PHARMACODYNAMIC EFFICACY OF OPTIMIZED INTRAVITREAL AXITINIB IMPLANT (OTX-TKI) IN A VEGF CHALLENGE RABBIT MODEL

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Ocular Therapeutix

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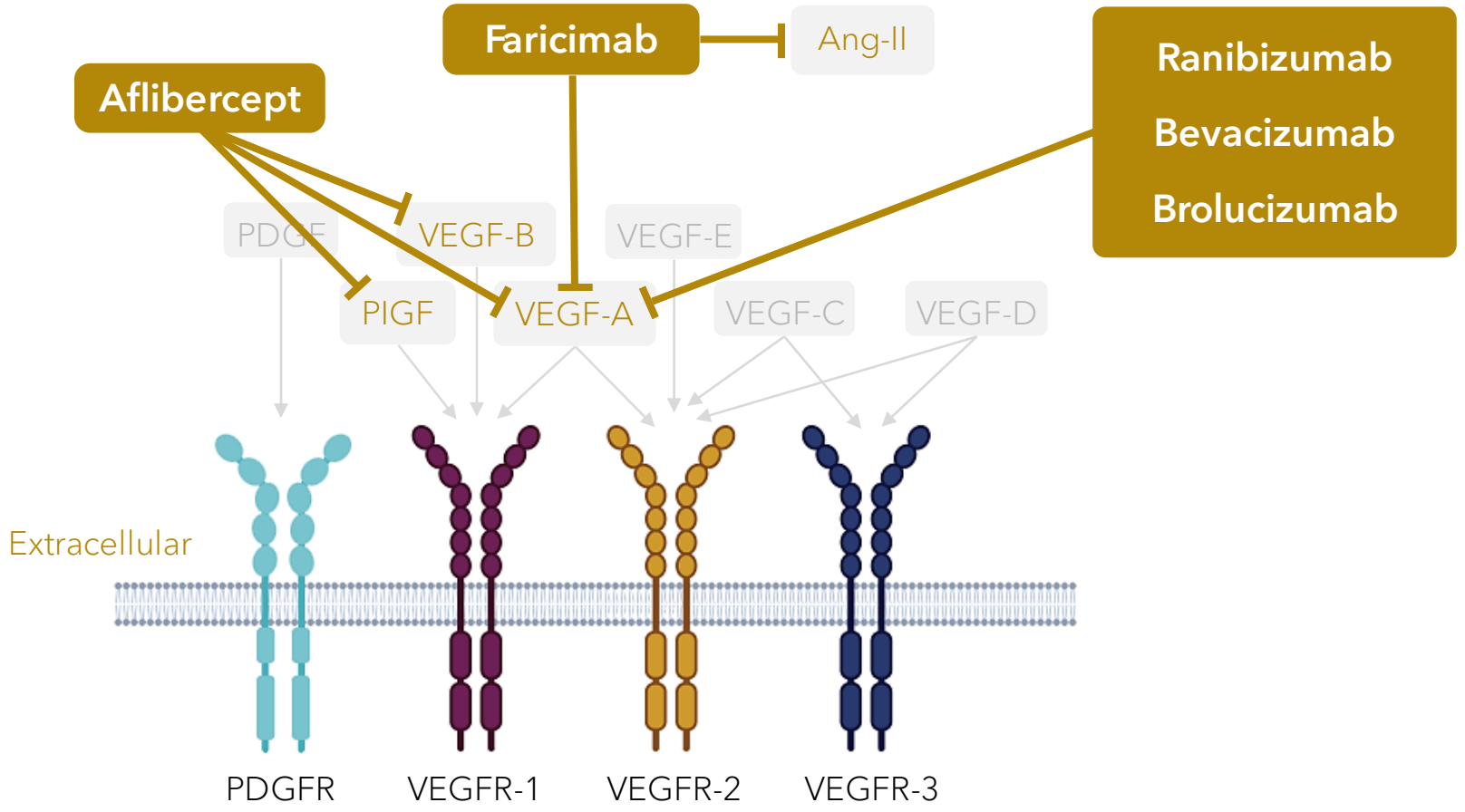
The following presentation discusses an investigational drug, OTX-TKI, in development. OTX-TKI's efficacy and safety profiles have not been established, and it has not been approved for marketing by the FDA.

CURRENT ANTI-VEGF THERAPIES SELECTIVELY TARGET ONLY EXTRACELLULAR VEGF RECEPTORS

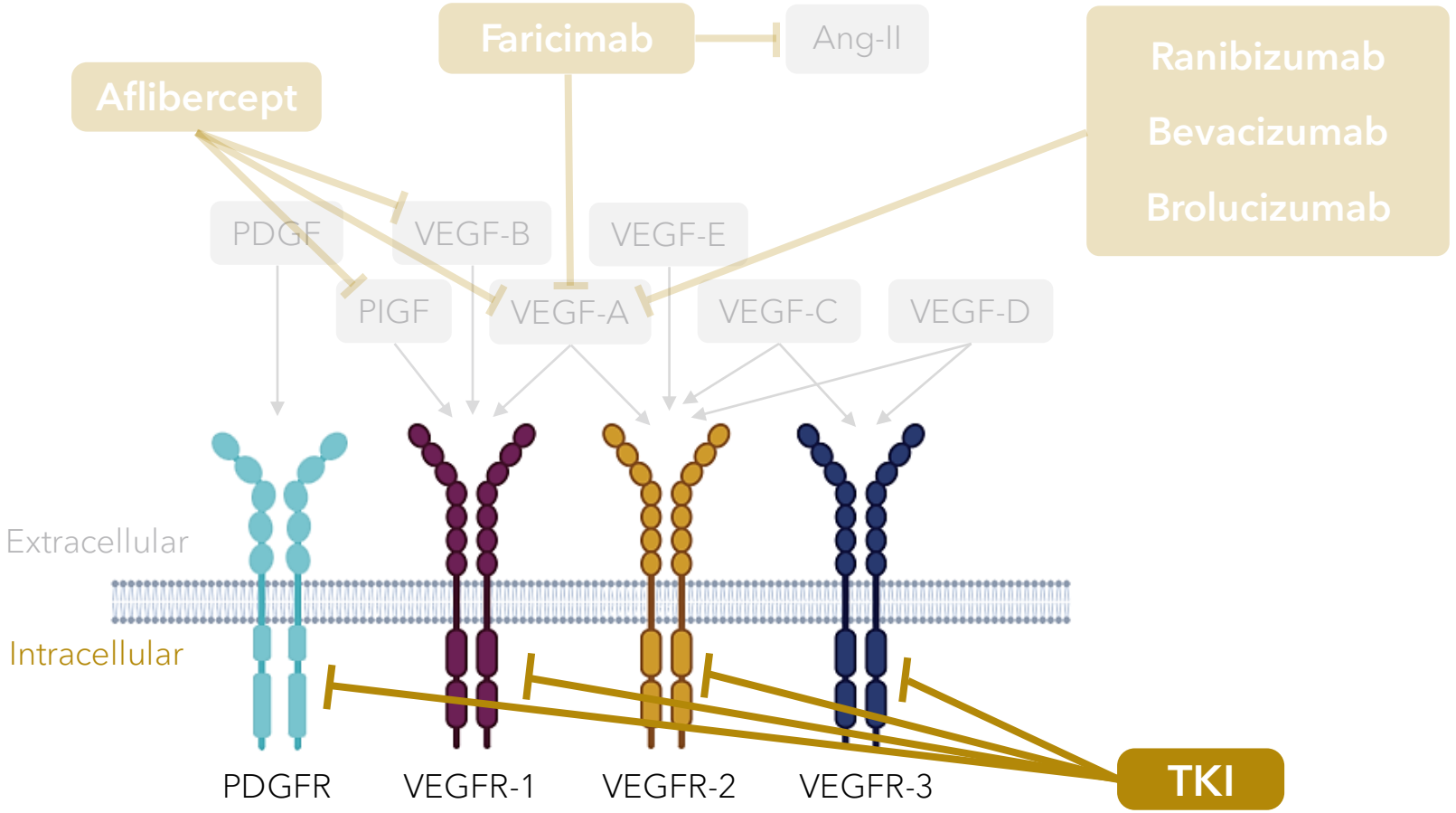
Anti-VEGFs act on the extracellular side by binding selective ligands, like VEGF-A, to prevent receptor binding and pro-angiogenic activity



Ang-II (Angiotensin-II); nAMD (Neovascular age-related macular degeneration); PDGF(R) (Platelet-derived growth factor [receptor]); PIGF (Placenta growth factor); VEGF(R) (Vascular endothelial growth factor [receptor]).
Created with BioRender.
Tan CS, et al. *Clin Ophthalmol.* 2022;16:917-933. doi:10.2147/OPTH.S231913.

AXITINIB ACTS INTRACELLULARLY TO INHIBIT VEGF RECEPTORS

TKIs bind the intracellular tyrosine kinase domains of VEGF receptors, inhibiting ATP binding and preventing activation of pro-angiogenic signaling



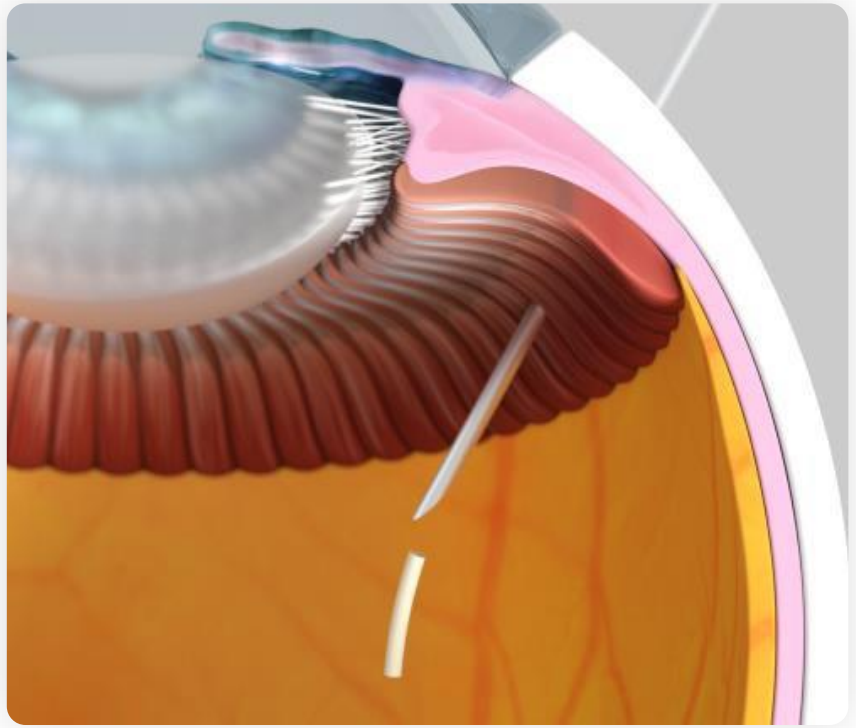
Ang-II (Angiotensin-II); ATP (Adenosine triphosphate); nAMD (Neovascular age-related macular degeneration); PDGF(R) (Platelet-derived growth factor [receptor]); PIGF (Placenta growth factor); TKI (Tyrosine kinase inhibitor); VEGF(R) (Vascular endothelial growth factor [receptor]); ATP (Adenosine triphosphate); TKI (Tyrosine kinase inhibitor).
Created with BioRender.

Tan CS, et al. *Clin Ophthalmol*. 2022;16:917-933. doi:10.2147/OPTH.S231913.

OTX-TKI (AXITINIB INTRAVITREAL IMPLANT): SUSTAINED RELEASE OF A POTENT TKI FOR RETINAL VASCULAR DISEASES

OTX-TKI HYDROGEL IMPLANT

- Delivers axitinib, a TKI
- IVT administration with single-use applicator (25G needle)
- Steady-state axitinib release until implant bioresorption
- Hydrogel implant bioresorbs at 8 to 9 months
- Optimized in same hydrogel but with a more soluble form of axitinib, delivering the targeted daily release rate in a 0.45-mg dose
- Terminal drug release at bioresorption creates a flexible redosing period



OTX-TKI PROGRAM STATUS

- Phase 3: Neovascular age-related macular degeneration[1]
- Phase 1: Non-proliferative diabetic retinopathy[2]

TKI (Tyrosine kinase inhibitor); IVT (Intravitreal).
Imagine shown is for illustrative purposes only.
1. NCT06223958. **2.** NCT05695417.

AXITINIB IS A POTENT PAN-VEGFR INHIBITOR, HIGHLY SELECTIVE, WITH NO TIE2 ACTIVITY AT PHYSIOLOGIC OCULAR TISSUE CONCENTRATIONS

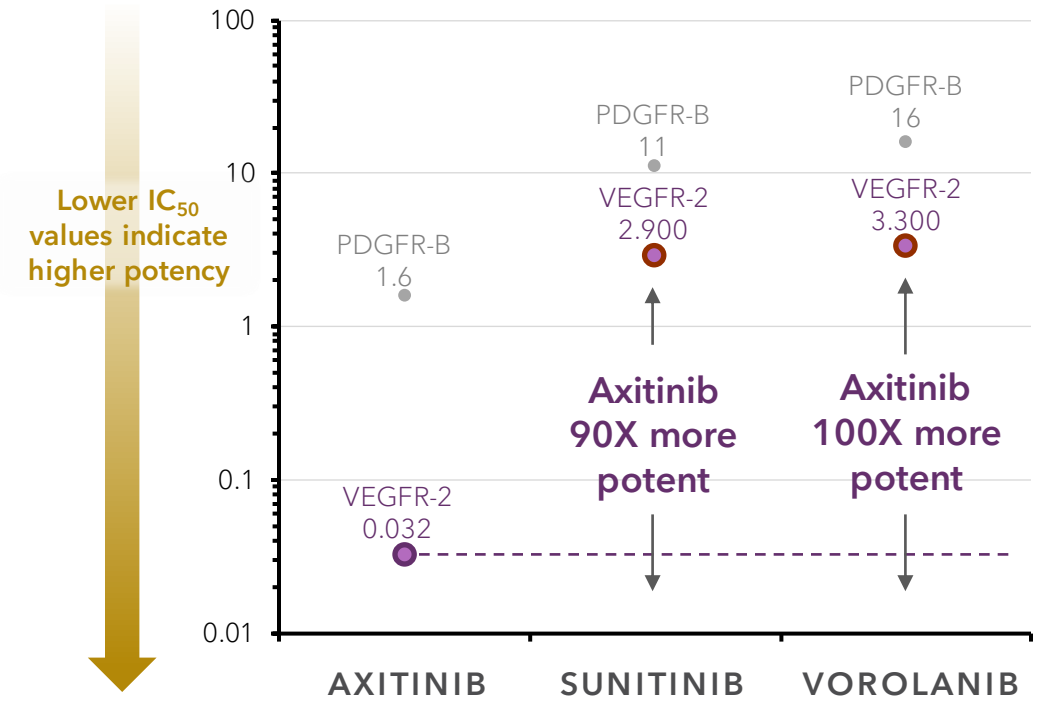
Axitinib has **high selectivity for VEGFR and PDGFR**[1,2]

Axitinib was **~100X more potent** for VEGFR-2 compared to sunitinib and vorolanib[3]

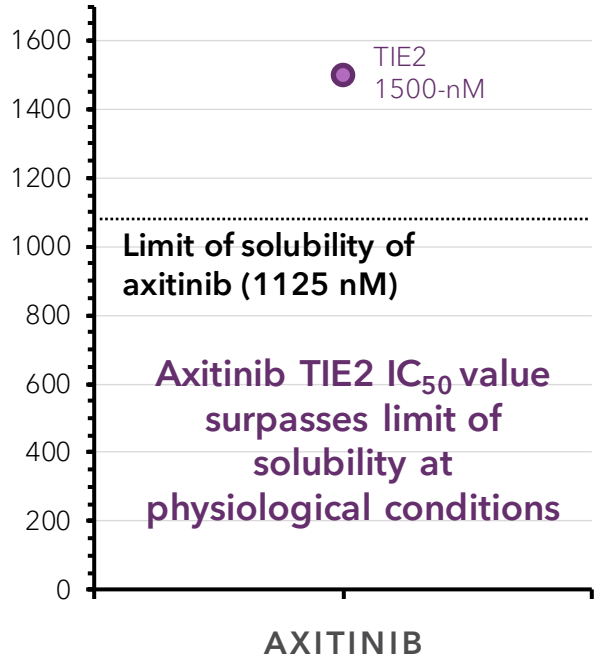
IC_{50} values for axitinib and sunitinib are **consistent with literature**[1,2]

No TIE2 inhibition at physiological tissue concentrations* via the gold standard cell phosphorylation assay

IC_{50} Values with Cell Phosphorylation[3] (nM)



IC_{50} Values of Axitinib on TIE2 Receptors[3] (nM)

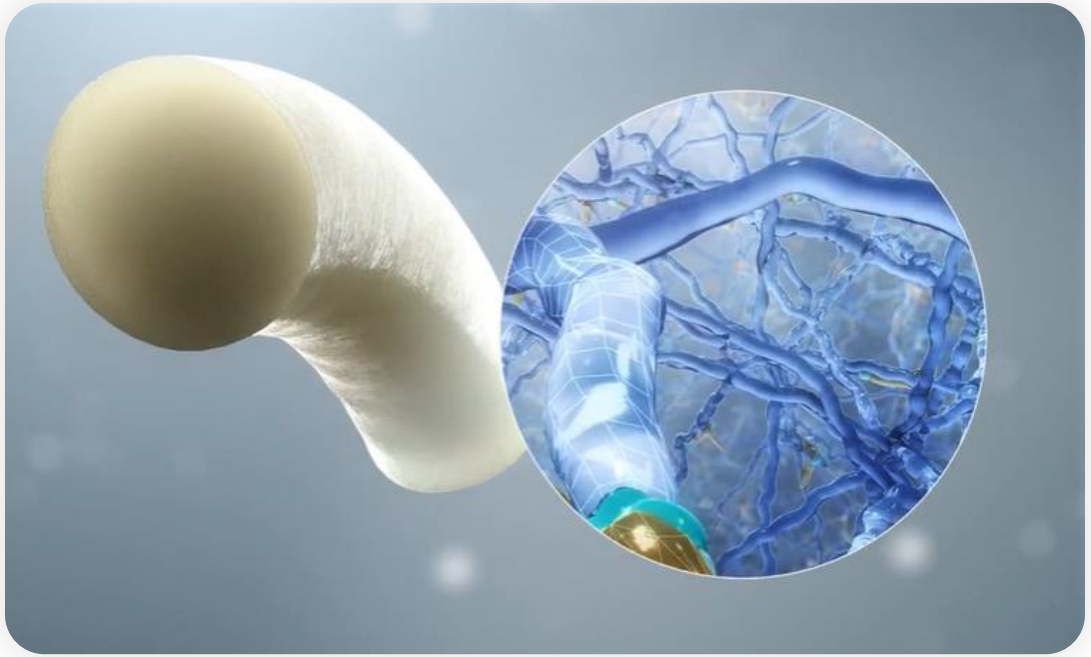


Limit of solubility is 1 µM for axitinib in physiological conditions; therefore, testing conducted at concentrations exceeding the drug's saturation concentration (eg, 10 µM by adding in co-solvents like DMSO) to evaluate for TIE2 inhibition is not reflective of expected effects in humans, as there are no organic solvents in the eye.

*Following extensive protein and melanin binding in ocular tissues.
CHO (Chinese hamster ovary); HUVEC (Human umbilical vein endothelial cells); MET (Mesenchymal-epithelial transition); PDGFR (Platelet-derived growth factor receptor); IC_{50} (Half-maximal inhibitory concentration); TIE2 (Tyrosine kinase with immunoglobulin-like and EGF-like domains-2); VEGFR (Vascular endothelial growth factor receptor); DMSO (Dimethylsulfoxide).

1. Hu-Lowe DD, et al. *Clin Cancer Res*. 2008;14(22):7272-7283. **2.** McTigue M, et al. *Proc Natl Acad Sci U S A*. 2012;109(45):18281-18289. **3.** Unpublished data; Data on File. In vitro cell-based assays used to characterize IC50 values of axitinib for receptors VEGFR-2 (using HUVECs), PDGFR-Beta (in murine fibroblast cells), and a non-target receptor TIE2 (utilizing CHO cells).

AXITINIB RELEASED FROM HYDROGEL BY SLOW DIFFUSION



1. HYDROGEL MESHWORK

Cross-linked multi-arm PEG hydrogel network with hydrolyzable ester linkages[1]

2. DRUG SLOWLY DIFFUSES OUT OF HYDROGEL

Micronized axitinib entrapped in hydrogel steadily dissolves into vitreous, then diffuses into ocular tissues[1,2]

3. DRUG RELEASE AND IMPLANT BIORESORPTION

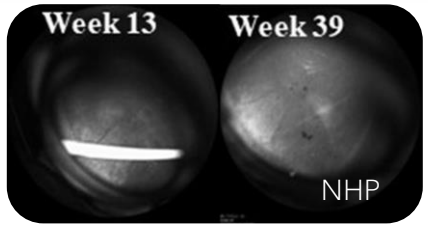
Hydrogel degrades via hydrolysis (like dissolvable sutures), implant bioresorbs, and remaining axitinib is released for continued delivery[1,3]

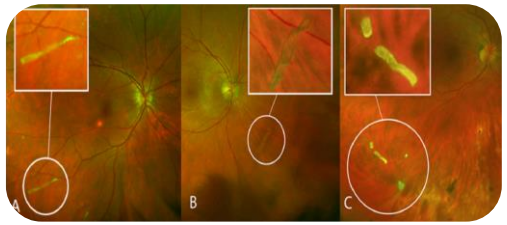
Drug release is regulated by drug solubility, implant shape, and clearance mechanisms[4]

PEG (Polyethylene glycol); VEGF (Vascular endothelial growth factor).
Image shown is for illustrative purposes only.
1. Li J, et al. *Nat Rev Mater.* 2016;1(12):16071. **2.** Jarret PK, et al. Efficacy and tolerability of OTX-TKI, a sustained hydrogel delivery system for a tyrosine kinase inhibitor, in a VEGF-induced retinal leakage model through 12 months. Presented at the Association for Research in Vision and Ophthalmology. May 2019, Honolulu, Hawaii. **3.** Müller DA, et al. *J Orthop Surg Res.* 2016;11(1):111. **4.** Nafo W. Hydrogel biomaterials for drug delivery: mechanisms, design, and drugs. *Hydrogels - From Tradition to Innovative Platforms with Multiple Applications*. Published online March 1, 2023. https://www.intechopen.com/chapters/80823.

HYDROGEL:
A DIFFERENTIATED PLATFORM FOR RETINAL DRUG DELIVERY

		Hydrogel	PLA/PLGA	PVA
Key Platform Characteristics	Rigidity	Soft	Rigid	Rigid
	Mechanism of release	Diffusion	Degradation	Bioerosion
	Biodegradation	Bioresorbs completely and synchronized with drug release	Biodegrades completely long after drug release	Bioerodes completely long after drug release
	Byproducts upon biodegradation	PEG polymer chains	Local acidic milieu (lactic and glycolic acid)	PVA polymer chains
Examples	Investigational retinal candidates	Axitinib intravitreal implant (OTX-TKI, Ocular Therapeutix)	No investigational candidates currently	Vorolanib intravitreal implant (EYP-1901, EyePoint Pharmaceuticals)
Key Attributes of Retinal Product	Formulated as a single implant per dose	✓	N/A	✗
	Redosing interval	6-12 months[1]	N/A	6 months[3]
	Vehicle persistence	8-9 months[1]	Months to years[2]	18 to 24 months[4]





Images for illustration purposes only.
PEG (Polyethylene glycol); PLA/PLGA (Polylactide/Polylactide-co-glycolic acid); PVA (Polyvinyl alcohol); NA (Not applicable).

1. Khanani A. et al. 12-month update on randomized, controlled, trial of OTX-TKI (axitinib intravitreal implant) for the treatment of wet AMD. Presented at Clinical Trials at the Summit. June 10, 2023. Park City, UT.
2. Han, et al. *Retina*. 2020;40(11):2221-2225. **3.** Wykoff C. The DAVIO 2 Trial: Topline data from a phase 2, multicenter study of a single injection of EYP-1901 (Vorolanib in the Durasert E Technology) vs. aflibercept for previously treated wet age-related macular degeneration. Presented at the Angiogenesis, Exudation and Degeneration Meeting. February 3, 2024. Virtual. **4.** EyePoint Pharmaceuticals. TD Cowen 44th Annual Health Care Conference. March 5, 2024. https://investors.eyepointpharma.com/events-and-presentations.

AXPAXLI WAS OPTIMIZED TO SYNCHRONIZE AXITINIB DELIVERY WITH IMPLANT RESORPTION

DRUG SOLUBILITY

Modified to use a more soluble axitinib form

DAILY RELEASE RATE

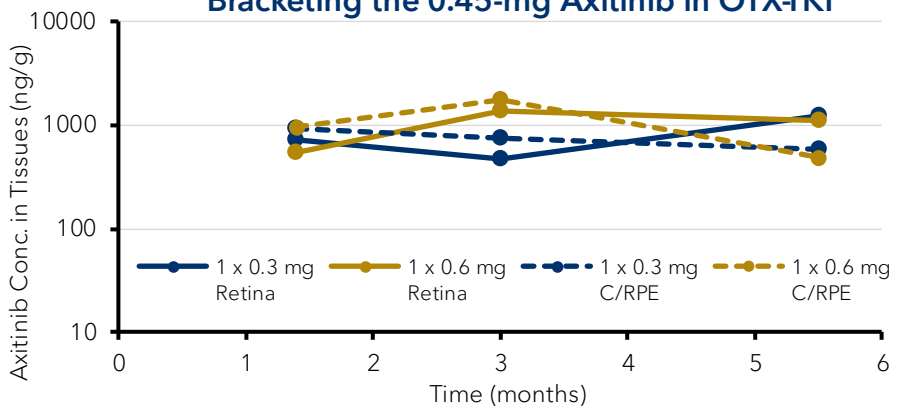
Provides greater daily release rate of axitinib than implants in the US trial and comparable release rate to 3 implants used in the AUS trial

STEADY STATE RELEASE

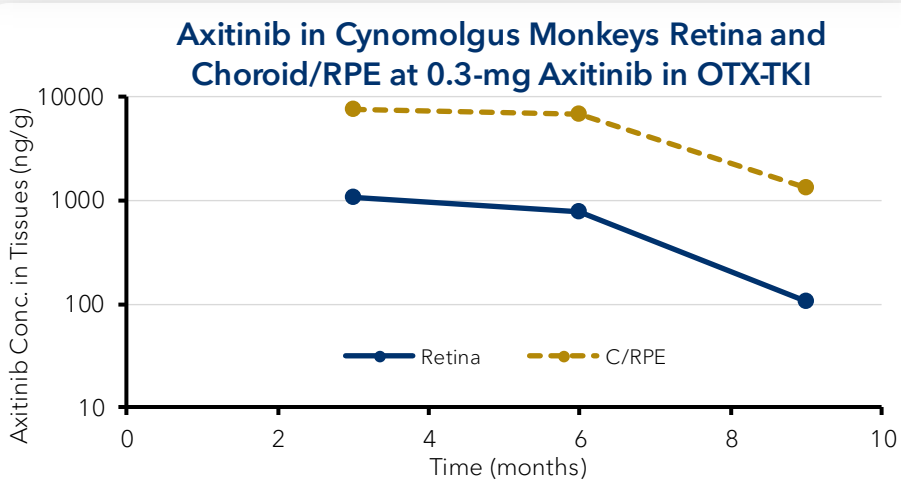
Better maintains steady-state concentrations after hydrogel bioresorption

DRUG RELEASE

Designed to improve synchronization of axitinib drug depletion with hydrogel bioresorption



Steady axitinib tissue concentrations in DB rabbits through 5.5 months bracketing 0.45-mg dose



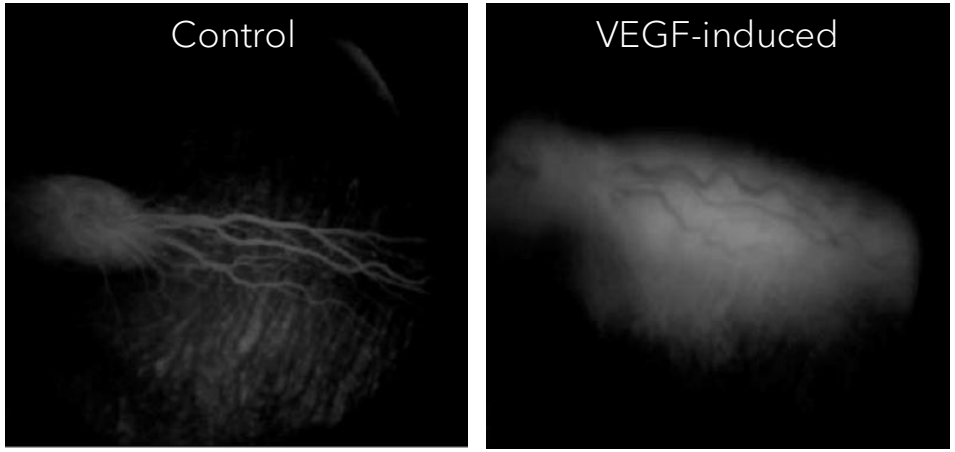
Steady axitinib tissue concentrations in NHP through 6 months prior to depletion. Dose well synchronized to NHPs

DB (Dutch-Belted); NHP (Non-human primate); RPE (Retinal pigment epithelium).

NONCLINICAL STUDY EVALUATING OTX-TKI EFFICACY IN THE VEGF CHALLENGE MODEL OF nAMD

VEGF CHALLENGE MODEL IN RABBITS[1,2]

- VEGF injection creates transient retinal vascular leakage
- Leakage peaks 2-3 days post VEGF injection
- Very useful to quickly assess anti-VEGF efficacy



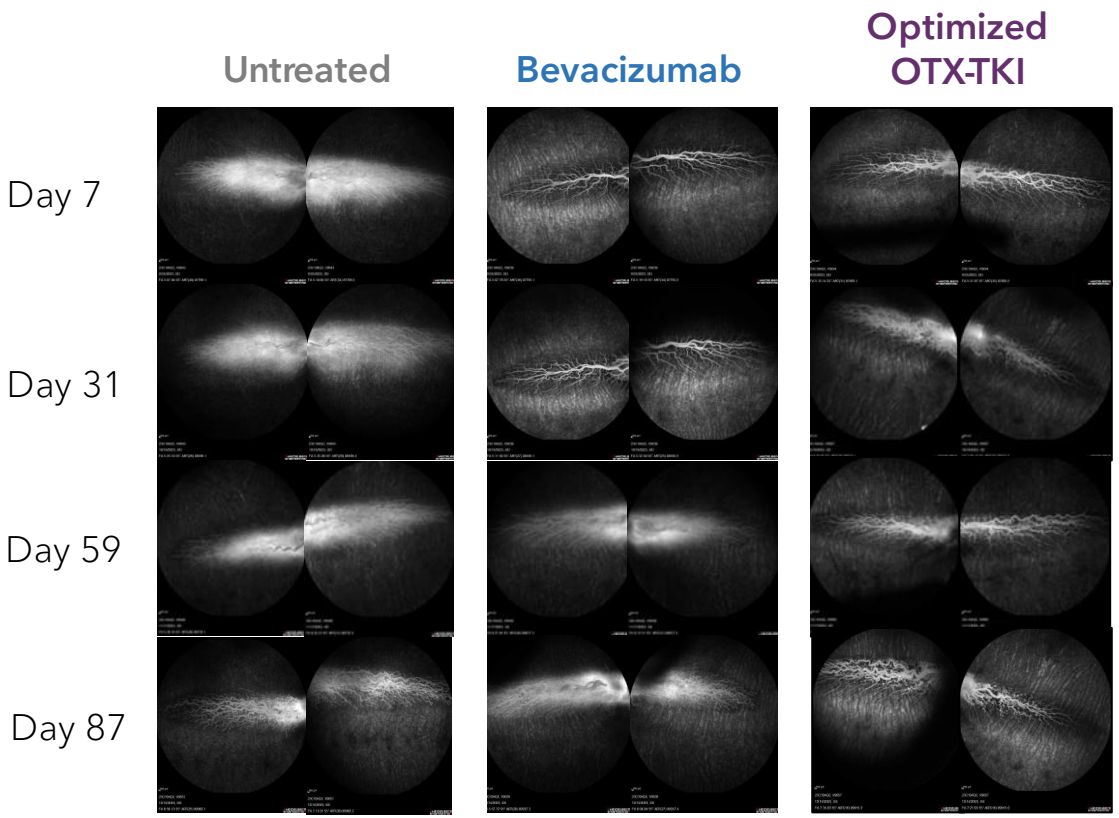
OTX-TKI STUDY DESIGN

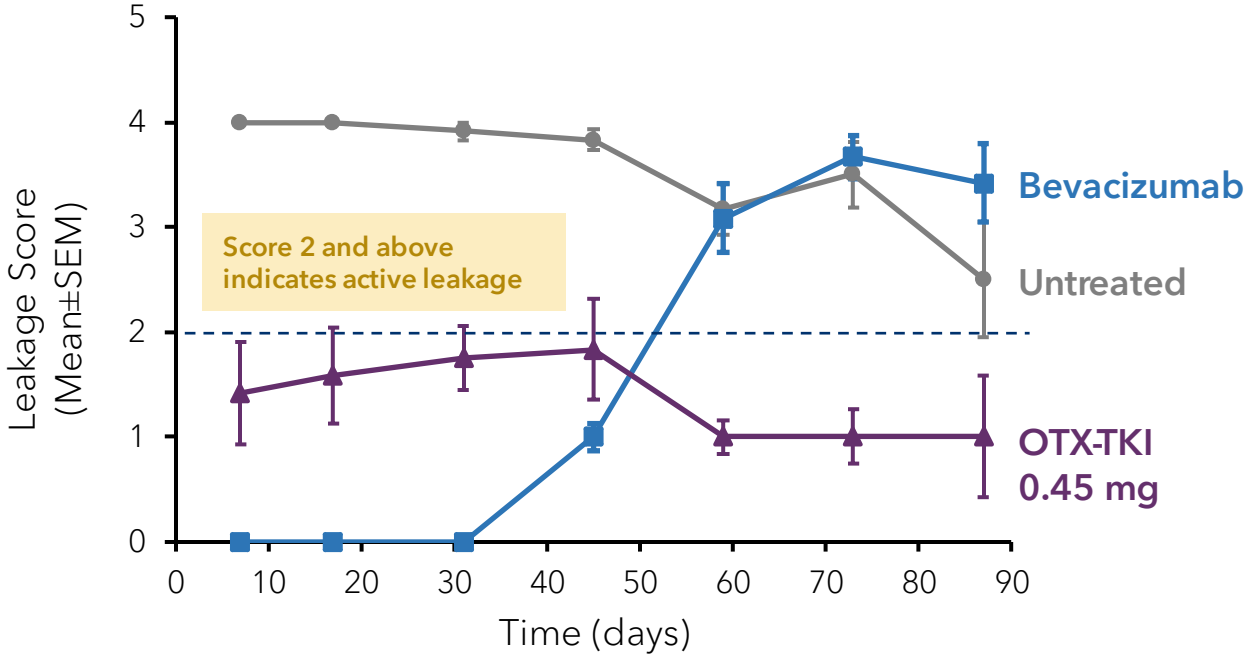
- Day 0: Dutch-Belted rabbits administered bilateral IVT injections of 0.45-mg optimized OTX-TKI, bevacizumab, or nothing (untreated control)
- 1-µg VEGF IVT given to induce retinal blood vessel leakage
- Three days post VEGF challenge, fluorescein injected and severity scoring performed after 5-6 min using fluorescein angiography (below)
- N=6 eyes/timepoint over 87 days

Score	Scoring Descriptor
0	Major vessels straight, some tortuosity of smaller vessels, no vessel dilation
1	Increased tortuosity of major vessels and/or some vessel dilation
2	Leakage between major vessels, significant vessel dilation
3	Leakage between major and minor vessels, minor vessels still visible
4	Leakage between major and minor vessels, minor vessels poorly/not visible

IVT (Intravitreal); nAMD (Neovascular age-related macular degeneration); VEGF (Vascular endothelial growth factor).
Unpublished data on file.
1. Edelman JL, et al. *Exp Eye Res*. 2005;80(2):249-258. **2.** Giddabasappa A, et al. *Exp Eye Res*. 2016;145:373-379.

SUBSTANTIAL REDUCTION IN VASCULAR LEAKAGE WITH OPTIMIZED 0.45-MG OTX-TKI IN VEGF-CHALLENGED RABBITS





OTX-TKI maintained low leakage scores throughout the study period

- Bevacizumab had a marked reduction in efficacy after day 31
- At day 73, bevacizumab had similar scores to untreated control

VEGF (Vascular endothelial growth factor).
Unpublished data on file.

CONCLUSIONS

Current anti-VEGFs only target extracellular VEGFR ligands vs TKIs that act intracellularly by binding pan-VEGF receptors to inhibit neovascularization

OTX-TKI (axitinib hydrogel implant) is a sustained-release potent TKI currently in a Phase 3 trial for nAMD

Optimized 0.45-mg implant designed to improve synchronization of axitinib drug depletion with hydrogel bioresorption

In the nonclinical study, 0.45-mg optimized OTX-TKI implant reduced vascular leakage following repeat VEGF challenges, demonstrating sustained activity and surpassed duration over bevacizumab

OTX-TKI has potential to continuously control retinal vascular diseases with a sustained-release TKI

nAMD (Neovascular age-related macular degeneration); TKI (Tyrosine kinase inhibitor); VEGF(R) (Vascular endothelial growth factor [receptor]).


THANK YOU