Sustained Release Tyrosine Kinase Inhibitors: The Future of Retinal Disease Management

THE PHYSIOLOGICAL SIGNIFICANCE OF VEGF AND INFLAMMATION IN RETINAL DISEASE

Vascular endothelial growth factor (VEGF) is a critical protein involved in angiogenesis and vascular development.[1] A member of the VEGF/platelet-derived growth factor (PDGF) family of extracellular signaling molecules, VEGF consists of (but is not limited to) several growth factor members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PIGF).[1] VEGF ligands bind to the extracellular domain of tyrosine kinase receptors in a highly targeted manner, with specific downstream effects.[1-3]

Due to its key role in promoting vascular permeability,[4] VEGF-A has emerged as a common pharmacologic target of anti-VEGF therapy. However, agents that selectively inhibit VEGF-A, even at higher doses, may offer limited efficacy due to involvement of other VEGF isoforms and angiogenic pathways.

Retinal diseases are multifactorial, with inflammation playing a key role in their pathogenesis beyond angiogenesis.[5,6] Interleukin-6 (IL-6) is a pro-inflammatory cytokine implicated in wet age-related macular degeneration (AMD) and diabetic macular edema (DME) that sustains inflammation and leads to increased VEGF production. Together, IL-6 and VEGF compound damage to the blood-retinal barrier.[7-9]

CHALLENGES WITH THE STANDARD OF CARE

Despite the remarkable clinical benefits of anti-VEGF drugs, important unmet needs still exist in the management of retinal disease.[10-12] All anti-VEGF agents approved to date are large-molecule biologics with short half-lives that bind a subset of VEGF ligands extracellularly.[13] Notably, current anti-VEGF dosing regimens typically require frequent injections in the office, which can be burdensome to both patients and physicians and result in poor patient adherence or early discontinuation.[11] Owing to the treatment burden associated with current therapies, patients with wet AMD are often undertreated.[11,12] Undertreatment has been associated with worse long-term vision outcomes in wet AMD,[12] possibly explaining why visual outcomes with anti-VEGF therapies in the real-world setting may be worse than those reported in monitored clinical trials.[12,14] Though discrepancies in the durability of anti-VEGF agents in clinical practice versus clinical development may be due to differences in disease activity criteria and monitoring in the trial setting,[15] improved durability and reduced treatment burden was found to be among the most important factors to consider in treatment decisions for over 75% of retina specialists.[16]

Further, existing intravitreal anti-VEGF therapies have other intrinsic limitations. Multiple studies show that fluid fluctuations during anti-VEGF treatment are associated with worse visual outcomes in wet AMD.[17-20] Intermittent, pulsatile treatment with non–sustained-release therapies may permit recurrence of exudative activity, contributing to retinal instability and tissue damage.[17] In addition, traditional anti-VEGFs only target one aspect of disease pathogenesis, while leaving other contributory processes such as inflammation unaddressed. Response to anti-

VEGF treatments may also be limited by lack of comprehensive VEGF blockade at the receptor level. The potential consequences of selective VEGF blockade were explored by Cabral el al.[21] In one study (n=23), as would be expected, intravitreal bevacizumab was associated with reductions of VEGF-A concentration in aqueous humor. However, statistically significant increases were also observed in VEGF-C (165.93% increase) and six other vasogenic biomarkers (Ang-2, endothelin1, fullistatin, HB-EGF. HGF, and interleukin 8) after a 2-month follow up.[21]

CONTINUOUS TARGET INHIBITION

There are at least 58 known tyrosine kinase receptors in the human proteome[22] and more than 50 FDA-approved tyrosine kinase inhibitors (TKIs).[23] Though their clinical utility has been validated with existing indications and applications in oncology, TKIs represent a novel mechanism of action in the treatment of retinal disease, offering comprehensive, multitarget blockade. Vorolanib is a potent, highly selective TKI with a novel multi- mechanism of action, working intracellularly to suppress angiogenesis via inhibition of all VEGFRs and PDGFR, while also suppressing inflammation through inhibition of IL-6 signaling **(Figure 1)**.[24-26]

Though ophthalmic TKIs have been previously investigated in a variety of administration forms, several assets currently in development are administered via intra- or periocular injection. Oral formulations of vorolanib have been investigated in participants with wet AMD in phase 1, open-label dose escalation studies conducted at 5 US retinal clinics (NCT01674569)[27] and at 6 China sites

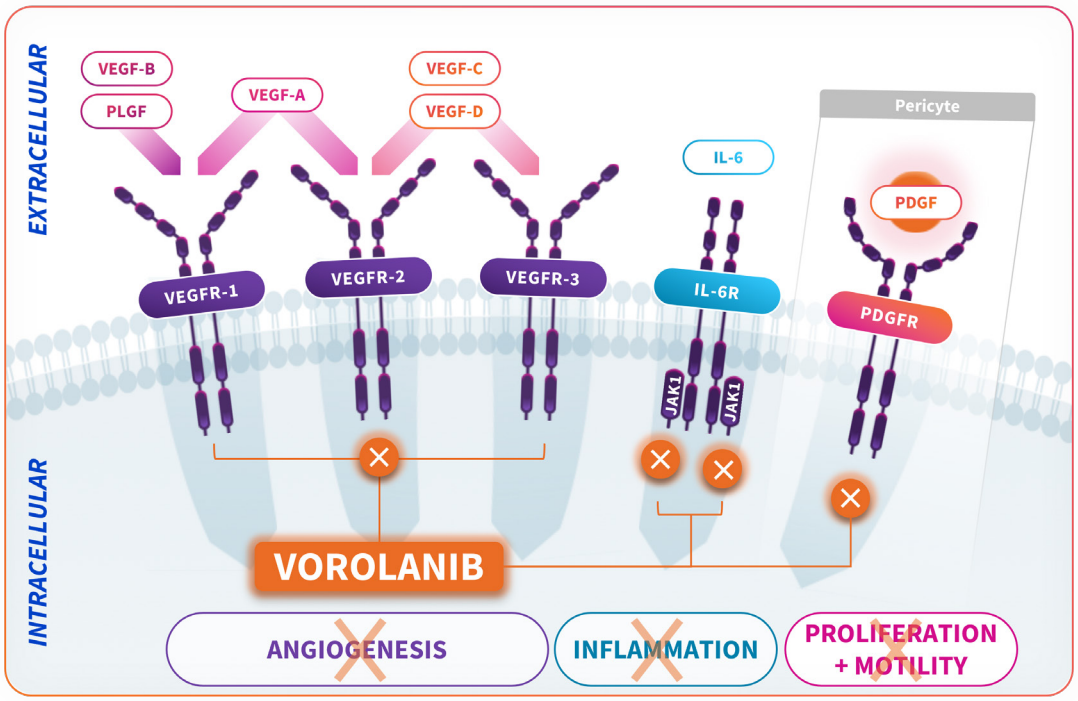

Figure 1. Vorolanib mechanism of action.

Vorolanib binds intracellularly to VEGFR-1, -2, and-3 and PDGFR to inhibit downstream angiogenic signaling, and also inhibits pro-inflammatory IL-6 signaling.

(NCT02452385).[28] In a phase 2 study (NCT02348359; APEX), oral vorolanib demonstrated noninferiority in visual acuity compared with placebo and a decreased intravitreal injection burden.[28,29] Elevations in alanine aminotransferase and aspartate aminotransferase were seen in all groups that received oral vorolanib;[27-29] however, these systemic safety concerns were consistent with previously studied TKIs, suggesting a potential pharmacological class effect with oral administration.[30] Notably, no treatment-related ocular serious adverse events (SAEs) were observed with oral vorolanib.[27-29]

Currently under clinical investigation in a sustained-release formulation delivered via intravitreal injection, vorolanib exhibits certain distinctions in drug delivery technology and pharmacokinetic profile. EYP-1901 (vorolanib intravitreal insert; EyePoint) is a bioerodible sustained-release intravitreal insert that combines vorolanib with the Durasert E™ drug delivery technology. The Durasert E™ matrix does not contain PEG or PLGA. Each EYP-1901 insert is composed of 94% drug and 6% matrix. Administered intravitreally via a pre-loaded syringe injector, EYP-1901 is designed to deliver a daily therapeutic dose of vorolanib for at least 6 months with no fluctuations. In preclinical studies, vorolanib reaches target tissues at therapeutic levels within hours of administration.[31,32] After depletion of the drug, the minimal polymeric matrix is designed to fully erode over time, ensuring no free-floating drug particles **(Figure 2)**.[33] The combination of continuous drug delivery and intracellular multitarget inhibition may help patients maintain visual acuity while meaningfully extending treatment intervals, and can potentially offer sustained clinical benefit for patients who struggle with adherence to current anti-VEGF dosing regimens.

EYP-1901 has been investigated for the treatment of wet AMD in the phase 1 open-label, dose-escalation DAVIO study (NCT04747197) and the phase 2 randomized, double-masked DAVIO 2 study (NCT05381948), the largest phase 2 clinical trial completed for a sustained-release intravitreal TKI to date. DAVIO 2 met its primary endpoint, demonstrating statistically noninferior change in best corrected visual acuity with a single EYP-1901 dose compared to aflibercept 2.0 mg every 8 weeks (q8W)

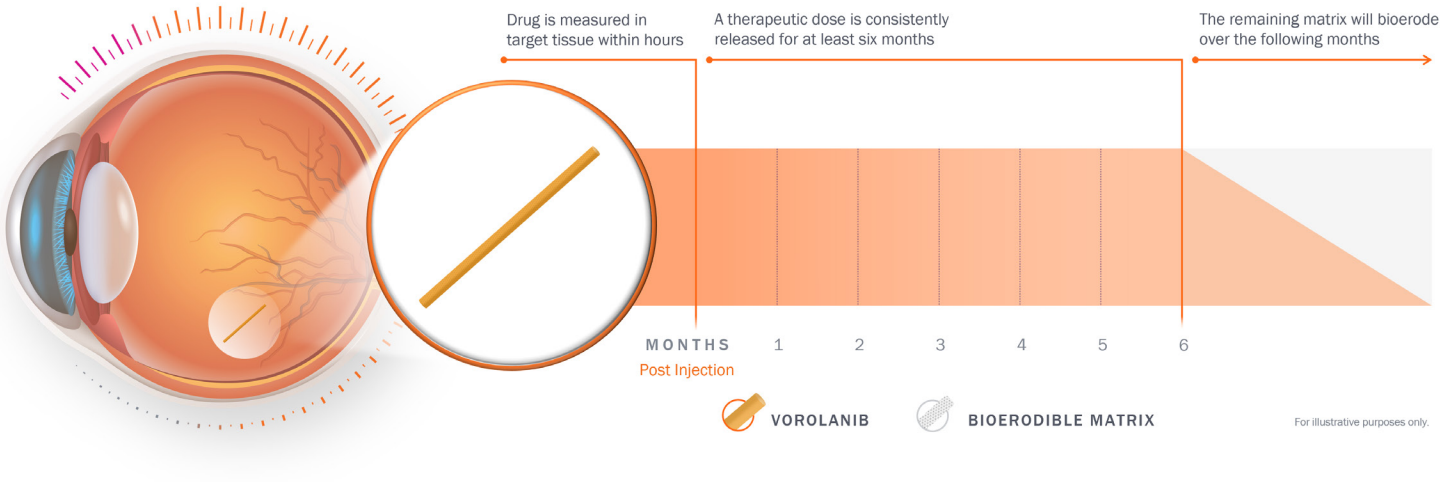

Figure 2. Bioerodible EYP-1901 (vorolanib intravitreal insert) with Durasert E™ technology.

Using next-generation drug delivery technology, EYP-1901 is designed to deliver a therapeutic dose of vorolanib for at least 6 months. The matrix is designed to erode after full elution of vorolanib, ensuring no free-floating drug particles.

and a favorable safety profile with no EYP-1901-related ocular or systemic SAEs in patients with previously-treated wet AMD. The trial also achieved key secondary endpoints, including an over 80% reduction in treatment burden, nearly two-thirds of eyes supplement-free up to six months and over 80% receiving only zero or one supplemental anti-VEGF injection up to six months.[34]

EYP-1901 was also assessed in the phase 2 randomized VERONA trial (NCT06099184), which enrolled patients with active DME. VERONA met its primary endpoint, with a single EYP-1901 dose extending time to first supplemental anti-VEGF injection versus a single injection of aflibercept 2.0 mg. Vision and anatomic improvements with EYP-1901 were observed at 4 weeks following treatment (the first post-treatment visit), suggesting early bioavailability of vorolanib with EYP-1901.[35] As of this current publication, EYP-1901 has been investigated in over 190 patients with no EYP-1901-related safety signals observed across 4 completed clinical trials, including 3 phase 2 trials.

Two pivotal phase 3 clinical trials assessing EYP-1901 with 6-month redosing intervals versus on-label aflibercept q8W in wet AMD are ongoing **(Figure 3)**. LUGANO (NCT06668064) and LUCIA (NCT06683742) randomized 432 (U.S.) and 475 (U.S. and ex-U.S.) patients with wet AMD, respectively.[36] Based on interim masked safety data, the observed safety profile is consistent with previous EYP-1901

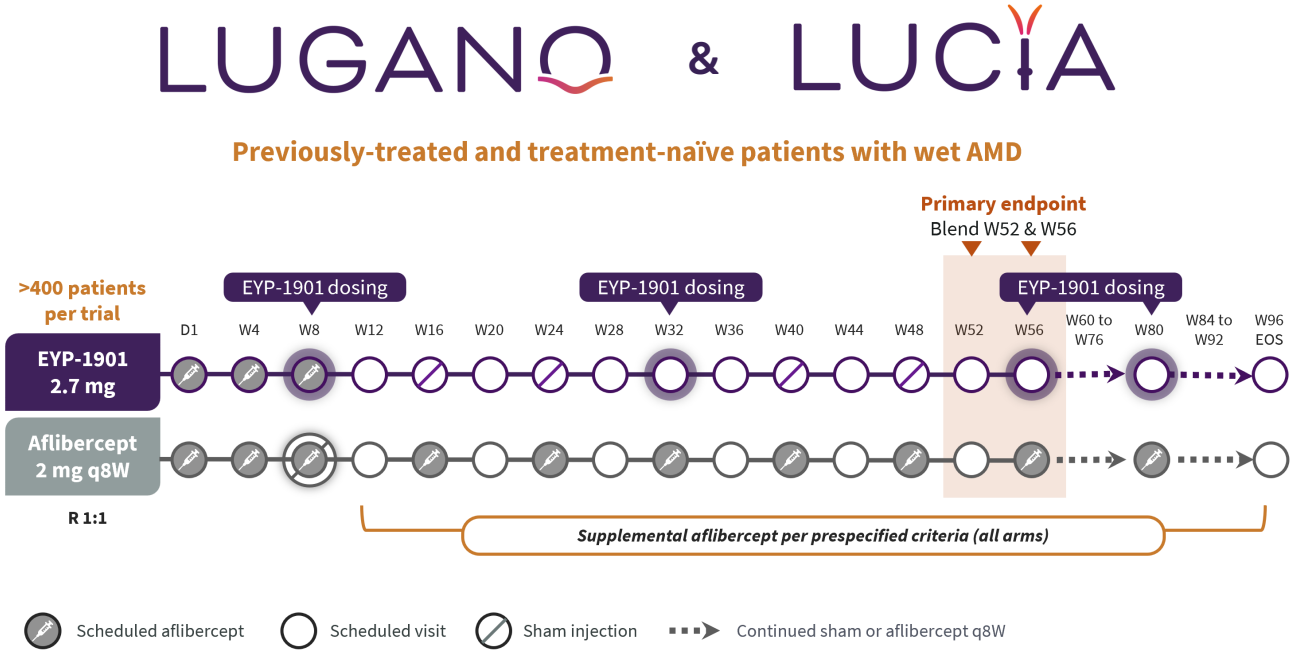

Figure 3. EYP-1901 wet AMD phase 3 trial designs

LUGANO and LUCIA aim to demonstrate that a dose of EYP-1901 2.7 mg, when administered every 6 months, achieves similar visual outcomes to on-label aflibercept while reducing treatment burden in previously-treated and treatment-naive patients with wet AMD. The primary endpoint is mean change in BCVA from Day 1 to one year (Week 52/56 averaged).

clinical trials.[37] Topline data are anticipated in mid-2026 for LUGANO, with LUCIA to shortly follow.[36]

Initiation of the pivotal phase 3 program evaluating EYP-1901 in DME is underway. The paired COMO and CAPRI trials (ClinicalTrials.gov registration pending) will each enroll approximately 240 patients with DME **(Figure 4)**. First patient dosing in both trials is expected in first quarter of 2026.[36]

FUTURE CONSIDERATIONS

The pathogenesis of retinal exudative disease can be considered a multifaceted process that involves multiple signaling pathways and many growth factors, not limited to a single ligand such as VEGF-A.

Though anti-VEGF treatments have revolutionized retinal disease management, the selective binding of VEGF ligands and requirement for frequent in-clinic injections may represent insufficient long-term therapy in a significant percentage of patients. Sustained-release TKIs that target multiple pathways with a consistent therapeutic dose, such as EYP-1901, may help optimize long-term patient outcomes.

Disclaimer: *DURAVYU™ has been conditionally accepted by the FDA as the proprietary name for EYP-1901. EYP-1901 (vorolanib intravitreal insert) is an investigational medicine product; it has not been approved by any health agencies or regulatory authorities in any country. Approval and timeline for marketing authorization is uncertain.*

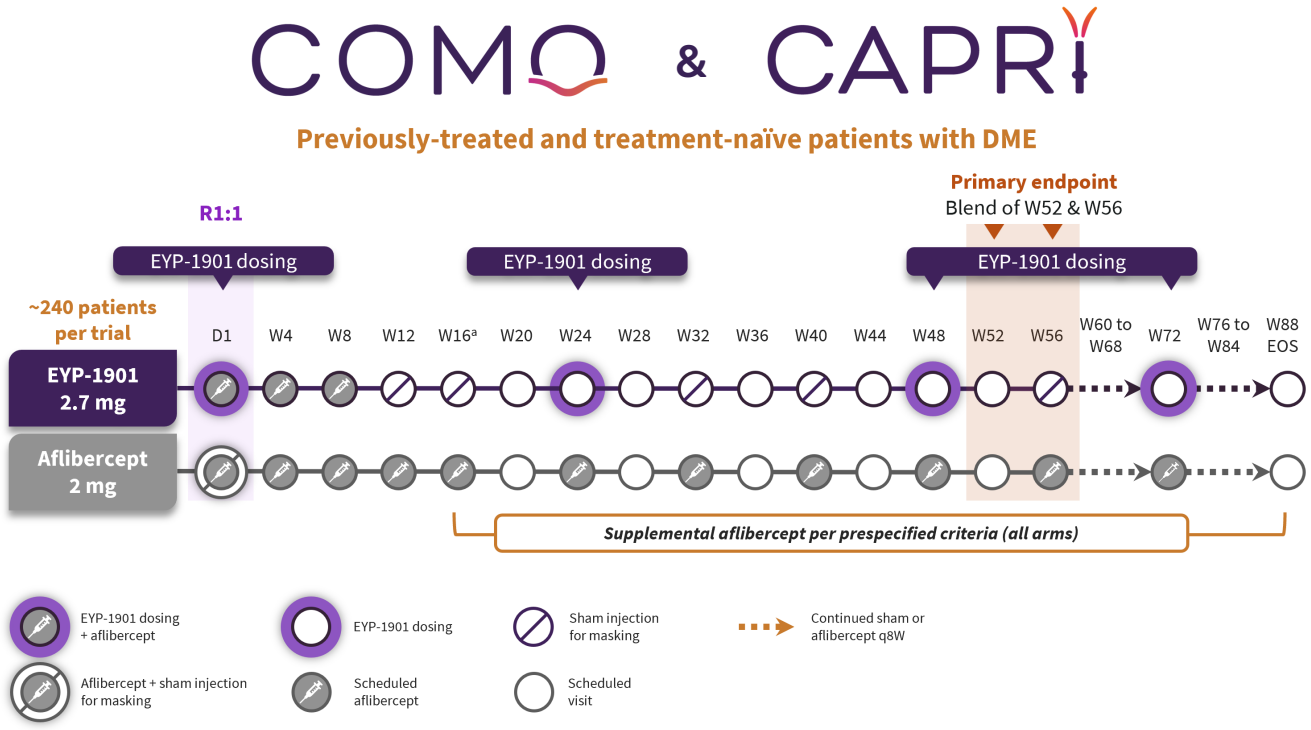

Figure 4. EYP-1901 DME phase 3 trial designs

COMO and CAPRI aim to demonstrate that a dose of EYP-1901 2.7 mg, when administered every 6 months, achieves similar visual outcomes to on-label aflibercept while reducing treatment burden in previously-treated and treatment-naive patients with DME. The primary endpoint is mean change in BCVA from Day 1 to one year (Week 52/56 averaged).

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