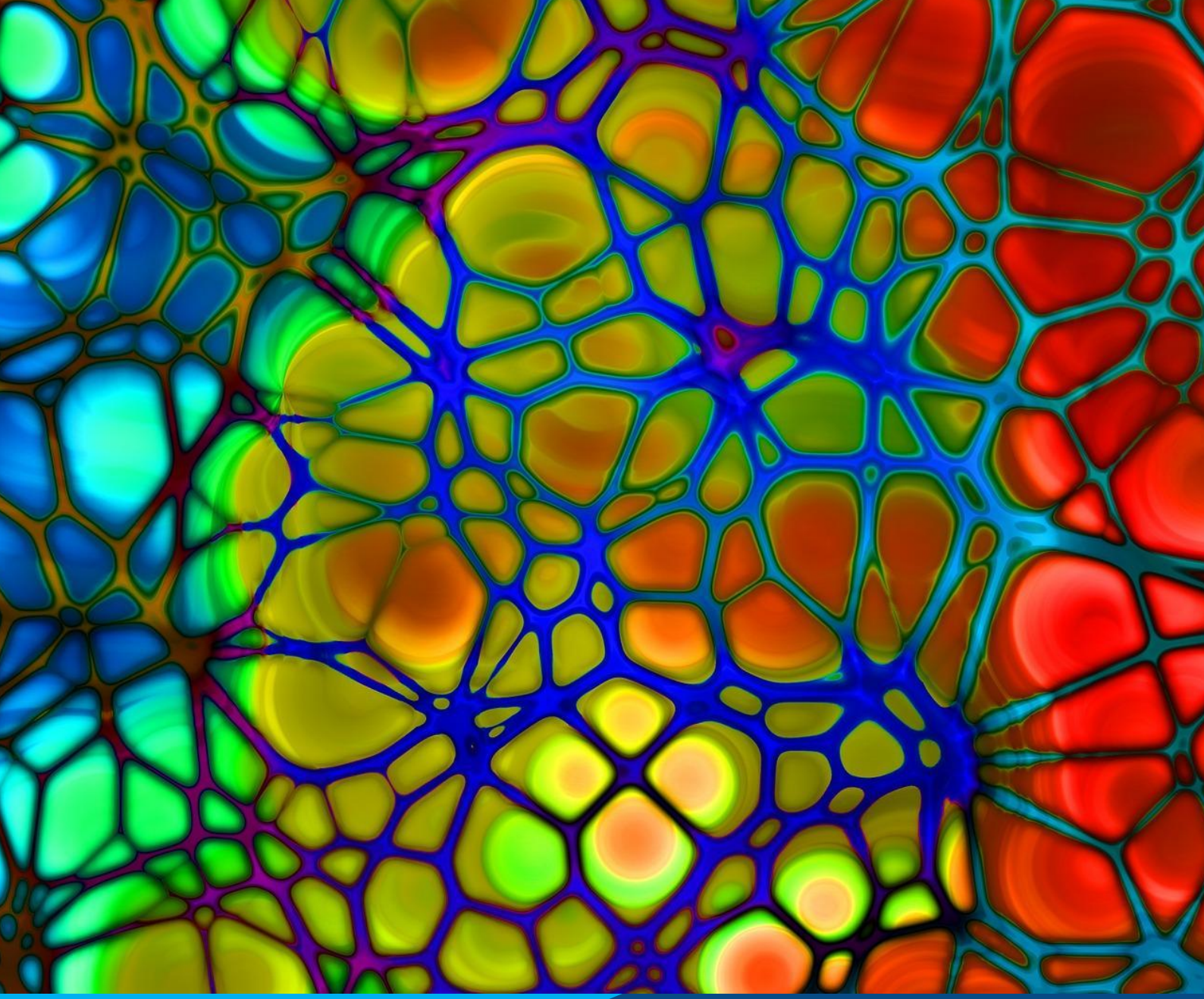

STONEGATE HEALTHCARE

Beyond VEGF: Therapies Revolutionizing Diabetic Eye Disease

SHP Market Intelligence – June 2023

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1.0 Executive Summary

The market for diabetic eye diseases, including diabetic retinopathy (DR) and diabetic macular edema (DME), is substantial and fast growing. With around 13 million Americans impacted by these conditions, the market is experiencing significant growth due to factors such as the rising prevalence of diabetes, an increasing geriatric population, and advancements in technology.

Over the past decade, the introduction of Anti-VEGF therapies greatly transformed the treatment of diabetic eye diseases by eliminating the need for riskier procedures like laser coagulation and vitrectomy. Despite these advancements, several significant unmet needs remain in three areas:

1. Many cases of DR/DME go untreated in the early stages due to delayed diagnosis, unpredictable onset, uncertain progression of disease, and the invasive nature of current treatments.
2. Standard intravitreal injection (IVT) anti-VEGF treatments have been found to be ineffective in approximately 50% of patients.
3. Patients tend to discontinue therapy in the long-term because of the invasive nature of treatments and poor long-term clinical outcomes.

We believe that the future of diabetic eye disease treatment lies in Beyond VEGF therapies with the following characteristics:

- Novel mechanisms of treatment, especially ones that are VEGF agnostic, like plasma kallikrein inhibition and senolytics.
- Oral therapies with the potential to systemically protect vasculature in the eyes, kidneys, heart, brain, and nervous system.
- Technologies that lessen or eliminate the need for invasive procedures that improve long-term outcomes.
- Therapies that are potentially preventative and are safe for early-stage patients.

We anticipate that non-invasive therapies will use alternative regulatory endpoints and expand the treatable population of DR/DME patients.

After analyzing numerous companies focused on innovations in the diabetic eye disease sector, we believe the following companies will lead the revolution of Beyond VEGF therapies:

	Oculis	Ocuphire Pharma	OcuTerra	Rezolute	Roche	Unity Biotech
Novel MOA	X	✓	✓	✓	✓	✓
VEGF Agnostic	✓	X	X	✓	X	✓
Systemic	X	✓	X	✓	X	X
Non-Invasive	✓	✓	✓	✓	X	X
Potentially Preventative	X	✓	✓	✓	X	X
Pivotal Data	X	X	X	X	✓	X
Commercial Expertise	X	X	X	X	✓	X

1.1 Current Developments in The Space:

1. Companies developing non-invasive treatments for DR/DME, such as Ocuphire Pharma, OcuTerra Therapeutics, Rezolute, and Valo Health, are utilizing a 2-step or greater improvement in the diabetic retinopathy severity scale (DRSS) as a phase 2 clinical outcome. This approach suggests that the FDA will employ a new route to approval for non-invasive treatments that have the potential to prevent progression of diabetic eye disease.

2. Regeneron and Bayer are codeveloping a high dose (8mg) Eylea to extend treatment intervals for patients to 48 weeks. The FDA announced priority review of the program in Feb 2023.

    a. Also in Feb 2023, Bayer submitted 8mg Eylea for regulatory approval in neovascular (wet) age-related macular degeneration (nAMD) and DME to the EU and Bayer submitted a similar approval to the MHLW in Japan.
    b. Regeneron received approval of Eylea for the infant version of DME from the FDA in Feb 2023.

3. Rezolute held a KOL event in which they discussed the unmet need in DME treatment and how they aim to address that need with their oral plasma kallikrein inhibitor RZ402, currently in phase 2 trials.

4. Unity Biotechnology announced positive results from phase 2 Behold study of UBX1325 in patients with DME.

5. Roche's Vabysmo demonstrated superior drying of the eye as compared to Eylea in phase 3 BALATON and COMINO studies.

6. Oculis presents positive results from Diamond stage 1 of a phase 3 OCS-01 study for patient with DME.

1.2 Upcoming Developments in The Space:

1. Oculis expects to begin an OCS-01 eye drop stage 2 phase 3 trial in 2H 2023.

2. Ocuphire Pharma expects to complete an end of phase 2 meeting with the FDA 2H 2023 for their oral therapy, APX3330.

3. OcuTerra expects completion of the OTT166 eyedrop phase 2 trial in March 2024.

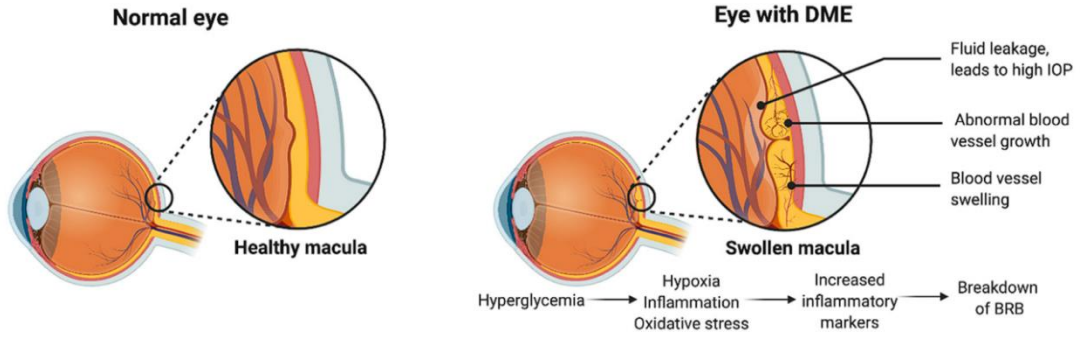
4. Rezolute expects topline data from its phase 2 trial of RZ402 oral therapy in early 2024.

5. Unity Biotechnology expects to move forward with a phase 2b trial of UBX1325 in 2H 2023.

2.0 Beyond VEGF: Therapies Revolutionizing Diabetic Eye Disease

2.1 Diabetic Retinopathy/Diabetic Macular Edema is a Large and Growing Market

DR (diabetic retinopathy) is a common complication of diabetes that affects the eyes, and if left untreated, it can lead to more severe forms of diabetic eye disease such as proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME) causing vision loss and blindness. Although patients with severe nonproliferative diabetic retinopathy (NPDR) are more likely to develop DME than patients with mild NPDR, DME can develop at any stage of DR causing distorted vision and progressive vision loss, and making it difficult to read, drive, or perform other daily activities.

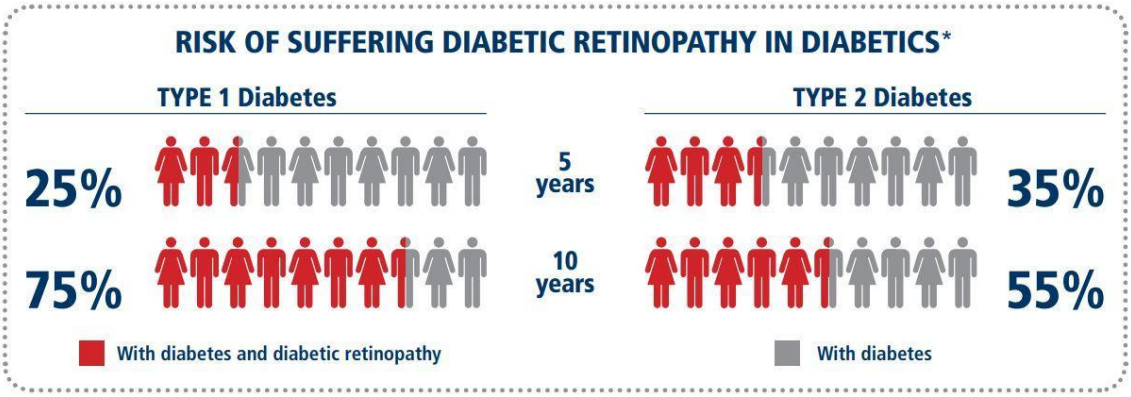


Source: Chauhan, Muhammad Z., et al. "Current and Novel Therapeutic Approaches for Treatment of Diabetic Macular Edema." MDPI, Multidisciplinary Digital Publishing Institute, 17 June 2022, https://www.mdpi.com/2073-4409/11/12/1950.

DR develops when high levels of blood sugar damage the microvasculature in the eye. According to the World Health Organization (WHO), DR is the leading cause of blindness among working-age adults (20-65 years) globally. The WHO estimates that approximately 2.2% of the world's population has DR, which translates to around 146 million people. Among people with diabetes, the prevalence of diabetic eye disease is even higher, affecting around one-third of people with diabetes. Demographics in the US are comparable with an approximate 13 million Americans effected by DR and DME.

Because DR worsens over time, developing into PDR, and eventually DME, the need for DME treatments is growing. A review of studies investigating progression of diabetic eye disease showed a significant worsening of retinal vascular health over time. The review found a 24 - 39% incidence of disease worsening over a 4 – 6 year period with cumulative incidence growing to 64.1 - 83.1% in 25 year follow-ups.

This figure illustrates the risk of suffering from diabetic eye disease and its progression over time.



Source: Klein, R., Klein, B. E., Moss, S. E., Davis, M. D., & DeMets, D. L. (1984). The Wisconsin Epidemiologic Study of Diabetic Retinopathy: III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Archives of ophthalmology, (1984).

The incidence of diabetic eye disease is increasing worldwide due to several factors, including:

- Rising prevalence of diabetes: Diabetes is a major risk factor for DME, and the number of people with diabetes is increasing worldwide due to changing lifestyles, rising rates of obesity and aging populations.
- Improved screening and diagnosis: With advances in medical technology, healthcare providers are better able to screen for and diagnose DME, leading to an increase in reported cases.
- Longer life expectancy: People are living longer, which means they have a greater risk of developing DME and other age-related eye diseases.
- Lack of access to healthcare: In some regions of the world, people do not have access to the healthcare they need to prevent or manage diabetes and DME, leading to higher incidence rates.

2.2 Anti-VEGF Therapies Revolutionized DME Treatment …

The treatment of DME has been revolutionized by anti-VEGF (vascular endothelial growth factor) medications, which have improved visual outcomes and decreased the requirement for treatments like laser photocoagulation and vitrectomy. Clinical trials have demonstrated the effectiveness of anti-VEGFs, including Lucentis, Eylea, and Avastin, in reducing macular edema and improving visual acuity in patients with DME. Anti-VEGF medications work by blocking the action of VEGF, a protein that promotes the growth of abnormal blood vessels in the retina and contributes to the development of DME. By inhibiting VEGF, these medications can reduce the leakage of fluid into the macula, improve retinal function, and prevent further vision loss.

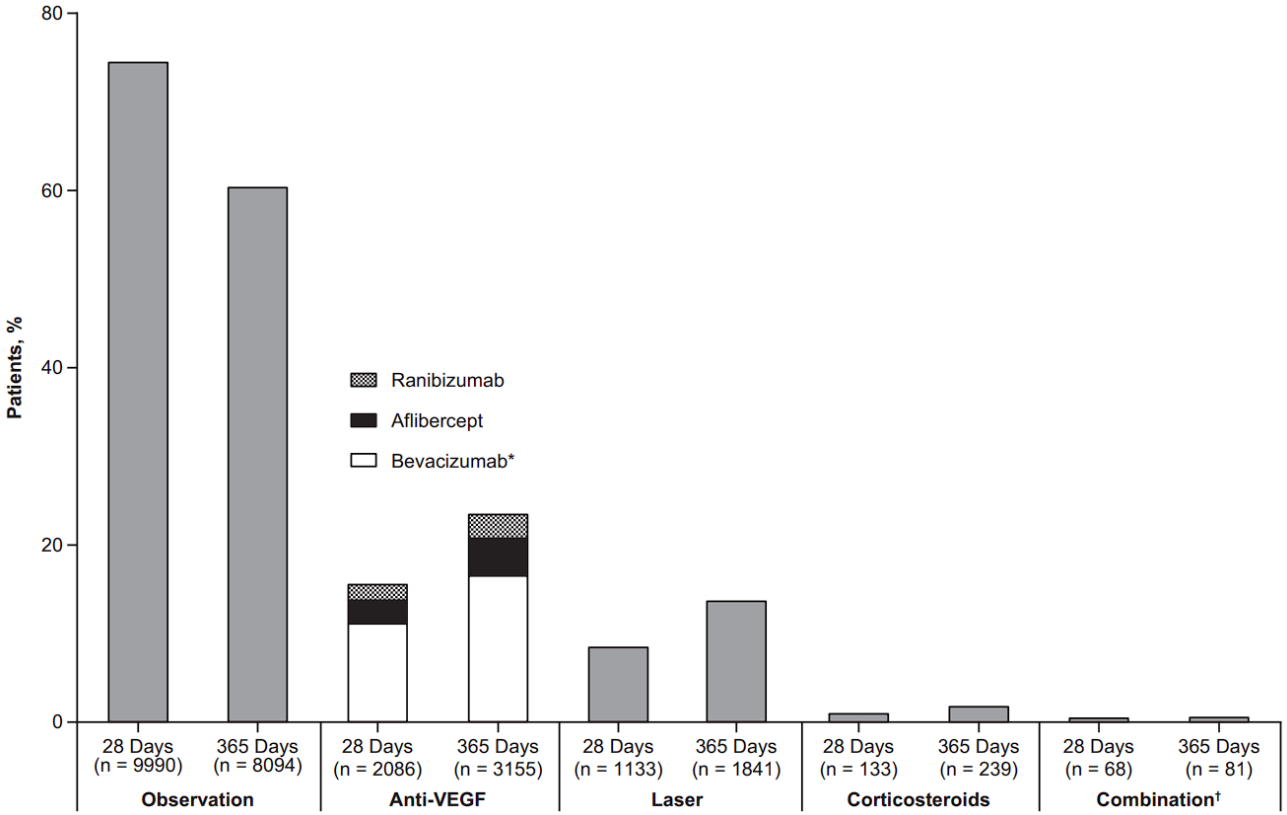
Before the introduction of anti-VEGF treatments, laser photocoagulation was the mainstay of DME treatment. However, this treatment was associated with significant side effects, including visual field loss, and could only be used in specific cases where the leakage was from identifiable blood vessels. In contrast, anti-VEGF treatments can be used in a wider range of DME cases, including those where there is diffuse retinal thickening with no identifiable leaking blood vessels. By 2013, an estimated 90% of retinal specialists in the United States reported using anti-VEGF therapy for initial management of vision loss from diabetic macular edema involving the macular center.

2.3 But Several Needs Remain Unmet

2.3.1 DR/DME is Largely Untreated in Early Stages

Many cases of DR/DME go untreated due to several reasons: lack of DR/DME diagnosis, the unpredictable onset and uncertain progression of the disease, as well as the invasive nature of available treatments. In particular, the burden of intravitreal injection (IVT) therapies requires diagnosis by a retinal specialist before treatment can begin.

The image below represents an analysis of the IRIS Registry, which studied approximately 13,000 patients with DME, found that 75% of patients remained untreated 28 days after diagnosis and 60% were untreated one year after diagnosis. Only 15% of patients received anti-VEGF therapy at 28 days, which increased to 23% at one year.



Source: Treatment Patterns for Diabetic Macular Edema: An Intelligent Research ... https://www.aaojournal.org/article/S0161-6420(19)32176-1/fulltext.

- Lack of Diagnosis: A study evaluating approximately 2000 patients published in the Journal of the American Medical Association found that only 63% of patients with diabetes complete recommended annual dilated eye exams, with lower rates: 32 – 49% among African Americans and Hispanics.
- Unpredictability of Disease Onset: A person with diabetes may develop the anatomical changes associated with DR and DME such as increased retinal vascular permeability and swelling of the macula before they observe any vision loss. Symptoms of early diabetic eye disease include blurred vision and difficulty seeing in dim light. These relatively mild issues can be overlooked, failing to prompt an eye examination.
- Uncertainty in Timing of Disease Progression: Approximately 25% of patients with DR have PDR and 75% have NPDR. Although patients with severe NPDR are more likely to develop DME than patients with mild NPDR, DME can develop at any stage of DR. Therefore, all patients with DR are at risk of developing DME and vision loss.
- High Treatment Burden of Invasive Therapies: Due to the potential risk associated with IVT therapy and other Invasive interventions for DR, patients are essentially left untreated until retinal specialists diagnose vision loss via comprehensive eye exams measuring the quality of their vision and the state of their retinal vascular health.

2.3.2 Standard of Care Intravitreal anti-VEGF Treatment is Ineffective in ~ 50% of Patients

Nearly half of the patients receiving IVT anti-VEGF therapy are unresponsive, and those who do respond require subsequent injections every 4-8 weeks to maintain therapeutic effect. Clinical trials involving near monthly IVT anti-VEGF treatment have shown that over 35% of DME patients do not achieve a ≥10-letter improvement in best-corrected visual acuity (BCVA) within the first year of treatment. After two years of anti-VEGF therapy, more than 55% of patients fail to achieve a ≥15-letter improvement. It is worth noting that the FDA requires a minimum 15-letter improvement in BCVA, as well as a reduction in macular swelling measured by central subfield thickness (CST), for IVT therapy to be approved.

2.3.3 Invasive Treatments Have Low Compliance, High Risk, and Poor Long-Term Efficacy

Although IVT therapies are effective for some patients, they pose several treatment-related challenges and risks. Regular visits to a retinal specialist for injections directly into the eye can lead to poor patient compliance due to fear, discomfort, inconvenience, cost, and potential side effects. A 2018 study in the Journal of Ophthalmology reported that about 26% of DME patients had missed IVT therapy appointments.

The repetitive nature of IVT treatments amplifies the risks of this invasive therapy, including infection, bleeding, retinal detachment, increased intraocular pressure (IOP), and cataract formation. Moreover, the administration of these injections can affect the quality of care provided by retinal specialists due to the high number of procedures performed daily. In a recent webinar, KOL and retinal specialist Dr. Robert Bhisitkul estimated that he completes approximately 20-30 intraocular injections daily.

Long-term efficacy suffers most significantly due to poor long-term patient compliance. A 2022 study in the Patient Preference and Adherence Journal found that approximately 30% - 38% of DME patients were lost to follow-up. To improve long-term efficacy, strategies have been developed to extend the time between treatments. Surgical implants such as Iluvien, Ozurdex, and Susvimo use a sustained release approach to extend therapy effectiveness from six months to three years. Gene therapies like RGX-314 aim to reduce or eliminate the need for follow-up intraocular procedures. Although these therapies promise to alleviate treatment burden, they still pose significant risks and challenges to the patients, affecting long-term efficacy.

2.4 Successful Therapies will Expand Beyond VEGF, Evaluate New MOA's, Focus on Systemic Disease, and Improve Patient Compliance Long-term.

2.4.1 New MOAs

To address anti-VEGF non-responders, effective therapies targeting new pathways to reduce retinal tissue damage are needed. The tissue damage caused by diabetic eye disease is a complex biological reaction brought on due to hypoxia and oxidative stress caused by high blood sugar and underlying diabetes. This process implicates several parallel and connecting pathways involving a plethora of genes, proteins, and cell types. Focusing on a single growth factor (VEGF) limits treatment results to a subset of patients. This has prompted developers to explore other promising targets.

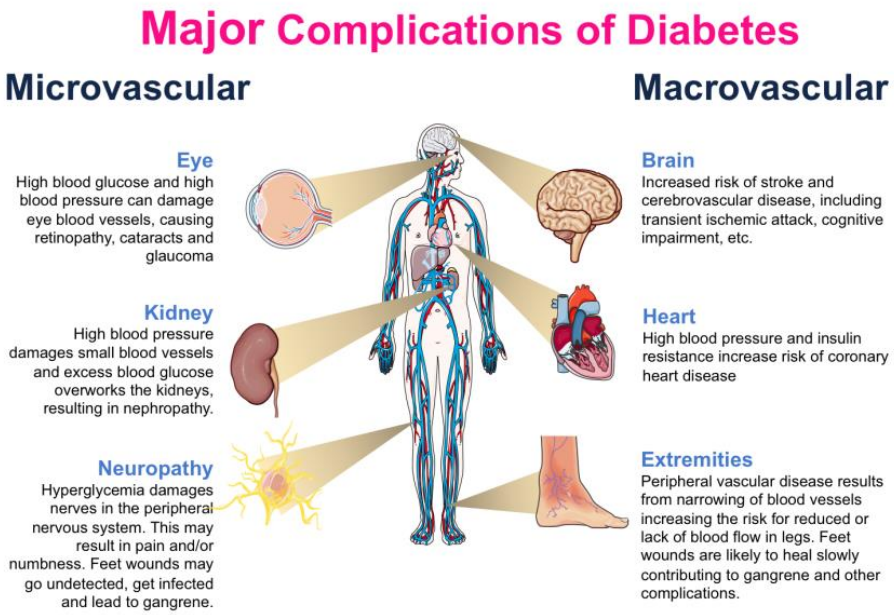
For instance, Rezolute is currently evaluating a plasma kallikrein (pkal) inhibitor in phase 2 trials to block downstream bradykinin production and inflammation, coagulation, and fluid-leakage cascades.

Pre-clinical models indicate that pkal inhibition can reduce vascular leakage by 80-90%. Unity Biotechnology is exploring a cellular approach to treat diabetic eye disease by evaluating a Bcl-xL inhibitor in phase 2 trials as a senolytic medicine designed to eliminate senescent cells. Other promising mechanisms with pre-clinical and clinical data include Ref-1 and integrins programs, which are being explored by Ocuphire Pharma and Ocuterra Therapeutics. These programs offer hope to patients who do not respond to anti-VEGF therapy.

2.4.2 Systemic Disease

Elevated glucose not only causes damage to the eye but also puts sensitive microvasculature in tissues such as the brain, heart, kidneys, and nervous system at risk. Systemic medications, or oral therapies, offer the advantage of protecting these delicate microvasculature structures. Ocuphire Pharma and Rezolute are currently developing oral medications for systemic treatment of diabetic eye disease. Phase 1 trials have confirmed their safety, and phase 2 trials are underway to evaluate efficacy and further confirm safety.

The figure below illustrates the vascular complications of diabetes and its effects on various organs throughout the body.



Source: "PDB101: Global Health: Diabetes Mellitus: Monitoring: Complications." RCSB, https://pdb101.rcsb.org/global-health/diabetes-mellitus/monitoring/complications?more=y.

While ongoing studies do not investigate the drugs' ability to address diabetes-related tissue damage beyond the eye, the favorable safety profile of these drugs suggests that systemic treatments are well tolerated in various tissues. It is worth noting that oral medications that stabilize hyperglycemia-induced inflammation in the eye can also have similar benefits in other organs. Several studies have shown that intensive glucose control is associated with a significant reduction in the incidence of kidney/eye damage and a trend towards reduced incidence of cardiovascular disease. These findings suggest that managing microvasculature dysfunction may help prevent complications associated with diabetes.

2.4.3 Long-term Compliance

Patients lost to follow-up can pose a challenge to the long-term effectiveness and compliance of invasive therapies. As mentioned earlier, a considerable proportion of laser therapy and IVT patients, ranging from 22-38%, are unable to adhere to their treatment plans. To improve patient adherence, successful therapies must reduce the burden of traditional DR/DME treatments by exploring alternative approaches such as oral and eye-drop therapies. Compared to injection-based treatments, oral and eye drop treatments have higher adherence rates.

A 2017 study published in the Journal of Ophthalmology found that patients with diabetes who were treated with oral medication had significantly better adherence rates than patients with DME who were treated with IVT therapies. The study followed 170 patients over a one-year period and found that 77% of those on oral medication were adherent, compared to only 50% of those on IVT treatment. This difference is not surprising, considering the cost, inconvenience, time, and risk associated with IVT treatment.

2.5 Non-Invasive Therapies Will Expand the Treatable Population of DR/DME Patients

While only around 1 million people in the US are diagnosed with DME, non-invasive therapies such as oral and eye drop treatments can benefit a much larger population of approximately 12 million Americans with early-stage diabetic eye disease (NPDR, PDR, and early DME) who currently do not receive any treatment. These non-invasive therapies have the potential to usher in an era of preventive medicine for diabetic eye disease, with the ability to expand beyond DR to benefit the broader diabetes population. If approved for diabetic eye disease prevention, the patient population has the potential to grow to include all diabetes patients, approximately 37 million Americans.

2.6 Non-Invasive Therapies Will Take Alternate Routes to FDA Approval

The approval pathway of non-invasive treatments is evolving due to their low treatment burden and targeting of early-stage disease. Companies like Ocuphire Pharma, OcuTerra Therapeutics, Rezolute, and Valo Health are already using a 2-step or greater improvement in diabetic retinopathy severity scale (DRSS) as a phase 2 clinical outcome, indicating that the FDA is creating a new route to approval for non-invasive and potentially preventative DME/DR treatments. DRSS is calculated by an ophthalmologist and is based on a variety of ocular abnormalities such as neovascularization, bleeding, and microaneurysms.

Preventative treatments will aim to stop progression in patients with early-stage disease who are currently not receiving any treatment. This is the case with the companies mentioned above. Ocuphire is evaluating DR and DME patients, while OcuTerra and Valo Health are evaluating only DR patients, and Rezolute is studying DME patients with limited prior anti-VEGF treatment. It is important to note that patients in early-stage disease have less anatomical damage to repair and thus measures of efficacy such as changes in CST meant to evaluate effectiveness of invasive IVT treatments will need to be recalibrated to properly assess the cost benefit analysis of a noninvasive treatment in early-stage diabetic eye disease.

2.7 Leading Innovators in DR/DME Healthcare

We believe successful therapies that can revolutionize diabetic eye disease treatment will likely involve novel mechanisms of treatment, potentially preventative therapies, and new technologies that improve long-term outcomes. Mentioned below are several companies employing such strategies in their development programs:

	Oculis	Ocuphire Pharma	OcuTerra	Rezolute	Roche	Unity Biotech
Novel MOA	X	✓	✓	✓	✓	✓
VEGF Agnostic	✓	X	X	✓	X	✓
Systemic	X	✓	X	✓	X	X
Non-Invasive	✓	✓	✓	✓	X	X
Potentially Preventative	X	✓	✓	✓	X	X
Pivotal Data	X	X	X	X	✓	X
Commercial Expertise	X	X	X	X	✓	X

2.7.1 Oculis

Oculis is a clinical stage biopharmaceutical company the develops novel topical treatments for ophthalmic diseases. The company's lead program OCS-01 is corticosteroid eye drop treatment enhanced by the company's' Optireach technology which represents the first potential topical treatment developed for DME.

Mechanism of Action: OCS-01 is a dexamethasone (15mg/ml) formulation enhanced by the Optireach technology which allow large complexes of the drug to be water soluble and thus more bioavailable. Dexamethasone functions as a nonspecific anti-inflammatory agent that blocks the production and release of cytokines.

Clinical Progress: Currently the drug is in a two-part phase 3 study. Stage 1 of the study aimed at validating the loading and maintenance dosing regimens in 148 patients. All primary and secondary endpoints were met, with OCS-01 showing anatomical benefit and significant improvement in visual acuity. Safety concerns were largely associated with IOP and cataract formation which require a longer and larger trial to settle. The stage 1 study required 11/100 patients the received the drug to be treated with IOP decreasing medication.

Current Update: Following the success of the phase 3 stage 1 study Oculis plans to initiate stage 2 which will provide 52-week data and include between 350 – 450 patients. The study is scheduled to begin 2H 2023. Stage 2 of the phase 3 study is meant to support an NDA for the drug.

2.7.2 Ocuphire Pharma

Ocuphire Pharma is a clinical-stage ophthalmic company focused on developing therapies for the treatment of refractive and retinal eye disorders. One of their lead programs is APX3330, a novel twice-daily oral treatment for DR and DME that relies on Ref-1 inhibition. Ocuphire's APX3330 represents the first potential oral, systemic, and preventative treatment for DR and DME.

Mechanism of Action: Ref-1 is an upstream regulator of VEGF and TNF-a signaling, blocking these signals prevent hypoxia and inflammation in the diabetic eye. Ref-1 is activated in the overexpression of VEGF and TNF-a, reducing Ref-1 returns VEGF and TNF-a to normal levels, avoiding side-effects from suppression of VEGF and TNF-a below baseline.

Clinical Progress: APX3330 was previously developed by Eisia for hepatic inflammation and by Apexian for advanced solid tumors acting as an anti-VEGF therapy. Ocuphire has completed phase 2 trials (n=103) for APX3330 in DR and has shown the ability slow DR progression as well as a good safety signal.

Current Update: Ocuphire anticipates the FDA will approve a 3-step or greater binocular DRSS improvement at week 52 as the primary endpoint for a phase 3 trial (i.e. sum of right and left eye change in DRSS). More information will follow an end of phase 2 meeting with the FDA around the end of Q3 2023. Phase 3 is likely to begin 1H 2024.

2.7.3 Ocuterra

Ocuterra is a mid-stage clinical ophthalmology company. Their DR program, OTT166, is an integrin inhibitor eye drop treatment. OTT166 is being studied in phase 2 clinical trials for DR. Ocuterra's OTT166 represents the first potential topical and preventative treatment developed for DME.

Mechanism of Action: OTT166 inhibits several integrin subtypes that act upstream of VEGF production. The molecule binds to integrin receptors and blocks the production of several growth factors such as VEGF, TGF-B, and bFGF. This inhibition leads to vascular stabilization and the prevention of pathological processes such as angiogenesis, neovascularization, vascular leakage, inflammation, and fibrosis in the eye.

Clinical Progress: A phase 1b study evaluating the safety of OTT166 in 40 patients with DME and DR demonstrated safety, tolerability and clear clinical evidence of biological activity as measured by decreases in central retinal thickness. Patients showed reductions in thickness of up to 263um at day 56 (50% reduction from baseline).

Current Update: A phase 2 dose ranging study began dosing patients in August 2023 and expects data readouts in 1H 2024. The study involves approximately 210 patients with DR. The study will evaluate optimal dose of OTT166 as well as treatment-emergent adverse events and percentage of patients who have a 2-step improvement in DRSS score.

2.7.4 Rezolute

Rezolute is a clinical-stage company focused on treating metabolic disease. Rezolute's DME program, RZ402 is a once-daily oral plasma kallikrein inhibitor (PKI). Rezolute's RZ402 represents the first potential oral, systemic, and preventative treatment for DME.

Mechanism of Action: RZ402 is a small molecule selective and potent plasma kallikrein inhibitor (PKI). By inhibiting the formation of kallikrein, RZ402 is designed to block downstream bradykinin production and pro-inflammatory, pro-coagulant, and fluid-leakage contact-activation cascades. RZ402 has been shown to reduce and prevent retinal vascular leakage in animal models by 80-90%.

Clinical Progress: Rezolute recently (Feb 2023) published topline data from its phase 1b study of RZ402. Results of the multiple-ascending dose study validate and support the potential for once daily dosing and enable initiation of a phase 2a proof-of-concept study. RZ402 was well tolerated across all doses and was adequately bioavailable in a dose-dependent manner. No serious adverse effects were observed.

Current Update: Rezolute initiated a phase 2a proof of concept study for RZ402 in Dec 2022. The phase 2 multi-center, randomized, double-masked, placebo-controlled, parallel-arm study will evaluate the safety, efficacy, and pharmacokinetics of RZ402 administered over a 12-week treatment period in patients with DME who are naive or have had three or less anti-VEGF injections. The study will measure changes in CST among other endpoints as defined by DRSS and BCVA.

2.7.5 Roche/Genentech

Roche has developed an implantable medical device known as Susvimo (Lucentis carrying implant), which extends the time between treatments to once every 6 months. Their lead DME therapy, Vabysmo is approved and gaining market share. Vabysmo has differentiated itself from currently approved therapies in the space thanks to a dual mechanism of action and extension of treatment effectiveness. Roche is also investigating an oral cannabinoid CV2 agonist as a potential oral DME treatment.

Mechanism of Action: Vabysmo is a bispecific antibody targeting VEGF and Ang-2. Inhibiting Ang-2 promotes vascular stability and desensitizes blood vessels to the effects of VEGF-A. This dual mechanism of action has resulted in Vabysmo's ability to treat 80% of patients every 3 months and 60% of patients every 4 months. Vabysmo has seen significant anatomical improvements in drying and CST.

Susvimo is an implantable medical device built on Roche's port delivery platform which allows for sustained release of drug cargo. Susvimo (carrying Lucentis) has shown to be effective for up to 6 months.

Current Update: Vabysmo was approved in 2022 and has seen strong uptake in the market. In October 2022 Roche received the permanent J-code for Vabysmo increasing beyond nAMD patients and into the DME patient population.

Susvimo was approved on OCT 2021 and recalled OCT 2022 for failure of the device which Roche attributed to manufacturing. Susvimo will be relaunching in approximately a year ~1H 2024.

2.7.6 Unity Biotechnology

Unity Biotechnology is a clinical-stage company focused on developing therapies to slow, halt, or reverse diseases of aging. Their lead candidate is UBX1325, an asset licensed from Ascentage Pharma. UBX1325 is a small-molecule inhibitor of Bcl-xL that could potentially extend treatment intervals to 6 months. Additionally, Unity is developing a Tie2/VEGF bispecific molecule for DME and AMD. Which is currently pre-clinical.

Mechanism of Action: UBX1325 is a novel Bcl-xL inhibitor. Bcl-xL is a member of the Bcl-2 family of apoptosis regulatory proteins which is found to be in high concentrations in retinal vasculature. UBX1325 is designed to inhibit the function of proteins that senescent cells rely on for survival, eliminating these cells while sparing healthy blood vessels and could potentially provide a valuable alternative or adjunctive treatment option to anti-VEGF therapies. In pre-clinical models of diabetes, Bcl-xL inhibition reduces inflammation and vascular leakage.

Clinical Progress: Phase 2, Behold study with 65 participants demonstrated significant improvement in BCVA and sustained improvement through week 24 with a single injection of UBX1325.

Current Update: Unity announced (April 2023) positive results from the phase 2 Behold study. A single injection of UBX1325 led to a clinically meaningful improvement in BCVA of 6.2 letters at week 48. Approximately 53% of UBX1325 treated patients did not require any intervention. Phase 2b/3 studies are estimated to begin in 2H 2023.

3.0 Approved Treatments for DME

Company	Drug	Approach	Frequency	~Revenue (m/year)
Regeneron/Bayer	Eylea	VEGF IVT	8 – 12 Weeks	9600 (combined)
Roche/Novartis	Lucentis	VEGF IVT	4 Weeks	1870 (Novartis) 1460 (Roche)
Roche	Vabysmo	VEGF/Ang-2 IVT	3 – 4 Months	300
Novartis	Beovu	VEGF IVT	8 – 12 Weeks	200
Allergan (Abbvie)	Ozurdex	Surgical Implant	6 Months	125
Alimera Sciences	Iluvien	Surgical Implant	36 Months	54

Alimera Sciences

Alimera Sciences is a commercial stage ophthalmology company focused on treating retinal disease. Alimera is responsible for Iluvien, a fluocinolone acetonide (corticosteroid) Implant lasting up to 3 years. In 2022 Alimera generated approximately 54 million in revenue from the use of Iluvien. Alimera has a collaborative agreement with EyePoint Pharmaceuticals for the development and sale of insert technology to deliver the implant. Alimera licensed Iluvien rights to Ocumension Therapeutics in Q2 2021 for its expansion and use in China and Western Pacific.

Alimera is currently conducting the New Day study, a randomized, controlled trial of the IVT Iluvien implant as baseline therapy in patients with early DME. The trial will compare the effectiveness of Iluvien against aflibercept. The study will last 19 months and include ~300 patients at over 40 sites in the U.S.

Allergan

Allergan develops branded pharmaceutical, device, biologic, surgical and regenerative medicine products worldwide (acquired by AbbVie in 2020). Allergan is responsible for Ozurdex, a Dexamethasone (corticosteroid) releasing implant lasting up-to 6 months. In 2019 Allergan generated ~125 million in revenue from the use of Ozurdex. Allergan held licensing agreements with Editas Medicine and Assembly Biosciences.

Roche

Roche believes that DME treatments need to look at new mechanisms of action. In order to address the highest unmet need in the space, the company is focusing on new mechanisms and durability by expanding beyond VEGF in a few different ways.

Roches is interested in moving into the DR space with an oral CV2 agonist (cannabinoid) which might be suitable as a preventative medication or delay onset of DME. Roche is also exploring biomarkers, digital endpoints, and personalized approaches for patients to effectively extend treatment intervals.

Vabysmo:

Vabysmo, based on Roche's Dutafab platform, is the first new mechanism in DME treatment in the last 20 years. Vabysmo is a bispecific antibody that targets both VEGF and Ang-2. Roche aims to tackle issues with patient compliance and treatment adherence with Vabysmo. The company was able to take 80% of patients out to treatment every 3 months and 60% of patients out to every 4 months with Vabysmo.

Patients on Vabysmo saw anatomical improvements relating to drying in CST. This response can be attributed to the Ang-2 mechanism that stabilizes blood vessels and prevents further leakage complementary to VEGF. In October 2022 Roche received the permanent J-code, for Vabysmo, prior to that most of the patients in the commercial setting were AMD patients. Post the J-code, Roche has seen a rapid uptake in DME patients. Vabysmo (approved Jan 2022) generated ~5 million in revenue in Q4 2022.

Susvimo:

Susvimo is a port delivery system carrying Lucentis which extends effectiveness out to 6 months. Dosing every 6 months increases adherence and reduces disease burden on patients that might not be close to a retinal disease specialist or those that find it hard to travel often. The procedure is 30mins, done in office. Susvimo is going to relaunch purposefully as a medical device, meaning retinal specialists will need to be trained in its use and administration.

Lucentis:

Lucentis is a human monoclonal antibody injection targeting VEGF administered approximately once a month. In 2021 Roche generated ~1.46 billion in revenue from the use of Lucentis. U.S. rights for Lucentis are held by Roche while ex-U.S. rights are retained by Novartis.

Novartis

Novartis has chosen to focus on therapeutic areas other than ophthalmology. They continue to support Lucentis and Beovu as IVT therapies for DME but are not looking to develop additional candidates in the retinal space. In 2021, Lucentis was responsible for ~1.87 billion in revenue for Novartis while Beovu brought in ~200 million in sales.

Regeneron

Regeneron leads sales in DME with Eylea, an IVT treatment for wet AMD that targets VEGF and placental growth factor (PIGF) administered every 8-12 weeks. In 2022, Regeneron generated ~6.3 billion in revenue from the use of Eylea.

Regeneron is beginning to see competition from Vabysmo's increased adoption. However, Regeneron still has a strong dominance in the market. Continued use of Vabysmo will tell how significant a threat it poses to Eylea sales. Regeneron is currently evaluating a higher dose aflibercept (8mg) formulation that promises extended treatment intervals to match Vabysmo's longer (3 or 4 month) intervals. This high dose Eylea program was assigned priority review for a biologics license application by the FDA (Feb 2023).

4.0 Treatments in Development

Due to the large unmet need in DR/DME a variety of therapies are in development with an aim to better patient outcomes. Treatment approaches include systemic oral medication, eye drops, long-term implants, gene therapies, and IVT therapies focused on extending interval of therapeutic effectiveness.

The following table is not reflective of all treatments in development.

Company	Drug	Approach	Durability	Stage
Adverum Biotechnologies	ADVM-022	Gene Therapy (aflibercept)	Single Injection	Phase 2
Aerie Pharma (Alcon Inc)	AR-1105	Steroid Implant	6 Months	Phase 2
Ashvattha Therapeutics	D-4517.2	Hydroxyl Dendrimer SubQ	SubQ/Oral	Phase 2
Clearside Biomedical	CLS-301	Integrin Inhibitor Suprachoroidal	TBD	Pre-Clinical
Curacle/Thea	Cu06-1004	VEGF/Ang2 Oral	Oral	Phase 2
Glaukos Corporation	3 Programs (Title TBD)	Steroid/Multi-kinase Inhibitor/VEGF	6 Months (steroid)	Pre-Clinical
InflammX	Xiflam	Connexin43 Hemichannel Oral	Oral	Phase 2
Innovent Biologics	IBI324	VEGF/Ang2 Intravitreal	TBD	Phase 1
Kalvista Pharma	KVD001	Kallikrein Intravitreal	TBD	Phase 2
Kodiak Sciences	KSI-301	VEGF Intravitreal	6 Months	Phase 3
Kowa Pharma America	Pemafibrate	PPAR Agonist Oral	Oral	Phase 3
OccuRx	OCX063	G Protein-Coupled Receptor Oral	Oral	Phase 1
Ocugen	OCU200	Trasnferrin-Tumstatin Intravitreal	TBD	IND Submitted
Ocular Therapeutix	OTX-TKI	Tyrosine Kinase Inhibitor Implant	6 Months	Phase 1
Oculis	OCS-01	Dexamethasone Eye Drop	Eye Drop	Phase 3
Ocuphire Pharma	APX3330	VEGF & Ref-1 Oral	Oral	Phase 2
Ocuterra Therapeutics	OTT166	Integrin Inhibitor	Eye Drop	Phase 2
Opthea	OPT-302	VEGF/Eylea Intravitreal	TBD	Phase 2
Outlook Therapeutics	ONS-5010 (Lytenava)	VEGF Intravitreal	4 – 8 Weeks	In Dev.
Oxular	Oxu-001	Suprachoroidal	TBD	Phase 2
Oxurion	THR-149	Kallikrein Intravitreal	4 – 8 Weeks	Phase 2
Palatin Technologies	PL9654	Melancortin Agonist Intravitreal	TBD	Pre-Clinical

Company	Drug	Approach	Durability	Stage
REGENXBIO	ABBV-RGX-314	Gene Therapy	Single Injection	Phase 2
Rezolute	RZ402	Kallikrein Oral	Oral	Phase 2
Singh Biotechnology	SBT-100	STAT3 Nanobody	SubQ	Pre-Clinical
Unity Biotechnology	UBX1325	BCL-XL Intravitreal	4 – 8 Weeks	Phase 2
Valo Health	OPL-0401	Rho Kinase	Oral	Phase 2
Verseon	VE-4840/ VE-3539	Kallikrein Oral	Oral	Pre-Clinical

Adverum Biotechnologies

Adverum is a public clinical-stage company with an ophthalmic gene therapy pipeline. Aflibercept gene therapy (ADVM-022) is a single-dose IVT gene treatment being developed for serious retinal vascular disease including DME and Wet AMD. Adverum uses a novel adeno-associated virus (AAV) vehicle to deliver the anti-VEGF protein aflibercept. The AAV vector contains a promoter designed to drive gene expression of aflibercept in retinal cells. The vector is manufactured on the baculovirus expression vector system which has been used on several FDA- and EMA-approved products. ADVM-022 is administered as a single, in-office IVT treatment, designed to deliver long-term efficacy and reduce the burden of frequent anti-VEGF injections.

Adverum has license and collaboration agreements with University of California, Cornell University, GenSight, Lexeo, and Virovek. A clinical phase 2 program, Luna, to assess the efficacy of ADVM-022 began 2H 2022 with first patients dosed in Sept 2022. Preliminary Luna data is anticipated throughout 2023. The phase 1 study in AMD patients has revealed sustained efficacy of ADVM-022 over a 3-year period (extension to follow patients to 5 years). BCVA and CST were maintained or approved over two years across all doses. Importantly, 53% of patients in the lower dose arm needed no anti-VEGF intervention over two years.

Alcon Pharmaceuticals

Aerie Pharmaceuticals is a public pharmaceutical company focused on the development of ophthalmic therapies. As of Nov 2022, Aerie operates as a subsidiary of Alcon Research. Aerie Pharma's DME program, AR-1105, is an implant that lasts up-to 6 months. The fully-bio erodible PRINT®-manufactured implant releases the corticosteroid dexamethasone. Aerie mentioned that the AR-1105 program was phase 3 ready in a Sep 2022 earnings call. No further development to report since Alcon's acquisition of Aerie Pharmaceuticals.

Ashvattha Therapeutics

Ashvattha Therapeutics is a company focused on developing nanomedicine hydroxyl dendrimer therapeutics (HDT) for ophthalmology, neurology, inflammation, and nuero-oncology. Their DME candidate, D-4517.2 is a subcutaneously administered product currently in phase 2 trials. D-4517.2 is an HDT with anti-angiogenic activity that can cross the blood-retinal barrier and target reactive inflammatory and retinal pigment epithelial cells, intracellularly blocking VEGF binding. Phase 2 data is expected in 2H 2023. The company has also tested pre-clinical effectiveness and safety of an oral formulation of D-4517.2.

Clearside Biomedical

Clearside Biomedical is a public company focused on revolutionizing the treatment of retinal disease. The company's DME program, CLS-301, is a suprachoroidal integrin inhibitor. Currently, Clearside is evaluating the ocular tolerability, distribution, and pharmacokinetics of CLS-301 in pre-clinical studies. Clearside has collaborations with Regenx Bio, Aura Biosciences, Bausch Health, and Artic Vision.

Curacle/Thea

Curacle Co is a South Korean bio-venture business focused on developing drugs for diseases caused by aging that result in damaged blood vessels. Their lead candidate, CU06-RE is a small molecule endothelial dysfunction blocker developed using the company's Solvadys platform. CU06 functions by modifying actin structure and stabilizing endothelial cells by inhibiting hyperpermeability and inflammation. The asset was out licensed to Thea Open Innovation, a private French ophthalmology company in October 2021. A phase 1 clinical trial was completed in June 2022. The license agreement with Thea specifies that Curacle is responsible for phase 1-2 trials. The phase 2a began recruiting in Oct 2022 and is estimated to complete around July 2023.

Glaukos Corporation

Glaukos Corporation is an ophthalmic medical technology and pharmaceutical company focused on developing novel therapies for glaucoma, corneal disorders, and retinal disease. The company is developing bioerodible sustained release implants carrying a variety of payloads including corticosteroids and small molecule multi-kinase inhibitor formulations for DME, RVO and AMD. Glaukos claims their implant can potentially last up to 6 months. The programs are currently pre-clinical.

InflammX Therapeutics

InflammX Therapeutics is a pharmaceutical company that focuses on developing therapies for eye disorders where the inflammasome pathway has become dysregulated. Their lead candidate, Xiflam, is an oral treatment designed to regulate the connexin43 hemichannel and the inflammasome in DME. Currently the Xiflam candidate is in phase 2b/3 trials, 6-month data is expected Q3 2023, and 12-month data is expected Q1 2024.

Innovent Biologics

Innovent Biologics is a public Chinese company focused on developing therapies in oncology, ophthalmology, immunology, and metabolic disease. Innovent's DME program, IBI-324 is an VEGF/Ang-2 bispecific antibody IVT therapy. The program is currently in phase 1 clinical trials. Innovent has strategic collaborations with NeoCura Bio-medical Technology, Roche, Ascentage Pharma, Eli Lilly and Bolt Biotherapeutics.

Kalvista Pharmaceuticals

Kalvista Pharmaceuticals is a public clinical-stage pharmaceutical company that develops small-molecule protease inhibitors for diseases with unmet need. The company's lead candidate for DME is KVD001. KVD001 is an IVT kallikrein inhibitor that failed to meet its primary endpoint of change in BCVA at 16 weeks in phase 2 trials. Kalvista has mentioned that it is now considering developing an oral plasma kallikrein inhibitor. This program is pre-clinical and hopes to incorporate lessons learned from its KVD001 clinical failure.

Kodiak Sciences

Kodaik Sciences is a public company focused on developing therapeutics to treat high prevalence retinal diseases. Their lead candidate, KSI-301 (Tarcocimab tedromer) is a novel anti-VEGF biologic

built on a propriety antibody biopolymer conjugate (ABC) platform. KSI-301 is designed to have extended ocular half-life, higher potency, and improved ocular tissue bioavailability. KSI-301 is administered as an IVT injection and designed to provide sustained inhibition of VEGF for up to 6 months.

KSI-301 is currently in a phase 3 Gleam and Glimmer trial consisting of 450 patients against Eylea. Year 1 primary endpoint data is expected 2H 2023. Kodiak is developing additional biologics based on their ABC platform such as KSI-501, a bispecific biologic that targets IL-6/VEGF and KSI-601, a triplet biologic designed for multifactorial diseases such as dry AMD.

Kowa Pharmaceuticals America

Kowa Pharmaceuticals America is a specialty pharmaceutical company that focuses on the acquisition and development of pharmaceutical products in cardiometabolic diseases among other indications. The company's DME program is pemafibrate, a selective PPAR modulator oral treatment which was in phase 3 clinical trial for patients with DME/DR (discontinued in 2022).

OccuRx

OccuRX is an Australian company that is focused on the development of treatment for ophthalmic disorders associated with retinal fibrosis and inflammation. The company's DME program, OCX063 is a G protein-coupled receptor (GPCR) inhibitor currently in phase 1 clinical trials.

Ocugen

Ocugen is a clinical-stage company focused on developing gene therapy to cure blindness. The company's DME program, OCU200, is a transferrin-tumstatin fusion protein targeting endothelial cells. The program is currently pre-clinical with Ocugen submitting an IND package with the FDA in Feb 2023. The company has strategic partnerships with CanSino Biologics Inc, and Bharat Biotech.

Ocular Therapeutix

Ocular Therapeutix is a commercial stage ophthalmology focused biopharmaceutical company. Their DME program, OTX-TKI, is an Axitinib IVT implant that aims to last up-to 6 months. OTX-TKI is a hydrogel implant incorporating a small molecule tyrosine kinase inhibitor being evaluated for wet AMD and diabetic retinopathy. The program is currently in phase 1 trials.

Oculis

Oculis is a clinical-stage company that develops novel topical treatments for ophthalmic diseases. The Oculis DME program, OCS-01 is a dexamethasone topical eye drop treatment for DME. OCS-01 has been developed using the OPTIREACH solubilizing nanoparticle technology, a proprietary platform that enables the formulation of drugs as non-invasive topical treatments, a longer residence time on the eye surface and enhances their bioavailability in the relevant eye tissues.

OCS-01 successfully completed a Phase 2 trial in DME with 144 patients providing a proof-of-concept in retinal edema. Oculis concluded stage 1 of a phase 3 trial in late May 2023. The study met all primary and secondary clinical outcomes. The study included 148 patients, with 100 receiving the drug. Patients saw a mean decrease in CST of 63.6um and mean increase in BCVA of 7.2 letters. Up to 25.3% of patients saw a BCVA increase of 15 letters at week 6. All efficacy signals were maintained out to week 12.

Of the 100 patients which received the drug, 22 had increased IOP with 11 of those patients receiving IOP decreasing medication. This is a manageable side effect as administration of an eye drop treatment can be stopped at any moment. Longer studies will need to be conducted to completely understand the risk of cataract formation. Oculis hopes to accomplish this in stage 2 of

the phase 3 study which will provide 52-week data in 350 – 450 patients. The study is scheduled to begin 2H 2023.

Ocuphire Pharma

Ocuphire Pharma is a late-stage clinical ophthalmology company. Their DR program, APX3330, is a novel twice-daily oral tablet drug candidate, specifically targets redox effector factor-1 (Ref-1) which is a transcription factor regulator protein. APX3330 has a dual mechanism of action in validated pathways, decreasing both abnormal angiogenesis and inflammation by blocking pathways downstream of Ref-1. APX3330 specifically blocks Ref-1's signaling leading to simultaneous decreases in the activity of HIF-1a to reduce VEGF and NF-kB to reduce TNF-α and other inflammatory cytokines. Inhibition of Ref-1 leads to reduction of VEGF and TNF-a to baseline levels.

APX3330 has been studied in over 340 subjects across 11 Phase 1 and Phase 2 non-ocular clinical trials, with few systemic adverse events reported and clinical data that support chronic administration. Ocuphire completed phase 2 trials for APX3330 around August 2022 for the treatment of moderately severe non-proliferative DR (NPDR) and mild proliferative DR (PDR), as well as patients with DME without loss of central vision. Ocuphire will move APX3330 to phase 3 after an end-of-phase 2 meeting with the FDA.

Opthea

Opthea Limited is an Australian clinical-stage company focused on developing therapies for eye disease. The company's lead molecule is OPT-302, a VEGF-C/-D ligand inhibitor which is used in combination with anti-VEGF-A monotherapy (e.g Eylea). Opthea conducted a Phase 1b/2a clinical trial on patients with persistent central-involved DME who were treatment-refractory to previous anti-VEGF-A monotherapy. The trial involved administering OPT-302 in combination with Eylea. Phase 1b was a dose-escalation study with 9 patients, while Phase 2a was a dose-expansion study with a 2:1 randomization of patients to receive either OPT-302 and Eylea or Eylea alone. The primary efficacy and safety endpoints of the study were achieved with OPT-302 combination therapy. Intravitreal 2.0 mg OPT 302 with aflibercept was generally safe and well tolerated with improvements from baseline in visual acuity and anatomic outcomes observed after 12 weeks of treatment in previously treated patients with persistent DME.

Outlook Therapeutics

Outlook Therapeutics is a late clinical-stage company focused on developing and commercializing monoclonal antibodies for ophthalmic indications. The company's lead candidate, ONS-5010 (lytenava) is a bevacizumab-vikg (VEGF agonist) IVT treatment for DME. The company completed pivotal phase 3 trials in wet-AMD and demonstrated significant safety and efficacy. Outlook intends to commence Norse Five and Norse Six, two clinical trials, to evaluate ONS-5010 in DME. Outlook has collaborations and license agreements with Amerisource Bergen, IPCA Laboratories Limited, Laboratories Liomont, BioLexis, and Zhejiang Huahai Pharmaceutical Co.

Oxular

Oxular Limited is an English company that is focused on developing therapies for patients with sight-threatening diseases. The company has two DME programs, delivered using their own Oxusphere drug delivery technology, OXU-001 and OXU-005. OXU-001 is a dexamethasone treatment currently in phase 2 trials scheduled to be completed in 2024. OXU-005 is a new chemical entity narrow spectrum kinase inhibitor treatment that Oxular aims to begin a phase 2 for patients with diabetic retinopathy in late 2024.

Oxurion

Oxurion is a clinical-stage company focused on developing therapies for eye disease. Oxurion's lead candidate is their DME program, THR-149, a plasma kallikrein IVT treatment lasting up to 6 months which was licensed from Bicycle Therapeutics. The company has collaboration agreements with INC Research and Galapagos NV.

A phase 2a trial showed a BCVA gain of 6.1 letters at month 3 and a post-hoc analysis, eliminating 2 patients with abnormalities, showed a 9.3 letter improvement in BCVA which was maintained up to month 6. The company is currently enrolling patients for a phase 2b trial meant to test effectiveness of THR-149 as compared to aflibercept. The phase 2b trial will also produce preliminary data on use of THR-149 in combination with anti-VEGF therapy.

Palatin Technologies

Palatin Technologies is a biopharmaceutical company focused on developing targeted receptor specific therapeutics. The company's DME program, PL9654 is a melanocortin receptor (MCr) agonist IVT treatment. The program is pre-clinical with IND filing planned for 2023.

REGENEXBIO

REGENXBIO is a clinical-stage company seeking to improve lives through the curative potential of gene therapy. REGENXBIO's lead program, ABBV-RGX-314, is an investigational one-time gene therapy built on the company's NAV® Technology Platform and being developed in collaboration with AbbVie for the treatment for wet AMD, diabetic retinopathy, and other additional chronic retinal conditions. ABBV-RGX-314 uses the NAV® AAV8 vector containing a gene encoding for a monoclonal antibody fragment. The expressed antibody fragment is designed to neutralize VEGF activity. ABBV-RGX-314 is currently in pivotal trials for the treatment of wet AMD subretinal delivery and a Phase II trial for the treatment of wet AMD using suprachoroidal delivery. ABBV-RGX-314 is also in a Phase II trial for the treatment of diabetic retinopathy using suprachoroidal delivery.

Singh Biotechnology

Singh Biotechnology is a pre-clinical stage biotechnology company focused on developing single domain antibodies for cancer and other indications. The company's lead candidate SBT-100 is a STAT3 inhibitor under development for a variety of cancers and diabetic eye disease. SBT-100 has shown an ability to suppress VEGF levels among other genes under the control of STAT3 in pre-clinical models. SBT-100 is meant to be a daily subcutaneous injection administered at home. The program is currently pre-clinical.

Valo Health

Valo Health is a drug discovery company leveraging it's Opal computational platform to develop therapies for neurodegenerative, oncological, and cardiovascular diseases. The company's DME program, OPL-0401 is an oral rho-kinase (ROCK) 1/2 inhibitor for DR. The program is currently in phase 2 trials.

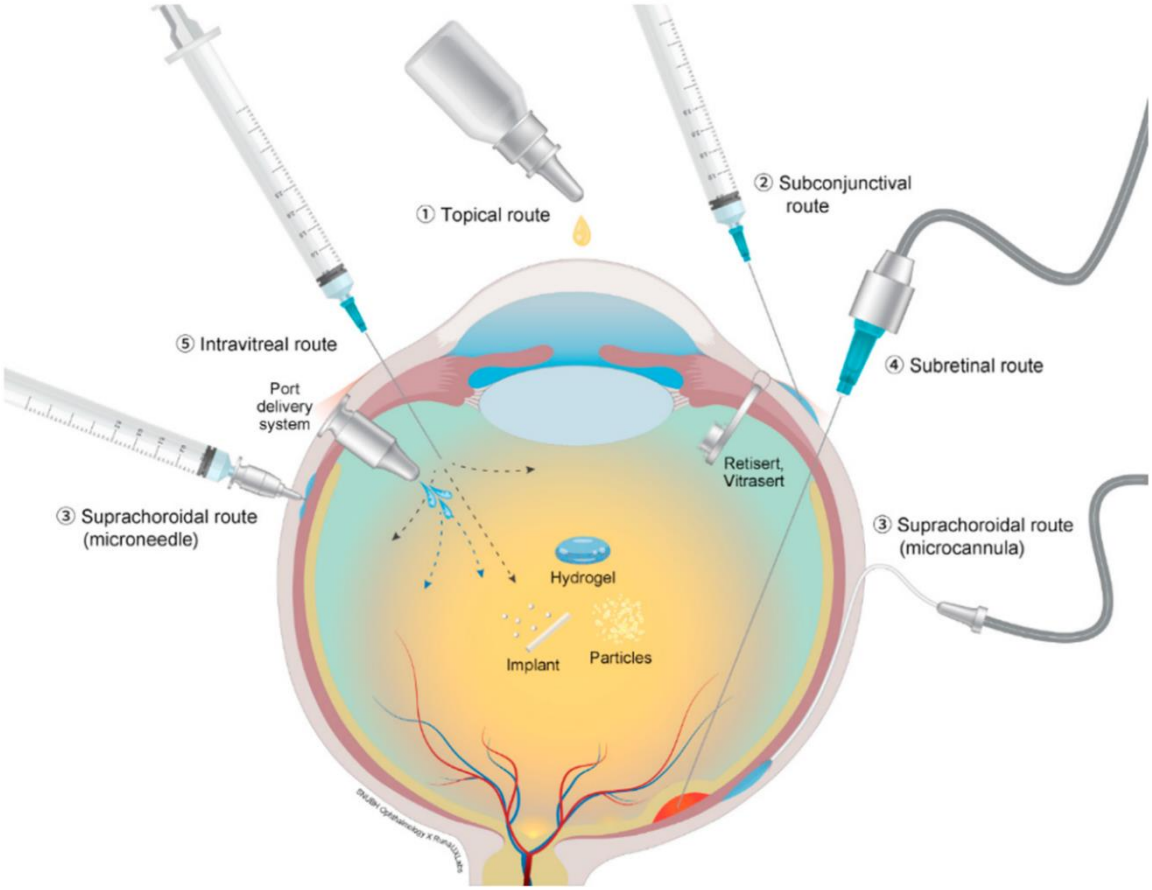
Verseon

Verseon is a clinical-stage pharmaceutical company focused on treating cardiometabolic disorders and cancer with novel small molecules that feature unique therapeutic profiles and are designed by their physics- and AI-based platform. The company has two pre-clinical candidates, oral kallikrein inhibitors, VE4840 and VE-3539, in their diabetic retinopathy program. Both programs have shown significant reduction of diabetes induced vascular permeability in in-vivo pre-clinical studies and are proceeding towards IND.

5.0 Treatment Approaches and Mechanisms of Action

5.1 Treatment Approaches

The figure below shows the various methods of administration of DME treatments. (1) topical route, (2) subconjunctival route, (3) suprachoroidal route with microcannula and microneedle, (4) subretinal route, and (5) intravitreal injection and port delivery system.



Source: Kim, Hyeong Min, and Se Joon Woo. "Ocular Drug Delivery to the Retina: Current Innovations and Future Perspectives." MDPI, Multidisciplinary Digital Publishing Institute, 15 Jan. 2021, https://www.mdpi.com/1999-4923/13/1/108.

5.1.1 Oral and Eye Drop Therapies

Oral and topical eye drop treatments represent the most innovative treatments in the DME space. Treatments administered in a non-invasive manner can easily expand beyond the DME market into the DR market acting as the first preventive care. It is important to note that these treatments can address patients in early stages of disease and will likely need to satisfy different clinical criteria for approval in these patients. Patients at early stages have less swelling in the macula and a change in DRSS score might help better inform treatment effectiveness in addition to changes in CST.

5.1.2 Intravitreal Injections (Chronic Injections or Gene therapy)

IVT treatments require patients to visit a retinal specialist who is trained to inject a therapy directly into the patients' eye. Numerous risk factors are associated with intraocular injections that have been listed above. It is important to note that although risks of severe adverse effects are low with these therapies, the risk is magnified as patients require subsequent injections to maintain therapeutic effect every 4 – 8 weeks. Some IVT treatments are able to extend effectiveness out to 3 - 4 months.

Gene therapy involves a single suprachoroidal injection likely delivering an anti-VEGF antibody such as aflibercept. Gene therapies can largely eliminate the need for follow-up injections however these therapies do present risks of their own.

5.1.3 Surgical Implants

Surgical implants for the treatment of DME largely contain corticosteroids or anti-VEGF molecules and are often bioerodible. The advantage of using implants is that they can provide sustained release of medication over a longer period than IVT treatments, maintaining therapeutic effect up-to 6 months or even 3 years. However, like any medical procedure, implantation also carries some risks, largely these are the same risks associated with IVT treatments in addition to device malfunction and insertion procedure related adverse effects.

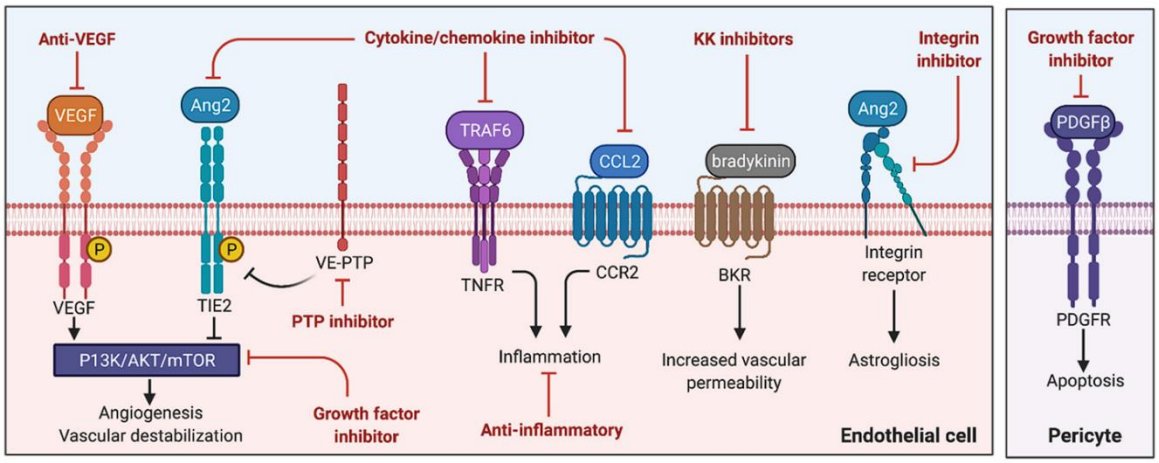
5.1.4 Laser Therapy and Subthreshold Micropulse Laser (SML)

In focal/grid macular laser surgery, a few to hundreds of small laser burns are made to leaking blood vessels in areas of edema near the center of the macula. Laser burns for DME slow the leakage of fluid, reducing swelling in the retina. However, side effects of the therapy included destruction of photoreceptors and epiretinal membrane formation causing patients to lose color and night vision. The procedure is usually completed in one session, but some people may need more than one treatment.

Unlike traditional laser therapy, which uses a high-energy laser to seal off leaking blood vessels in the retina, subthreshold micropulse laser (SML) uses a low-energy laser to target and stimulate cells in the retina without causing any visible damage. Studies have shown that patients with moderate macular swelling that are unresponsive to anti-VEGF treatment respond best to SML treatment. SML therapy is best applied as an add on treatment for patients with macular swelling below 400um and has been shown to stabilize the anatomic and functional retinal parameters 3 months after the procedure and can reduce the number of IVT treatment needed.

5.2 Mechanisms of Action

The figure below shows the various mechanisms of action by which therapies interfere with disease progression and prevent inflammation and aberrant blood vessel formation in the diabetic eye.



Source: Chauhan, Muhammad Z., et al. "Current and Novel Therapeutic Approaches for Treatment of Diabetic Macular Edema." MDPI, Multidisciplinary Digital Publishing Institute, 17 June 2022, https://www.mdpi.com/2073-4409/11/12/1950.

5.2.1 Vascular Endothelial Growth Factor (VEGF)

VEGF is a protein that stimulates the growth of new blood vessels in the retina. Chronic hyperglycemia damages vascular endothelial cells, leading to ischemia and overexpression of various growth factors, including VEGF. VEGF plays a crucial role in the pathogenesis of DME by mediating angiogenesis, protease production, and increasing vascular permeability. The process of angiogenesis occurs in low-oxygen areas, and pharmacotherapy that targets VEGF inhibits these processes and prevents the formation of leaking blood vessels. Anti-VEGF compounds, including aptamers, antibodies, antibody fragments, and fusion proteins, can be used to treat DME.

5.2.2 Plasma Kallikrein (PKal)

PKal inhibitors function to treat DME by blocking the activity of plasma kallikrein, which is a serine protease that contributes to inflammatory responses and retinal edema in DME. When plasma prekallikrein (PPK) is transformed into its catalytically active form, prekallikrein (PK), it cleaves kininogen to generate bradykinin, which induces vasodilation and increases vascular permeability. PKal inhibitors prevent the formation of PK, thereby reducing the production of bradykinin and decreasing vascular permeability, which can help to diminish retinal edema and improve visual outcomes in patients with DME.

5.2.3 Redox Factor-1 (Ref-1)

Ref-1 inhibitors have the ability to prevent the activation of NF-κB and reduce the expression of inflammatory mediators, such as IL-1β, TNF-α, and VEGF. Ref-1 inhibitors also target aldose reductase, an enzyme involved in glucose metabolism that is implicated in diabetic complications, including retinopathy. By inhibiting aldose reductase activity, Ref-1 inhibitors reduce oxidative stress and vascular dysfunction in animal models of diabetes. Overall, Ref-1 inhibitors have the potential to reduce inflammation, oxidative stress, and vascular dysfunction, which could improve retinal function and reduce the severity of DME.

5.2.4 Angiopoietin-2 (Ang-2)

The Angiopoietin-Tie2 signaling pathway is important in the regulation of angiogenesis and vascular stability. Ang-2 is a natural antagonist of angiopoietin-1 (Ang-1) and disrupts the Ang-1/Tie2 signaling pathway leading to endothelial cell destabilization and increased vascular permeability. In diabetic retinopathy, increased expression of Ang-2 has been found in the retina, which contributes to vascular leakage and retinal neovascularization. Ang-2 inhibitors bind to Ang-2 and prevent its interaction with the Tie2 receptor, leading to stabilization of blood vessels and reduction of vascular permeability. By inhibiting Ang-2, these drugs also decrease the production of VEGF.

5.2.5 Tyrosine Kinase

In the eye, tyrosine kinases are involved in the formation of new blood vessels, which can contribute to the development of DME. TKIs work by blocking the activity of these kinases, which can inhibit the growth of abnormal blood vessels and reduce inflammation in the retina. Different TKIs target different tyrosine kinases. For example, some TKIs target vascular endothelial growth factor receptors (VEGFRs). Other TKIs may target platelet-derived growth factor receptors (PDGFRs) or other tyrosine kinases that are involved in inflammation or fibrosis in the retina. By inhibiting these

pathways, TKIs can reduce inflammation and scarring in the retina, which can improve vision outcomes in patients with DME.

5.2.6 B-cell Lymphoma-Extra Large (BCL-XL)

BCL-XL is a protein that plays a key role in preventing programmed cell death (apoptosis) in cells. In people with diabetes, increased levels of BCL-XL have been observed in the retina, and it has been suggested that this may contribute to the development of DME by promoting the survival of cells that are involved in the formation of abnormal blood vessels. BCL-XL inhibitors work by blocking the activity of BCL-XL, which can induce programmed cell death in the cells that are involved in the formation of abnormal blood vessels in the retina. By inducing cell death in these cells, BCL-XL inhibitors may help to reduce the formation of abnormal blood vessels and decrease vascular permeability.

5.2.7 Corticosteroids

Corticosteroids, such as triamcinolone acetonide and dexamethasone, are nonspecific anti-inflammatory agents that play a key role in modulating inflammation in the retina through several mechanisms including blocking the production and release of cytokines. They act by stabilizing the blood-retina barrier, reducing capillary permeability, and enhancing endothelial tight junction activity. These actions lead to decreased vascular leakage and reduced edema in the retina, which can help improve visual acuity in patients with DME. Intravitreal injections of corticosteroids have been shown to improve vision in the short term, but their long-term use is limited by adverse effects such as elevated intraocular pressure and cataract development.

6.0 Acronyms:

DME – diabetic macular edema

DR – diabetic retinopathy

PDR – proliferative diabetic retinopathy

NPDP – nonproliferative diabetic retinopathy

DRSS – diabetic retinopathy severity scale

CST – central subfield thickness

BCVA – best corrected visual acuity

VEGF – vascular endothelial growth factor

Pkal – plasma kallikrein

Ang-2 – angiopoietin-2

Ref-1 – redox factor-1

Bcl-xL – B-cell lymphoma-extra large (apoptosis receptor)

SML- subthreshold micropulse laser

IOP – intraocular pressure

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