Multi-Mechanism of Action of EYP-1901 in Retinal Exudative Diseases: Inhibition of IL-6 Signaling, VEGFR and PDGFR by Vorolanib

Sharma, Sumit, MD[1]; Jeff Lynch, PhD[2]; Marcia Sellos-Moura, PhD[2]

1. Cleveland Clinic, Cleveland, OH
2. EyePoint Inc, Watertown, MA

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Disclaimer

EYP-1901 is an investigational product and the safety and efficacy of EYP-1901 has not been established. FDA has not approved EYP-1901 in the United States. The materials discussed in this presentation do not predict future FDA approval. Conclusive evidence of efficacy and safety of EYP-1901 will require further investigation in well-controlled phase 3 clinical trials.

Disclosures

Presenter disclosures

- Consultant: AbbVie, Alimera, Bausch + Lomb, Clearside Biomedical, EyePoint, Genentech, Inc., Regeneron, Regenxbio, Roche, 4D Molecular Therapeutics
- Research Support: EyePoint, Genentech, Gilead Sciences, Ionis, Roche, Santen

Study disclosures

- Funding was provided by EyePoint for the study and third-party writing support by Nibedita Gupta, PhD, CMPP, of Koahana, Inc.

Key Takeaways

EYP-1901 is a bioerodible intravitreal insert designed to provide sustained release of the TKI *vorolanib* for at least 6 months [1]

EYP-1901 is currently in phase 3 clinical trials for wet AMD and DME[2]

***Vorolanib* (active TKI in EYP-1901) has a multi-MOA for retinal diseases**[3,4]

1. Patel S, et al. *Ophthalmol Sci*. 2024;4(5):100527. **2.** Clinicaltrial.gov identifiers: COMO, NCT07449936; CAPRI, NCT07449923; LUGANO, NCT06668064; LUCIA, NCT06683742. **3.** Bakri SJ, et al. *PLoS One*. 2024;19(6):e0304782.
4. Singh R, et al. Presentation at The Associate for Research in Vision and Ophthalmology (ARVO) Annual Meeting: May 3–7, 2026; Denver, CO.
AMD, age-related macular degeneration; **DME,** diabetic macular edema; **IL-6,** interleukin-6; **MOA,** mechanism of action; **TKI,** tyrosine kinase inhibitor.

Data on file. Conclusive evidence of efficacy and safety of EYP-1901 will require further investigation in well-controlled phase 3 clinical trials.

EYP-1901 is a Bioerodible Intravitreal Insert Designed to Provide Sustained Release of Vorolanib for at least 6 Months

Each IVT insert is:

- **94% drug** / 6% matrix
- **1/5000th** of vitreous volume
- **Bioerodible**

No PEG/PLGA
Drug release ≥6 months

Therapeutic levels of vorolanib reached within hours[a]

Consistent daily dosing with target inhibition for **at least 6 months**

No free-floating drug particles

No cold storage required; **pre-loaded** IVT syringe injector

[a] Data from preclinical studies. Following a single injection of EYP-1901 in Dutch-Belted rabbits, vorolanib reached concentrations exceeding IC_{50} in the retina and RPE within 8 hours. Bakri SJ, et al. *PLoS One*. 2024;19(6):e0304782.
Lynch J, et al. Presentation at The Associate for Research in Vision and Ophthalmology (ARVO) Annual Meeting: May 3–7, 2026. Denver, CO. Patel S, et al. *Ophthalmol Sci.* 2024;4(5):100527. Wykoff CC, et al. *J Vitreoretin Dis*. 2024;8(5):577-586.
Singh RP, et al. Presentation at American Society of Retina Specialists (ASRS) Annual Meeting: July 28–August 1, 2023; Seattle, WA. Singh R, et al. Presentation at The Associate for Research in Vision and Ophthalmology (ARVO) Annual Meeting: May 3–7, 2026; Denver, CO.
IVT, intravitreal; **PEG**, polyethylene glycol; **PLGA**, poly lactic-co-glycolic acid.

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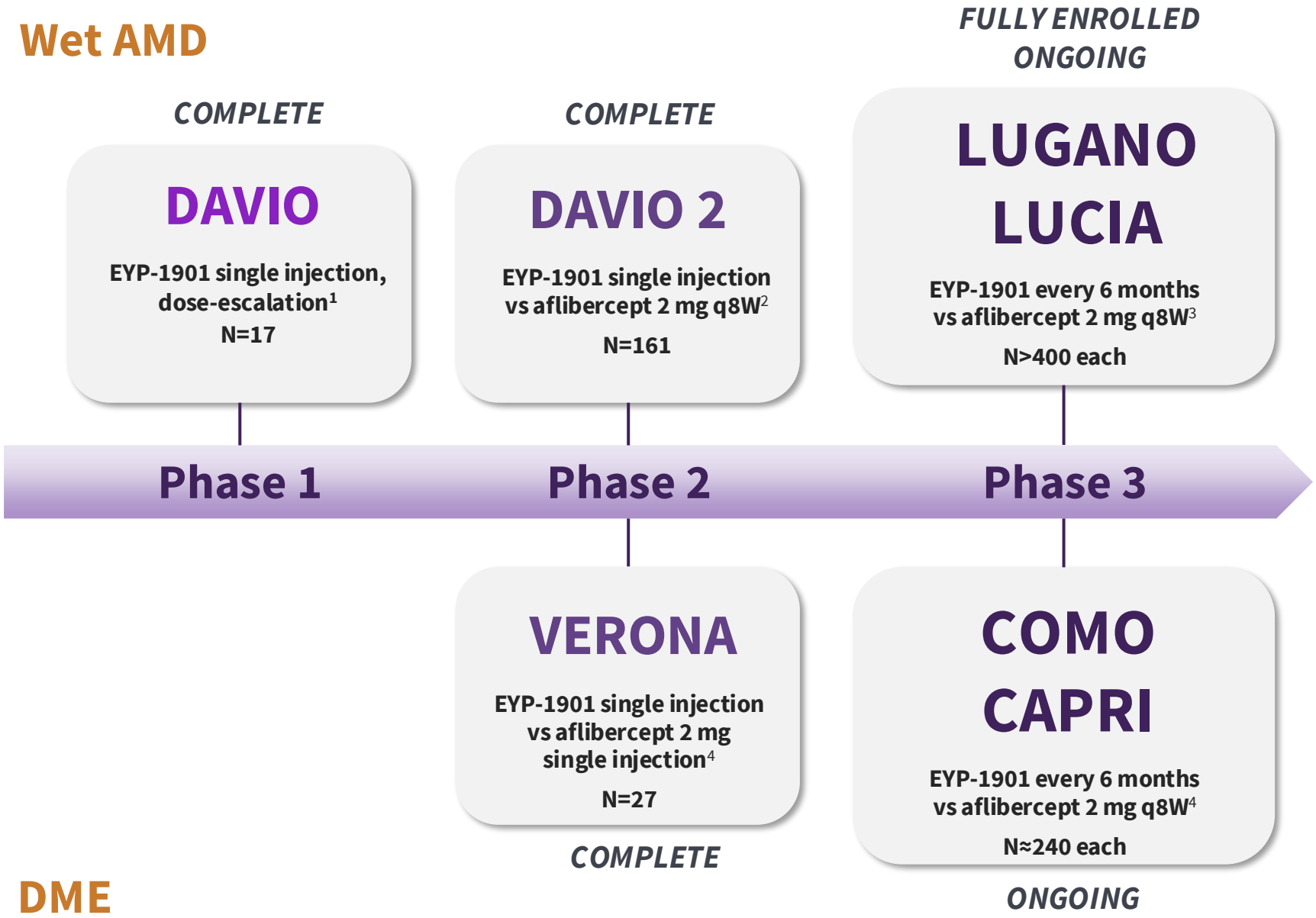
Clinical Trials for EYP-1901 in Wet AMD and DME

EYP-1901 is designed to provide disease control comparable with current, on-label SoC with fewer injections

Wet AMD



DME

1. Patel S, et al. *Ophthalmol Sci.* 2024;4(5):100527. **2.** Chakravarthy U. "EYP 1901 in nAMD: Updated DAVIO 2 Results." Presented at FLORetina ICOOR 12th International Congress on OCT and OCT Angiography; December 4–7, 2025; Florence, Italy. **3.** Runner M on behalf of Al-khersan H and Ribeiro R. "LUGANO and LUCIA Clinical Trial Update: Pivotal Phase 3 Noninferiority Studies of EYP-1901 vs On-Label Aflibercept in Neovascular Age-Related Macular Degeneration. Presented at FLORetina ICOOR 12th International Congress on OCT and OCT Angiography; December 4–7, 2025; Florence, Italy. **4.** Grewal DS and Ribeiro R. "VERONA Phase 2 Clinical Trial: Visual, Anatomic, and Angiographic Outcomes with Bioerodible EYP-1901 (vorolanib intravitreal insert) Versus Aflibercept for Diabetic Macular Edema." Presented at 49th Macula Society Annual Meeting; February 25–28, 2026; San Diego, CA.
DME, diabetic macular edema; **AMD**, age-related macular degeneration; **q8W**, every 8 weeks; **SoC**, standard of care.
Clinicaltrial.gov identifiers: COMO, NCT07449936; CAPRI, NCT07449923. DAVIO, NCT04747197; DAVIO 2, NCT05381948; LUGANO, NCT06668064; LUCIA, NCT06683742; VERONA, NCT06099184.

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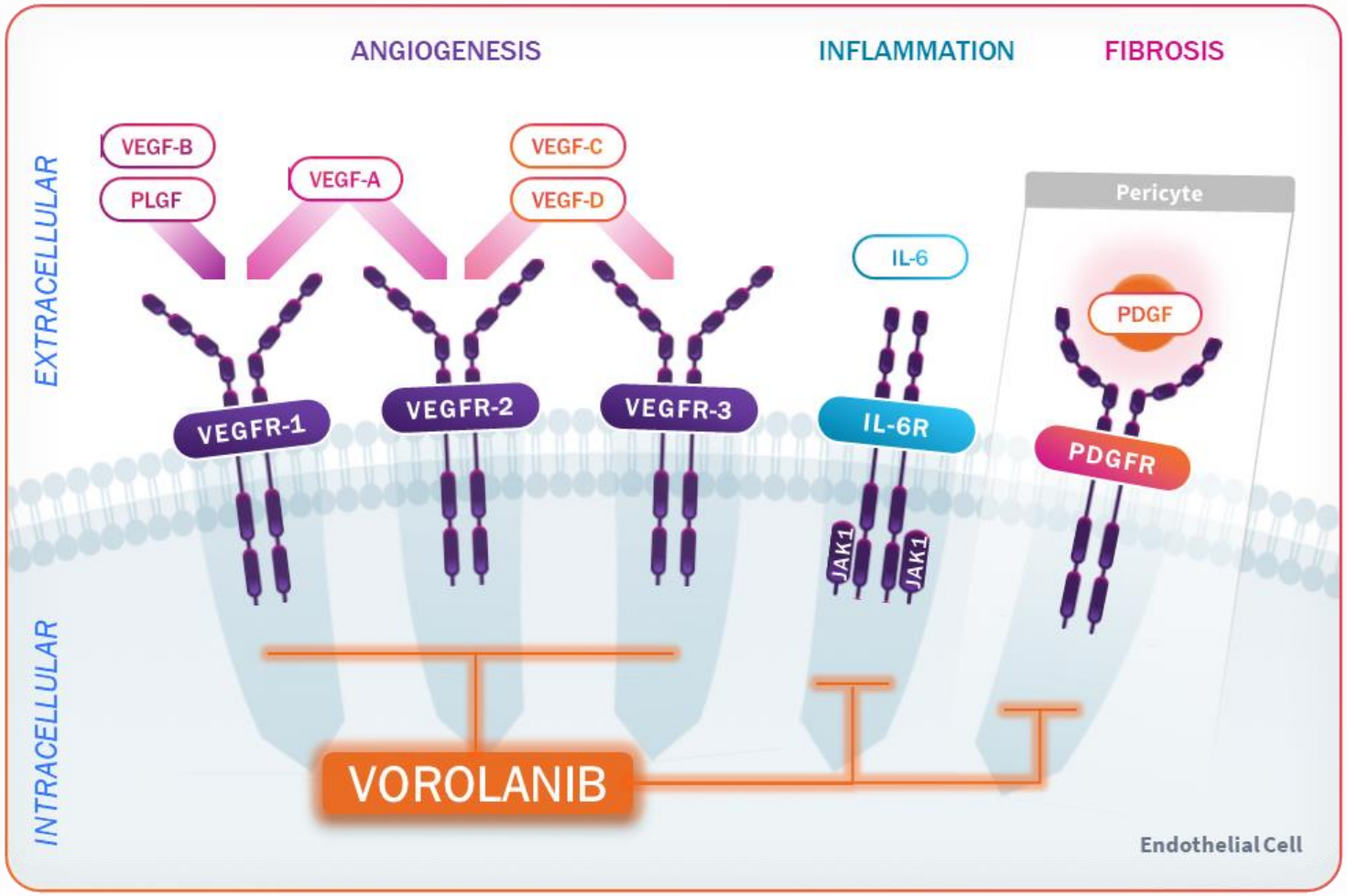
Vorolanib., the Active TKI in EYP-1901, has a Multi-MOA

- **Works intracellularly at the receptor level**
- **Blocks signaling from all VEGF receptors and PDGFR[1]**
- **Inhibits IL-6 signaling by targeting the associated JAK1[2]**



1. Bakri SJ, et al. *PLoS One*. 2024;19(6):e0304782. **2.** Singh R, et al. Presentation at The Associate for Research in Vision and Ophthalmology (ARVO) Annual Meeting: May 3–7, 2026; Denver, CO.

IL-6(R), interleukin-6 (receptor); **JAK1,** Janus kinase 1; **MOA,** mechanism of action; **PDGF(R),** platelet-derived growth factor (receptor); **TKI,** tyrosine kinase inhibitor; **VEGF(R),** vascular endothelial growth factor (receptor).

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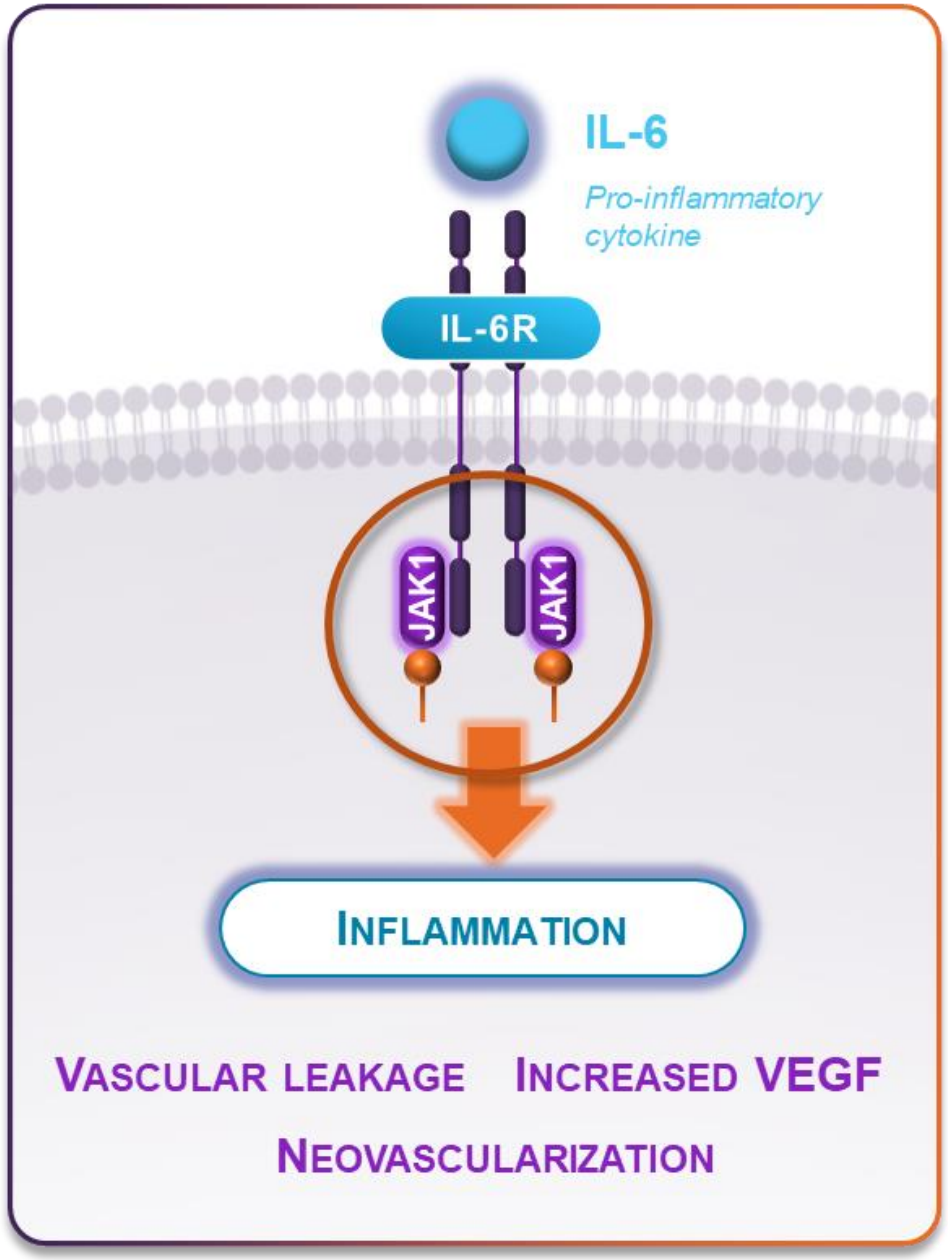
IL-6 is a Pro-inflammatory Cytokine Implicated in Wet AMD and DME

- **Together, IL-6 and VEGF compound damage to the blood-retinal barrier**[1,2]
- **IL-6 sustains inflammation and leads to increased VEGF production**
- **IL-6 implicated in UME, MESI**



JAK1 is a key mediator of IL-6–induced signaling

1. Yang JY, et al. *Int J Mol Sci.* 2023;24(5):4676. **2.** Tanaka T, et al. *Cold Spring Harb Perspect Biol.* 2014;6(10):a016295.
AMD, age-related macular degeneration; **DME,** diabetic macular edema; **IL-6(R),** interleukin-6 (receptor); **JAK1,** Janus kinase 1; **MESI,** macular edema secondary to inflammation; **UME,** uveitic macular edema; **VEGF,** vascular endothelial growth factor.

IL-6–mediated Inflammation May Have a Key Role in Wet AMD and DME

In real-world analyses, patients receiving JAK inhibitors for autoimmune diseases show reduced incidence of AMD[1]

Marketscan

49%
relative reduction

Patients with AMD:
10/9126 receiving JAK inhibitor
43/9126 not receiving JAK inhibitors

61.1% 55 years and older

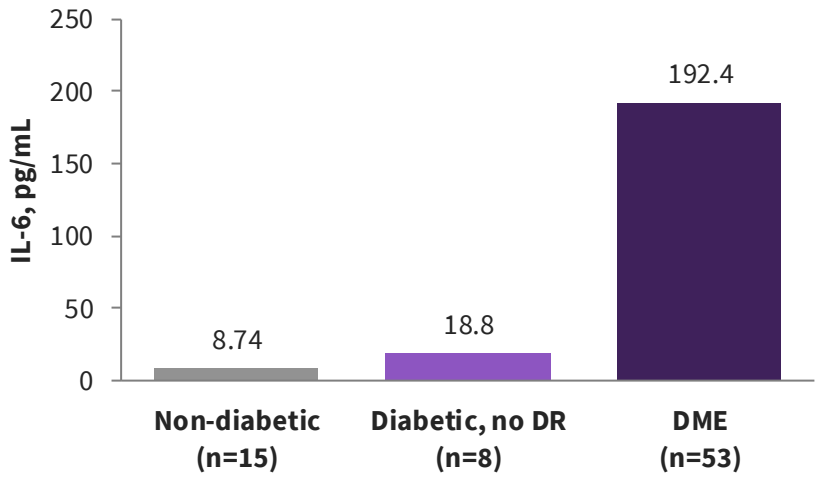
Optum

73%
relative reduction

Patients with AMD:
3/5667 receiving JAK inhibitor
71/5667 not receiving JAK inhibitors

69.2% 55 years and older

Levels of IL-6 are increased in eyes with DME[2–4]



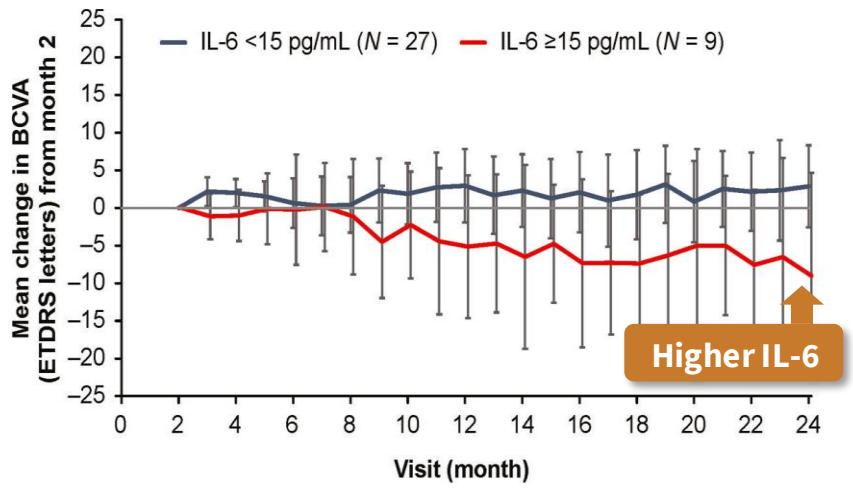
Retrospective case-control study; vitreous fluid samples collected during vitreoretinal surgery[2]

1. Hallak JA, et al. *JAMA Ophthalmol.* 2024;142(8):750-758. **2.** Funatsu H, et al. *Ophthalmology.* 2009;116(1):73-79. **3.** Sepah YJ, et al. *Eye.* 2024;38:1755-1761. **4.** Manda AR, et al. *Ophthalmol Retina* 2026; 10:81-7.
AMD, age-related macular degeneration; **DME**, diabetic macular edema; **DR,** diabetic retinopathy; **IL-6,** interleukin-6; **JAK,** Janus kinase.

Worse Vision Outcomes in Patients With High IL-6 Levels

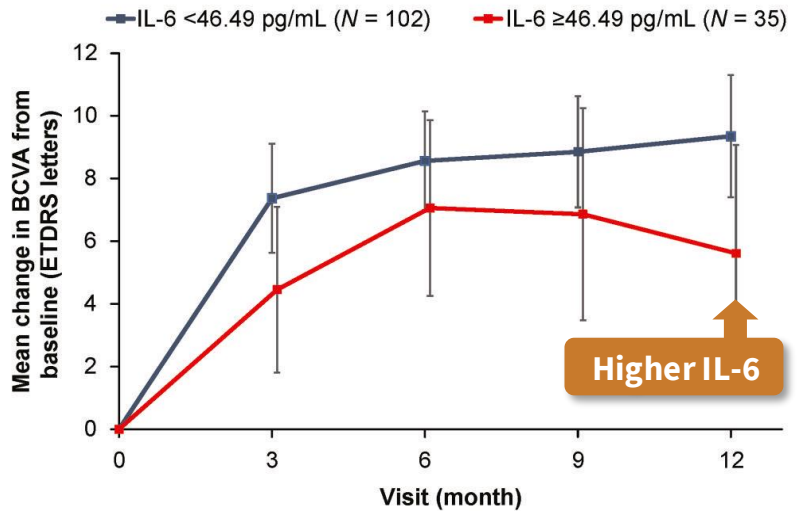
Elevated levels of IL-6 are associated with worse vision outcomes[1]

Wet AMD



Subanalysis of HARBOR trial of ranibizumab monthly or PRN

DME



READ-3 trial of ranibizumab monthly or PRN

Figure adapted from Sepah YJ, et al (2024)[1] by CC-BY 4.0 license: https://creativecommons.org/licenses/by/4.0/.

1. Sepah YJ, et al. *Eye*. 2024;38:1755-1761.

AMD, age-related macular degeneration; **BCVA,** best-corrected visual acuity; **DME**, diabetic macular edema; **ETDRS,** Early Treatment Diabetic Retinopathy Study; **IL-6,** interleukin-6; **PRN,** pro re nata [as needed].

FURTHER CHARACTERIZATION OF MULTI-MOA OF VOROLANIB

Demonstrating inhibition of IL-6 signaling in nonclinical studies

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Independent Third-Party Nonclinical Assays Demonstrate Vorolanib Inhibition of IL-6 Signaling

Initial target characterization

Primary kinase screen

Identifies inhibition targets

IC_{50} analyses

Determine inhibition potency

***In silico* modeling**

Simulate interaction of vorolanib with target kinases

Physiologically relevant cell-based assays to confirm vorolanib activity

Luciferase reporter assay

Impact of vorolanib on IL-6 signaling

TEER assay

Impact of vorolanib on cell junction/barrier integrity

Additional *in vitro* and *in vivo* assays are in progress

IC_{50}, half-maximal inhibitory concentration; **IL-6**, interleukin-6; **TEER,** trans-epithelial/endothelial electrical resistance.

Data on file. Conclusive evidence of efficacy and safety of EYP-1901 will require further investigation in well-controlled phase 3 clinical trials.

Independent Third-Party[a] Nonclinical Assay

Vorolanib Identified as a Potent JAK1 Inhibitor in a Primary Discovery Kinase Screen

- **High-sensitivity, gold-standard[1] radiometric kinase assay[2]**
- **Designed to identify potential targets while minimizing false negatives**
- **Primary screen hits require counter-screens and follow-up assays for validation**

TKI inhibition of proteins of interest in wet AMD and DME

Kinases	Vorolanib	Sunitinib	Axitinib
VEGFR3	99	100	99
VEGFR2	95	98	99
JAK1	95	95	42
PDGFRβ	95	99	99
TYK2	86	95	58
JAK3	85	91	70
JAK2	84	92	67
VEGFR1	78	93	96
TIE2	38	62	85

% Inhibition 100–75% | 74–65% | 64–50% | 49–0%

Higher number = stronger inhibition

Singh R, et al. Presentation at The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting: May 3–7, 2026; Denver, CO.

[a] Non-clinical assays were performed by Reaction Biology Corporation (PA) and funded by EyePoint. **1.** Ma H, et al. *Expert Opin Drug Discov.* 2008;3(6):607–621. **2.** Bakri SJ, et al. *PLoS One.* 2024;19(6):e0304782.

AMD, age-related macular degeneration; **DME,** diabetic macular edema; **IL-6**, interleukin-6; **JAK**, Janus kinase; **PDGFR**, platelet-derived growth factor receptor; **TIE2**, tyrosine kinase with immunoglobulin-like and EGF-like domains; **TKI**, tyrosine kinase inhibitor; **TYK2**, tyrosine kinase 2; **VEGFR**, vascular endothelial growth factor receptor.

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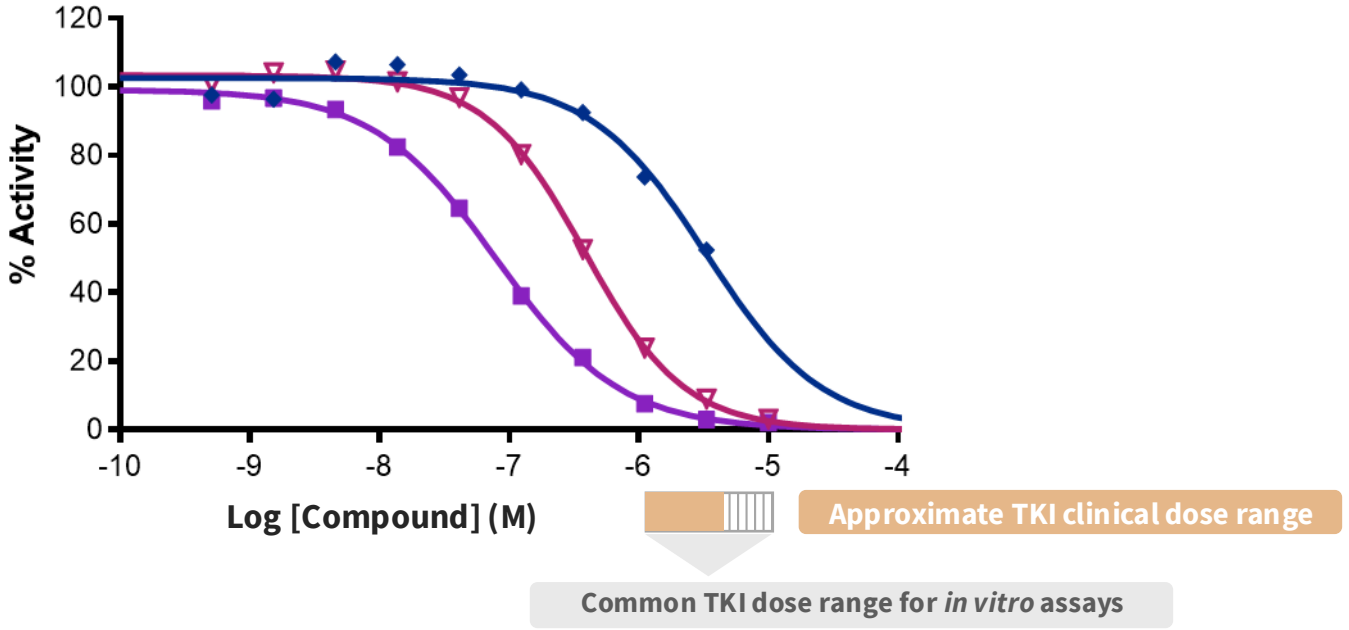
Independent Third-Party[a] Nonclinical Assay

Vorolanib Confirmed as a JAK1 inhibitor in Follow-up IC_{50} Analyses

- **Showed lower IC_{50} for JAK1 vs other TKIs, indicating stronger inhibition**

Compound IC_{50} data for JAK1

IC_{50} is a measure of a drug's ability to inhibit receptor activity by half



	Vorolanib	Sunitinib	Axitinib
IC_{50}	80 nM	386 nM	3310 nM

Lower IC_{50} number = higher potency

Singh R, et al. Presentation at The Associate for Research in Vision and Ophthalmology (ARVO) Annual Meeting: May 3–7, 2026; Denver, CO. Bakri SJ, et al. *PLoS One*. 2024;19(6):e0304782.

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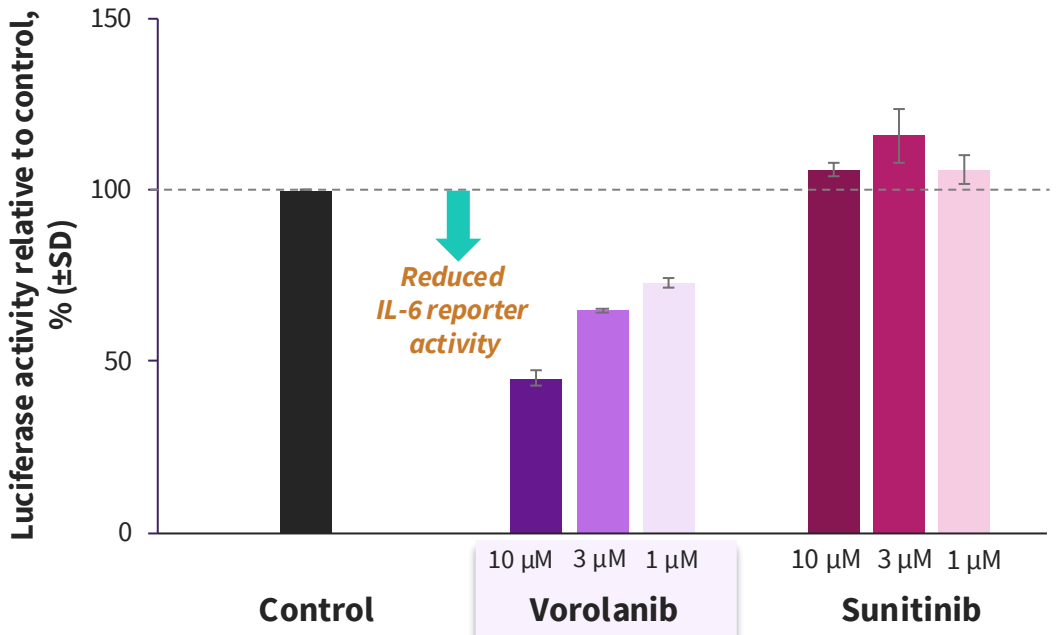
Vorolanib Binds JAK1 and Inhibits IL-6 Activity at Clinically Relevant Doses *In Vitro*

- **IL-6 reporter activity inhibited in a dose-dependent manner**

Independent Third-Party[c] Nonclinical Assay

Luciferase assay in HEK293 cells with stable expression of an IL-6-responsive STAT3 reporter[a]



*Clinically relevant doses[b] of vorolanib are in the range of **~1–10 µM** and are maintained in target ocular tissues for ~6 months following a single injection of EYP-1901*

Singh R, et al. Presentation at The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting: May 3–7, 2026; Denver, CO.

[a] IL-6 reporter activity shows >50% inhibition in the presence of vorolanib. Sunitinib did not show in-cell inhibition, which, although unexpected based on the kinase screen, was anticipated due to the lower IC_{50} of sunitinib for JAK1. Data shown are representative of three independent experiments. [b] Tested concentrations include those equivalent to the clinical dose; however, *in vitro* studies are not, by definition, directly translatable to clinical effects. [c] Non-clinical assays were performed by Reaction Biology Corporation (Germany) and funded by EyePoint. **IL-6**, interleukin 6; **JAK1**, Janus kinase 1; **STAT**, signal transducer and activator of transcription.

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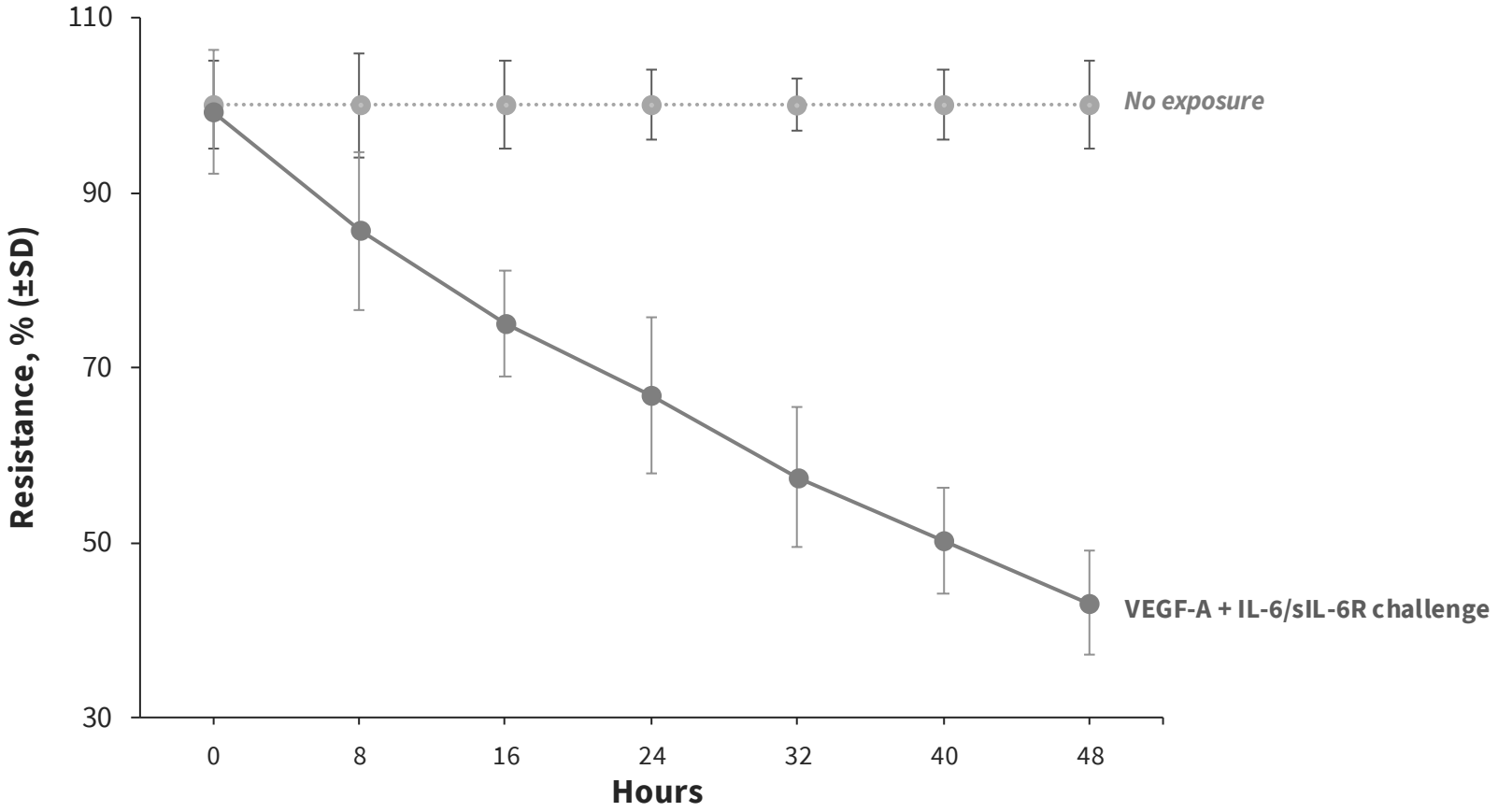
Vorolanib Maintains Cell Junction/Barrier Integrity *In Vitro*, With the Potential to Reduce Vascular Leakage

Combination of VEGF-A and IL-6/sIL-6R induced disruption of barrier integrity

Independent Third-Party[b] Nonclinical Assay

Cell-based TEER assay in HUVECs[a]



Higher resistance = Intact retinal barriers

Singh R, et al. Presentation at The Associate for Research in Vision and Ophthalmology (ARVO) Annual Meeting: May 3–7, 2026; Denver, CO.

[a] Immortalized HUVECs were pretreated with vorolanib, anti-IL-6 (siltuximab), anti-VEGF (aflibercept), or anti-VEGF + anti-IL-6 prior to stimuli challenge with hyper-VEGF-A + IL-6/sIL-6R. Integrity and maintenance of the cell junctions/barrier were monitored over time. [b] Non-clinical assays were performed by Creative Bioarray (NY) and funded by EyePoint.

IL-6, interleukin 6; **sIL-6R**, soluble IL-6 receptor; **TEER,** trans-epithelial/endothelial electrical resistance; **VEGF**, vascular endothelial growth factor.

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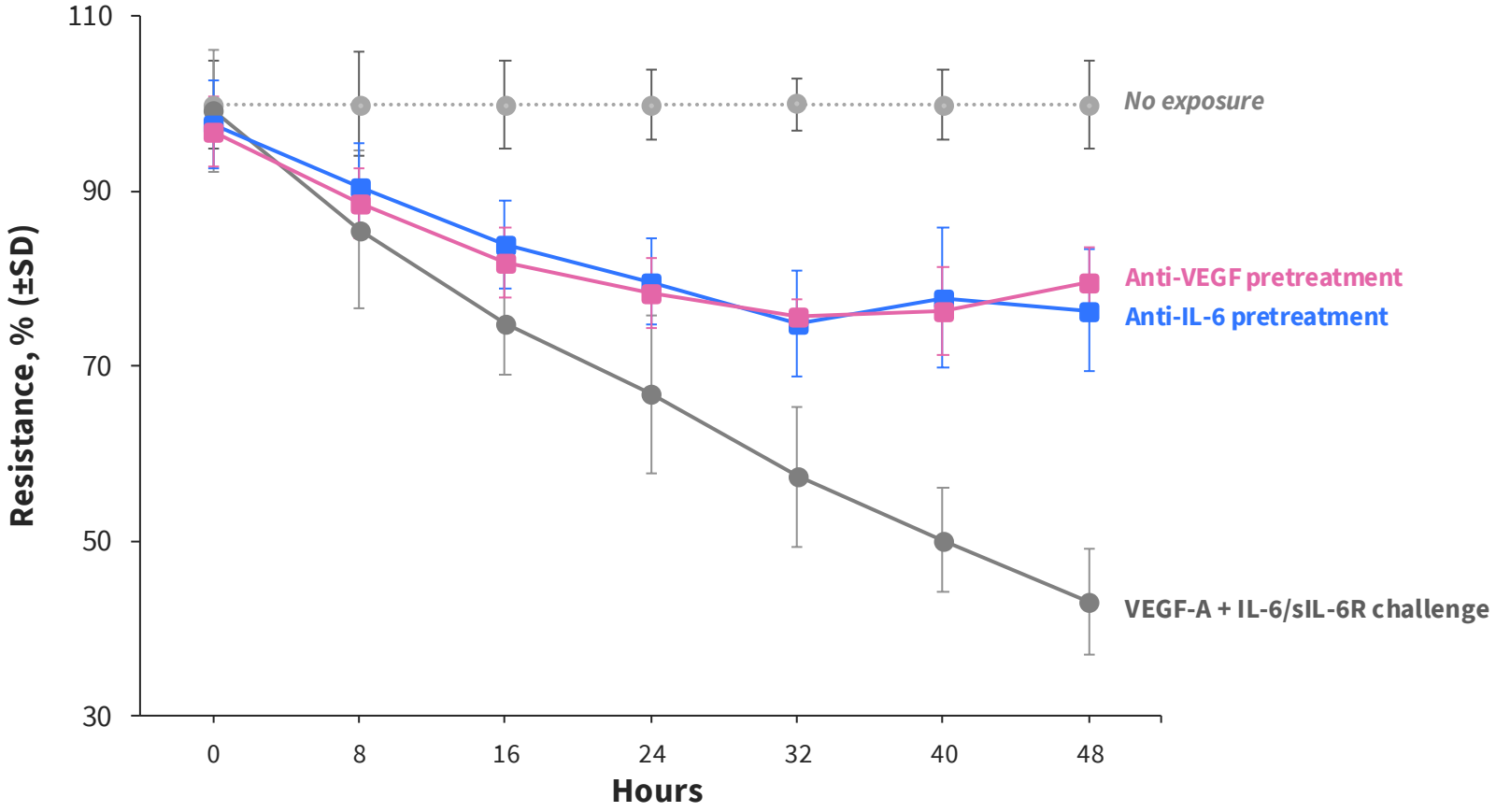
Vorolanib Maintains Cell Junction/Barrier Integrity *In Vitro*, With the Potential to Reduce Vascular Leakage

Anti-VEGF or anti-IL-6 alone only partially maintained barrier integrity

Independent Third-Party[b] Nonclinical Assay

Cell-based TEER assay in HUVECs[a]



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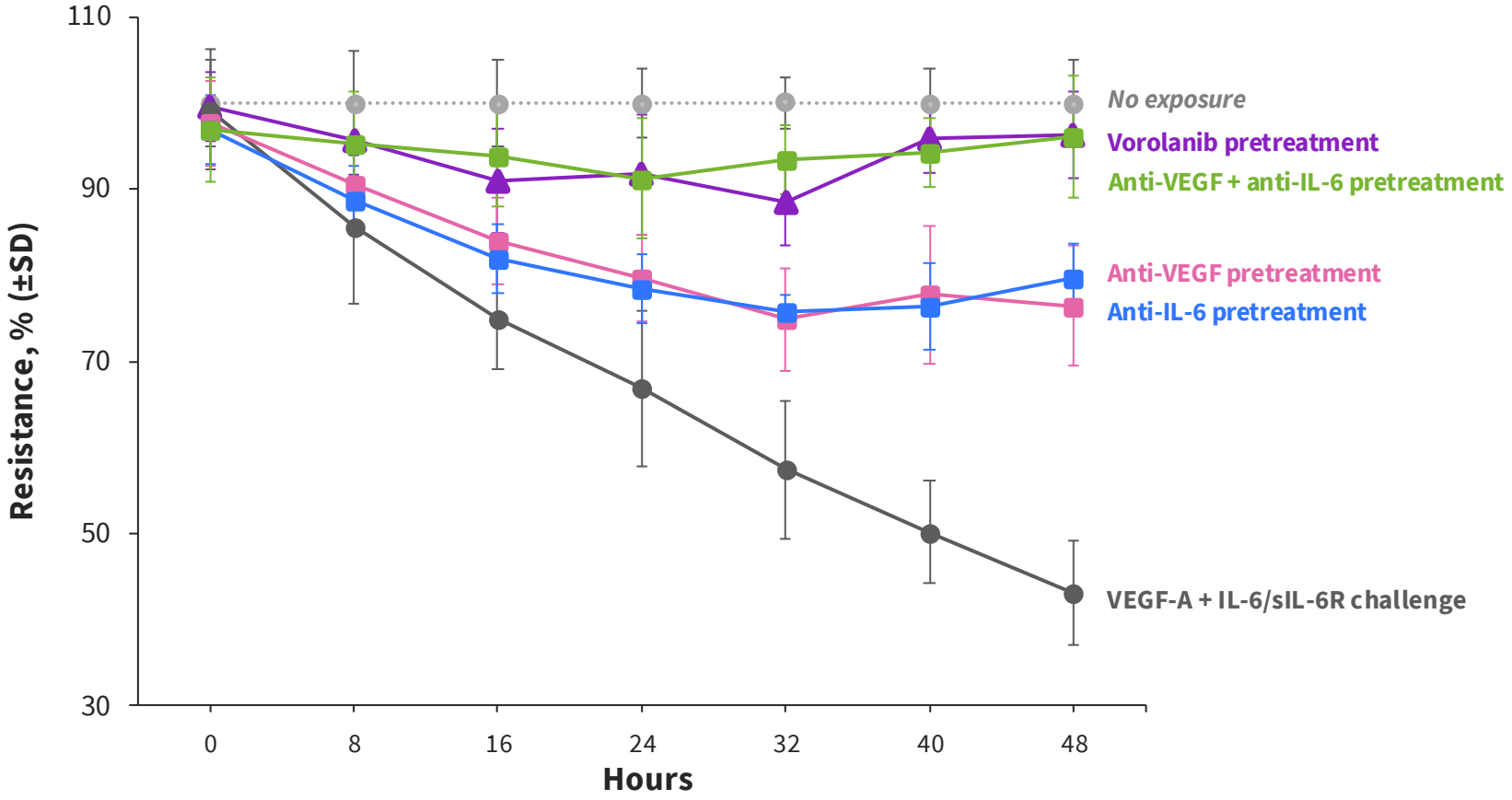
Vorolanib Maintains Cell Junction/Barrier Integrity *In Vitro*, With Potential to Reduce Vascular Leakage

Vorolanib maintained barrier integrity to a similar extent as the combination of anti-VEGF and anti-IL-6

Independent Third-Party[b] Nonclinical Assay

Cell-based TEER assay in HUVECs[a]



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Vorolanib Provides a Multi-MOA for the Potential Treatment of Retinal Diseases

Inhibits all VEGFRs and PDGFR[1] ● Blocks inflammatory IL-6 signaling[2]

Primary kinase screen

Vorolanib identified as a potential inhibitor of JAK1, a key mediator of IL-6 signaling

IC_{50} analyses

Confirmed as a potent JAK1 inhibitor

In silico modeling

Stable interaction of vorolanib with JAK1 in the ATP binding region

Luciferase reporter assay

Inhibits IL-6 activity at clinically relevant doses *in vitro*

TEER assay

Maintains vascular barriers which may reduce vascular leakage

***Wet AMD*: Phase 3 LUGANO topline data expected in mid-2026; LUCIA to follow**
***DME*: COMO and CAPRI: First patients dosed Q1 2026; topline data anticipated 2H 2027**

1. Bakri SJ, et al. *PLoS One.* 2024;19(6):e0304782. **2.** Singh R, et al. Presentation at The Associate for Research in Vision and Ophthalmology (ARVO) Annual Meeting: May 3–7, 2026; Denver, CO.
ATP, adenosinetriphosphate; **IL-6**, interleukin 6; JAk1, Janus kinase 1; **MOA**, mechanism of action; **TKI,** tyrosine kinase inhibitor. Clinicaltrial.gov identifiers: COMO, NCT07449936; CAPRI, NCT07449923; LUGANO, NCT06668064; LUCIA, NCT06683742.

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