Suprachoroidal CLS-AX (axitinib injectable suspension) as a Potential Long-Acting Therapy for Neovascular Age-Related Macular Degeneration (nAMD)

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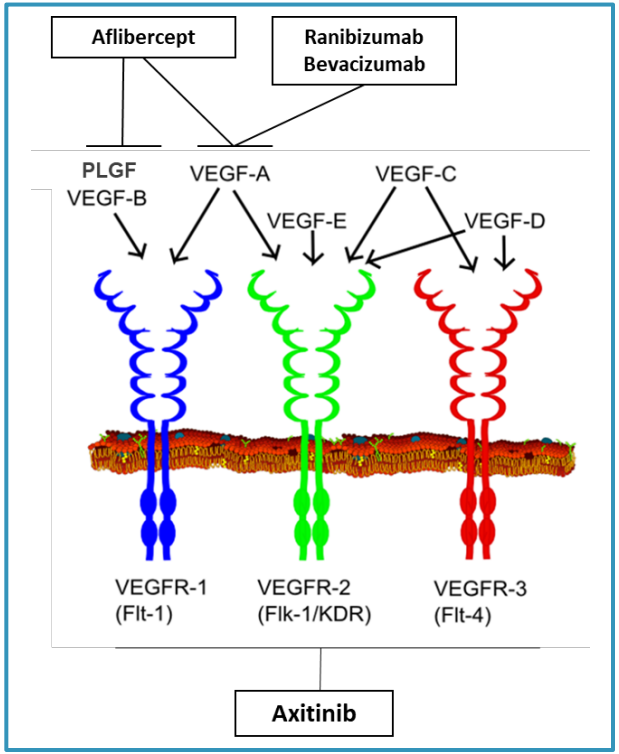
Financial Disclosures

- R. Bhisitkul:
  - RIBOMIC, Inc, medical advisor; Rezolute, Inc, medical advisor; Visgenx, scientific advisor; Unity Bio, consultant, medical monitor; Horizon Therapeutics, consultant; Genentech/Roche, research grants; Oculinea, patents and stock options
- T. Ciulla :
  - Clearside Biomedical, Inc.
    - Employee, stockholder
    - Salary, stock, stock options
- V. Kansara:
  - Clearside Biomedical, Inc.
    - Employee, stockholder
    - Salary, stock, stock options

Axitinib Inhibits VEGF 1, 2, 3 Receptors

Current AMD Therapies predominantly focus on VEGF-A blockade, not VEGF Receptors

- Anti-VEGF-A increases VEGF-C [1] & VEGF-D[2]
- Broad VEGF blockade may improve outcomes
- A Phase 2 study yielded better AMD outcomes with anti-VEGF-A,C,D vs anti-VEGF-A[3]

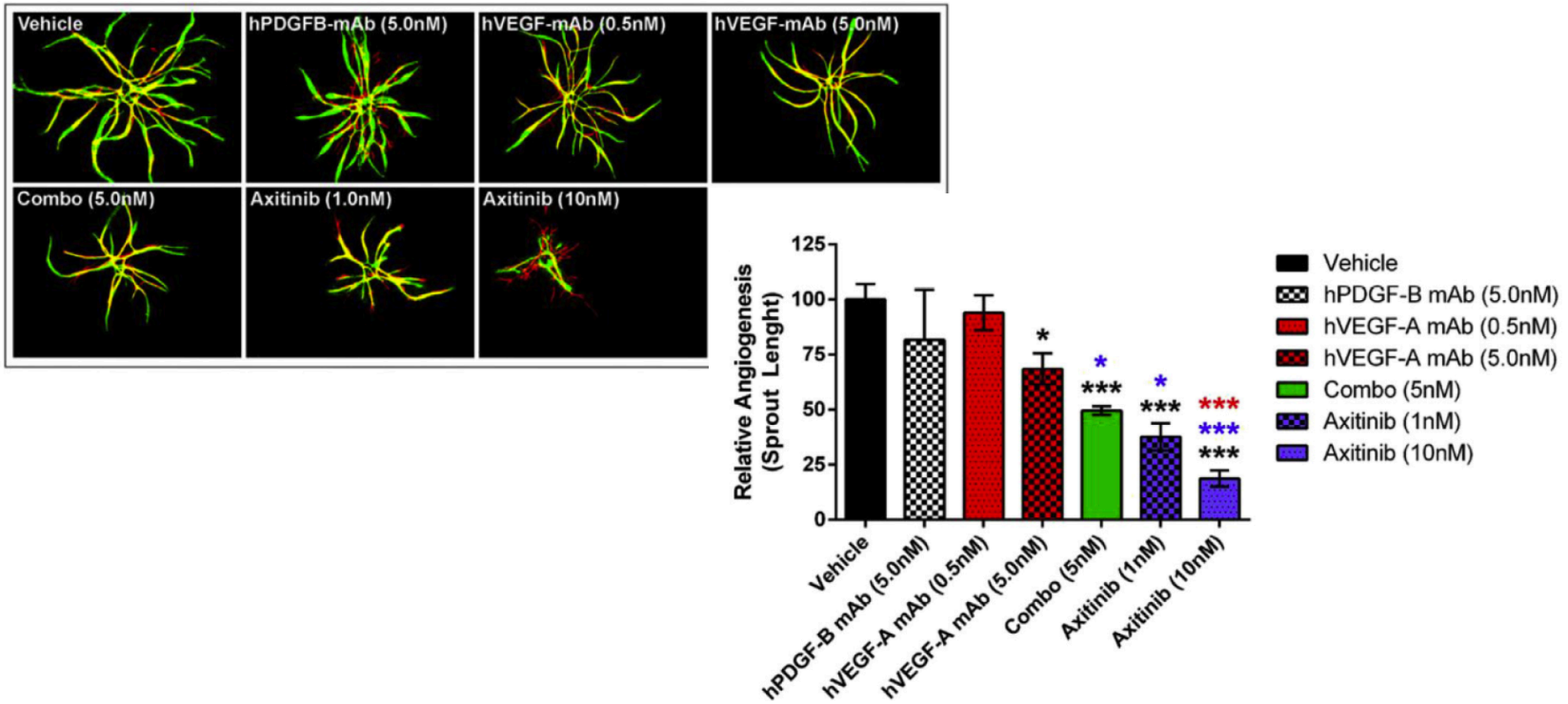


Suprachoroidal Axitinib provides broad VEGF blockade

- Inhibits VEGFR-1, VEGFR-2, VEGFR-3
- Inhibited corneal, retinal, and choroidal angiogenesis in animal models[4-8]
- More effective than other TKIs for experimental corneal neovascularization in animal models
- Better ocular cell biocompatibility than other TKIs[9]

Sources: 1. Cabral T et al. Bevacizumab Injection in Patients with Neovascular Age-Related Macular Degeneration Increases Angiogenic Biomarkers. Ophthalmol Retina. 2018 January ; 2(1): 31–37. doi:10.1016/j.oret.2017.04.004. | 2. Lieu et al. The Association of Alternate VEGF Ligands with Resistance to Anti-VEGF Therapy in Metastatic Colorectal Cancer. PLoS ONE 8(10): e77117. | 3. Jackson, Timothy. "EURetina Congress." Opthea, 5 Sept. 2019, opthea.com/wp-content/uploads/2019/09/20190905-EuRetina-ASX-Slides_Final2.pdf. | 4. Riquelme et al. Topical axitinib is a potent inhibitor of corneal neovascularization. Clinical and Experimental Ophthalmology 2018; 46: 1063–1074 | 5. Yuan et al. Ocular Drug Delivery Nanowafer with Enhanced Therapeutic Efficacy. ACS Nano. 2015 Feb 24;9(2):1749-58. | 6. Giddabasappa et al. Axitinib inhibits retinal and choroidal neovascularization in in-vitro and in-vivo models. Exp Eye Res. 2016, 145: 373-379. | 7. Nakano et al. Short-term treatment with VEGF receptor inhibitors induces retinopathy of prematurity-like abnormal vascular growth in neonatal Rats. Exp Eye Res. 2016. 143: 120-131. | 8. Kang et al. Antiangiogenic Effects of Axitinib, an Inhibitor of Vascular Endothelial Growth Factor Receptor Tyrosine Kinase, on Laser-Induced Choroidal Neovascularization in Mice. Curr Eye Res. 2012. 38: 119-127. | 9. Theile et al. Multikinase Inhibitors as a New Approach in Neovascular Age-Related Macular Degeneration (AMD) Treatment: In Vitro Safety Evaluations of Axitinib, Pazopanib and Sorafenib for Intraocular Use. Klin Monatsbl Augenheilkd 2013; 230: 247-254. | Image by Mikael Häggström, used with permission. Häggström, Mikael (2014). "Medical gallery of Mikael Häggström 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.008. ISSN 2002-4436. Public Domain.

Axitinib inhibits angiogenic sprouts more potently than anti-VEGF-A, anti-PDGF-B and combination thereof



Giddabasappa A, Lalwani K, Norberg R, et al. Axitinib inhibits retinal and choroidal neovascularization in in vitro and in vivo models. *Exp Eye Res*. 2016;145:373–379. doi:10.1016/j.exer.2016.02.010

Topical axitinib more effectively inhibits experimental murine corneal neovascularization than sunitinib, sorafenib (at same dose)

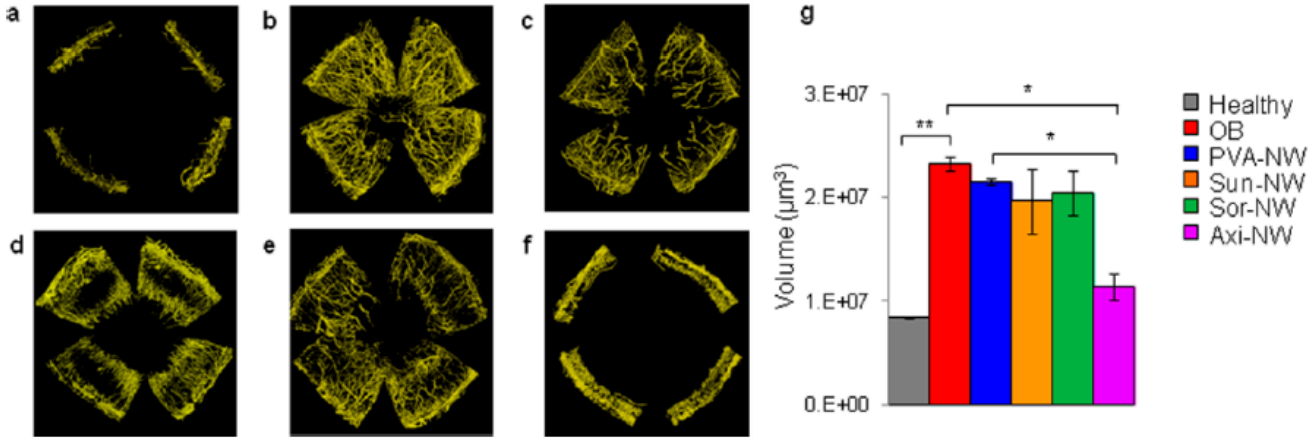
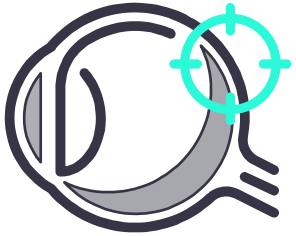


Figure 5. Selection of tyrosine kinase receptor inhibitor drugs. Screening of tyrosine kinase inhibitor drugs loaded nanowafers for their relative therapeutic efficacy in inhibiting corneal neovascularization after 10 days of treatment. Representative 3D reconstructed corneal images of fluorescence confocal microscopy: (a) healthy cornea (control); (b) untreated ocular burn (control); (c) blank PVA-NW; (d) Sora-NW; (e) Suni-NW; (f) Axi-NW. (g) Quantification of corneal neovascularization volume. *n* = 3 animals, **P* < 0.05 *vs* OB control and *P* < 0.05 *vs* PVA-NW, ***P* < 0.01. All error bars represent standard deviation from the mean.

Yuan et al. Ocular Drug Delivery Nanowafer with Enhanced Therapeutic Efficacy. ACS Nano. 2015 Feb 24;9(2):1749-58.

Differentiating Features of Treating Via the Suprachoroidal Space



DIRECTED TO CHORIO-RETINA

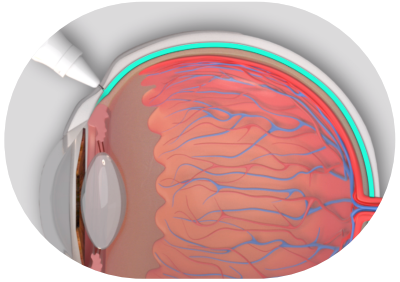
The macula and posterior pole are the key locations of many common retinal diseases[1]

for efficacy

COMPARTMENTALIZED

Drug is compartmentalized in the suprachoroidal space, away from non-diseased anterior segment tissues[2]

for safety



BIOAVAILABLE

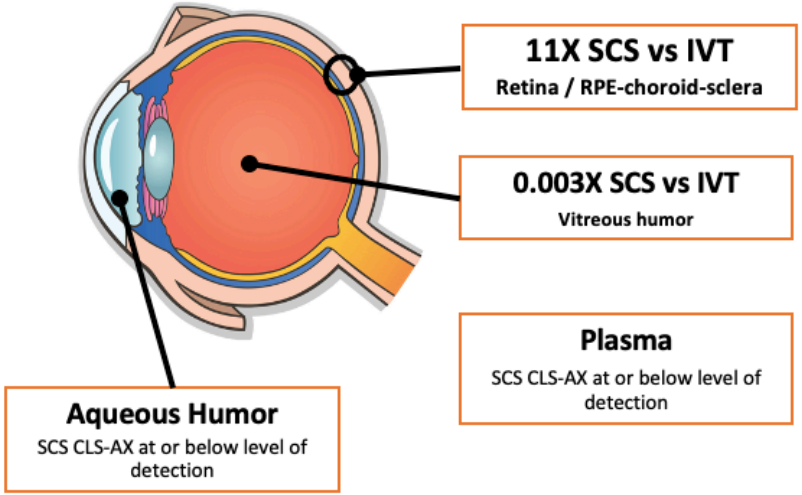
Fluid spreads circumferentially and posteriorly when injected within the suprachoroidal space, providing the choroid and adjacent areas with drug[3]

for durability

1. Rai UDJ, Young SA, Thrimawithana TR, et al. The suprachoroidal pathway: a new drug delivery route to the back of the eye. Drug Discov Today. 2015;20(4):491-495. 2. Chiang B, Jung JH, Prausnitz MR. The suprachoroidal space as a route of administration to the posterior segment of the eye. Adv Drug Deliv Rev. 2018;126:58-66. 3. Moisseiev E, Loewenstein A, Yiu G. The suprachoroidal space: from potential space to a space with potential. Clin Ophthalmol. 2016;10:173-178.

Suprachoroidal Injection of CLS-AX: Targeted, Durable in Preclinical Model

Targeted Delivery relative to IVT at Same Dose



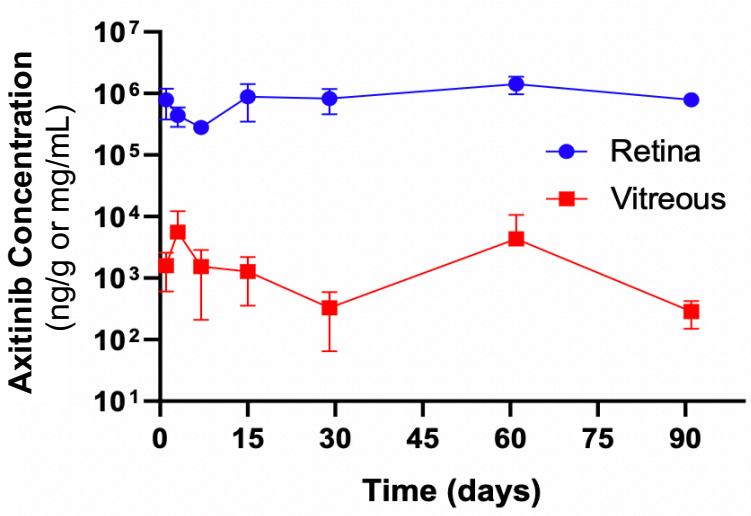
Values: area under the curve ratios, SCS / IVT

Rabbit Model

SCS: 1 mg/eye, 100 µL | IVT: 1 mg/eye, 25 µL

Single bilateral injection, 1-wk rabbit PK studies

Durable, High Drug Levels Maintained in the Retina

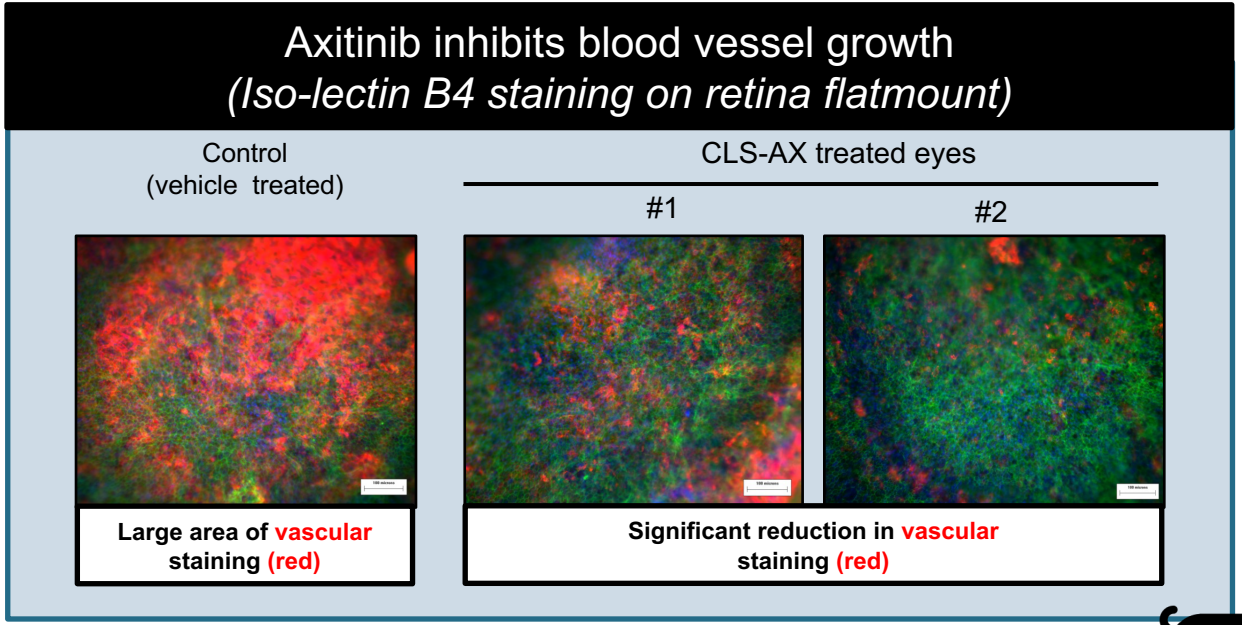


✓High Retina Levels: Sufficient to block VEGF pathway
✓Low Plasma Levels: <1 ng/mL

Abbreviations: CLS-AX: axitinib injectable suspension | SCS: Delivered via suprachoroidal injection | IVT: Delivered via intravitreal injection | PK: Pharmacokinetic | RPE: Retinal pigment epithelium

Source: Based on Clearside Biomedical preclinical data

Suprachoroidal Injection of CLS-AX: Iso-lectin B4 staining shows reduction in retinal vascular staining in pigs



Abbreviations: CLS-AX: Axitinib injectable suspension

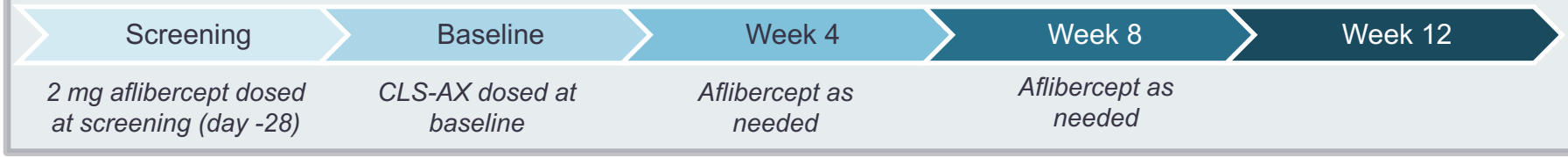
Source: Based on Clearside Biomedical preclinical data

CLS-AX Phase 1/2a Clinical Trial in Wet AMD

Trial Design

- Open-label study to assess the safety and tolerability of single doses of CLS-AX administered through suprachoroidal injection
- 3 Cohorts of 5 patients each: n=15
- Dose-escalation will begin at 0.03 mg CLS-AX; proceed to next cohort following review by Safety Monitoring Committee

Cohort Enrollment and Treatment



Key Inclusion Criteria

- Active subfoveal choroidal neovascularization secondary to AMD
- Two or more anti-VEGF treatments in the 4 months preceding the screening visit with a meaningful response
- BCVA score of ≥ 20 letters (20/400) and ≤ 75 letters (20/32) with < 5 letters change between screening and baseline to ensure patient stability after anti-VEGF

Primary Endpoint

- Safety and tolerability over 3 months of a single dose of suprachoroidally injected CLS-AX following IVT aflibercept

Note: aflibercept is dosed via intravitreal injection (IVT); CLS-AX is dosed via suprachoroidal injection

Axitinib (CLS-AX) for Suprachoroidal Injection

Potential Benefits

- Intrinsic high potency, pan-VEGF inhibition through receptor blockade
- Targeted therapy for affected tissue layers via suprachoroidal injection
- Prolonged duration observed in PK studies
- IND accepted, Phase 1/2a clinical trial in nAMD to begin enrolling in 2020