B0301

Design and Function of EYP-1901, a Sustained-Delivery Platform for Retinal/Choroidal Disease: Pan–Vascular Endothelial Growth Factor Receptor Inhibitor Vorolanib in a Bioerodible Intravitreal Insert

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Purpose

- EYP-1901 is a bioerodible, sustained-delivery, intravitreal insert delivering the pan–vascular endothelial growth factor (VEGF) receptor (VEGFR) inhibitor vorolanib to help maintain vision and lower treatment burden in VEGF-driven ocular diseases.[1-3]
- EYP-1901 preclinical studies of angiogenesis inhibition and pharmacokinetics, along with clinical studies in wet age-related macular degeneration (wAMD), are being investigated. This poster reports initial and topline findings of those studies.

Methods

Preclinical Studies

Mechanism of Action

- Half-maximal inhibitory concentration (IC_{50}) values were determined for pan-VEGFR inhibitors vorolanib, axitinib, and sunitinib.[4,5]

Pharmacokinetics

- Fifty male Dutch Belted rabbits were injected with a single dose of EYP-1901. Vorolanib concentrations were measured in ocular tissues and plasma at prespecified timepoints over 12 months using a validated liquid chromatography–tandem mass spectrometry bioanalytical method.[6]

Clinical Trial

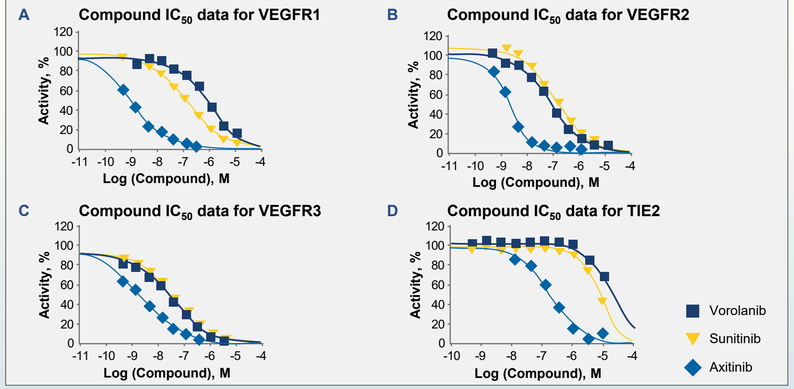
- **DAVIO 2** (NCT05381948) is a phase 2, randomized, double-masked, parallel trial of 2 doses of a single EYP-1901 treatment vs aflibercept 2 mg q8W in 161 patients previously treated for wAMD.
- Eyes in all arms could receive supplemental aflibercept injections based on set criteria.

Results

Mechanism of Action

- Vorolanib, axitinib, and sunitinib potently inhibited all VEGFRs in vitro at therapeutic drug levels (**Figure 1A-C**).[4,5]
- TIE2 (needed for vascular stability) was inhibited by axitinib but not vorolanib or sunitinib at therapeutic levels (**Figure 1D**).[4,5]
- Vorolanib, axitinib, and sunitinib suppressed angiogenesis in vitro and in vivo (additional details: ARVO Poster B0296).

Figure 1: Receptor Kinase Inhibition by Pan-VEGFR Inhibitors In Vitro



IC_{50}, half-maximal inhibitory concentration; VEGFR, vascular endothelial growth factor receptor.

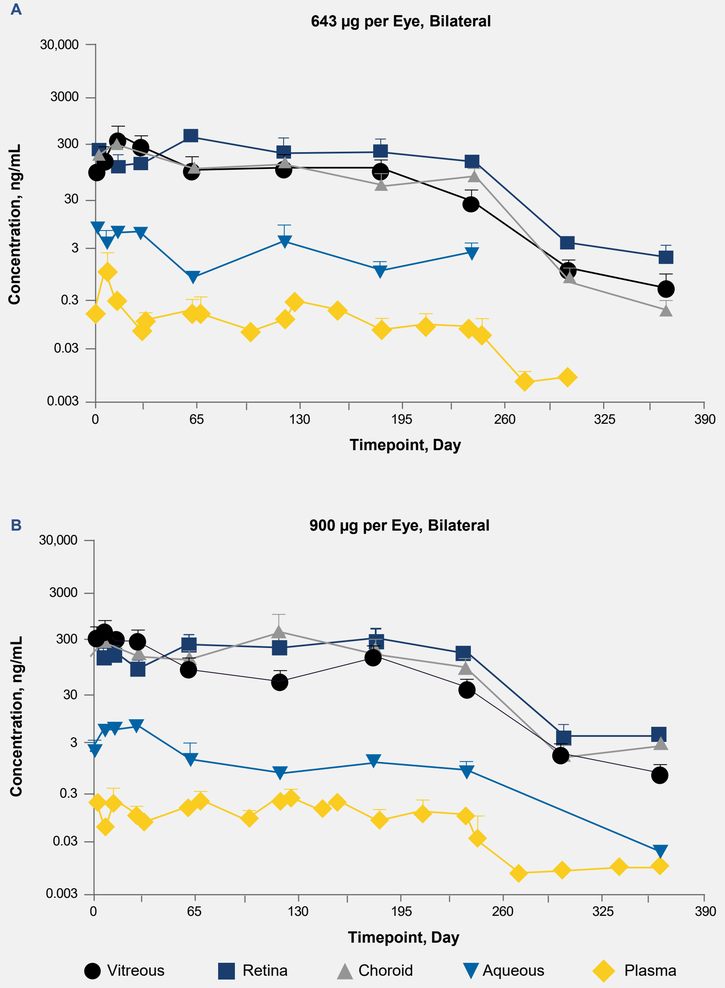
Results (cont.)

Pharmacokinetics

Single-Dose Study in Rabbits (N = 50)

- EYP-1901 showed rapid, steady delivery of vorolanib to target tissues (**Figure 2**).[6]
- Concentration remained above IC_{50} for VEGFR2 over 8 months in target tissues.
- Drug depletion occurred at 8–9 months.
- Plasma levels were below IC_{50} throughout the study, indicating low systemic exposure.[6]

Figure 2: Vorolanib Concentrations Over 12 Months Following Administration of EYP-1901

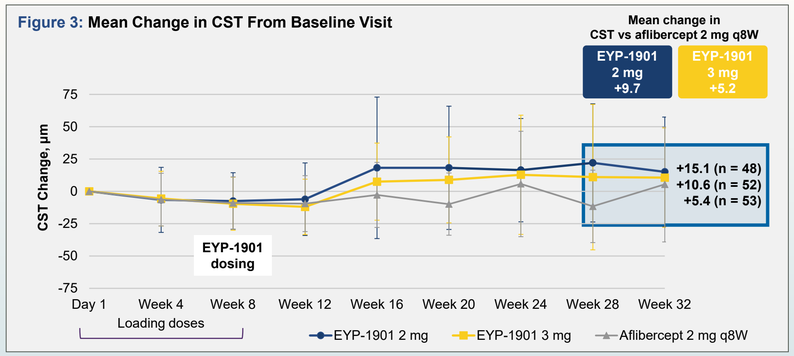


Results (cont.)

DAVIO 2 Phase 2 Trial

- Phase 2 trial of a single EYP-1901 treatment compared to aflibercept 2 mg q8W in previously treated patients with wAMD.
- Patients randomized 1:1:1.
- Most common adverse events (AEs) with EYP-1901 2 mg:
  - Worsening AMD, conjunctival hemorrhage, vitreous floaters.
- No serious AEs related to EYP-1901 were reported.
- The mean change in best-corrected visual acuity (BCVA) from baseline was +1.0 letters in the EYP-1901 2 mg arm, +0.9 letters in the EYP-1901 3 mg arm, and +1.3 letters in the aflibercept arm.
- The sawtooth pattern of central subfield thickness (CST) fluctuation often seen with anti-VEGF therapy was not seen with EYP-1901 (**Figure 3**).
- 65% and 64% of eyes were supplement-free up to 6 months with EYP-1901 2 mg and 3 mg, and treatment burden was reduced by 89% and 85% (additional details: ARVO Poster A0120).

Figure 3: Mean Change in CST From Baseline Visit



Error bars represent the standard deviation. CST units were µm. CST, central subfield thickness; q8W, every 8 weeks.

Conclusions

- Vorolanib inhibited multiple receptor kinases but did not inhibit TIE2 at therapeutic levels.
- EYP-1901 in rabbits provided rapid and steady concentrations of vorolanib above the IC_{50} in target tissues.
- Plasma exposures were consistently maintained below the IC_{50}. Therefore, no systemic effects are expected.
- EYP-1901 reduced the need for supplemental injections and demonstrated a reduction in treatment burden.
- DAVIO 2 demonstrated steady BCVA and CST in eyes treated with EYP-1901.
- EYP-1901 is designed to provide steady state concentrations of vorolanib and avoid large peak-to-trough differences in tissue concentrations.
- The sawtooth pattern of CST fluctuation often seen with aflibercept was not observed with EYP-1901 treatments.
- EYP-1901 may provide a treat-to-maintain regimen for patients with wAMD.

References: 1. Thomas CN, et al. *Br J Pharmacol*. 2022;179:1908-1937. 2. Sobolewska B, et al. *Clin Ophthalmol*. 2021;15:4317-4326. 3. Patel P, et al. *J Clin Med*. 2021;10:2436. 4. Bakri SJ. Presented at Retina Society Annual Scientific Meeting, New York, NY; October 13, 2023. 5. Bakri SJ, et al. Manuscript under review. 6. Singh RP, et al. Presented at American Society of Retina Specialists Annual Meeting, Seattle, WA; July 31, 2023.

Commercial Relationships Disclosure: B.K.: Clinical Research – Allergan, Apellis, Clearside, Genentech Inc, Ionis, IVERIC Bio, Novartis Pharmaceuticals, Regeneron Pharmaceuticals Inc, RegenXBio; Consultant – Allegro Ophthalmics, Allergan/AbbVie, Alimera, Amgen, Astellas, Aviceda Therapeutics, Clearside, Coherus, EyeBio; Eyedaptic, EyePoint, Genentech Inc, Glaukos Corporation, InflammX Therapeutics, IVERIC Bio, jCyte, Mobius, Molecular Partners, Novartis Pharmaceuticals, Ocular Therapeutix, Ocuphire, OphtiMedRx, Privitera, Regeneron Pharmaceuticals Inc, ReVana Therapeutics, Ripple Therapeutics, Roche Pharmaceuticals, Santen, Stealth Therapeutics, TechImmune, Theravance Biopharma, Visgenx; Speakers Bureau – Allergan, Genentech, Roche, Coherus. **M.H.-S., J.L., S.R., M.R.:** Employment – EyePoint Pharmaceuticals, Inc. **S.S.:** R&D Consultant – EyePoint Pharmaceuticals, Inc. **D.A.P.:** Former employee of EyePoint Pharmaceuticals.
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