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

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RETINA
Consultants of Houston

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- D. Brown: Relevant: Clearside Biomedical, Advisor, Clinical Trial Support
- T. Ciulla :
  - Clearside Biomedical, Inc.
    - Employee, stockholder
    - Salary, stock, stock options
- V. Kansara:
  - Clearside Biomedical, Inc.
    - Employee, stockholder
    - Salary, stock, stock options

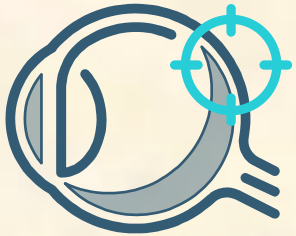
Axitinib for Suprachoroidal Injection (CLS-AX): A Potential Solution for Treatment Burden

Primary Need

Durable **maintenance of vision** and **reduced treatment burden** in neovascular AMD patients

Suprachoroidal Injection Procedure

Core Advantages of Treating Via the Suprachoroidal Space



TARGETED

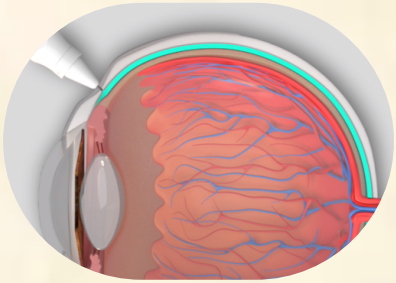
The back of the eye is the location of many irreversible and debilitating visual impairments[1]

for efficacy

COMPARTMENTALIZED

Drug is compartmentalized in the suprachoroidal space, which helps keep it away from non-diseased tissues[2]

for safety



BIOAVAILABLE

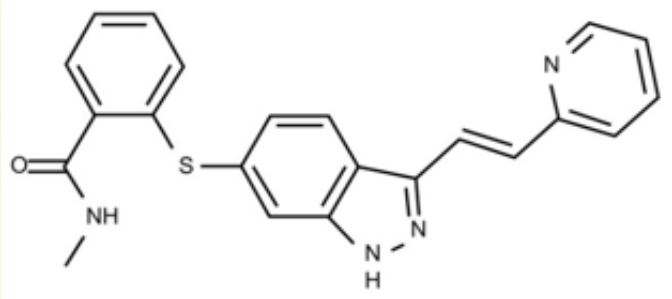
Fluid spreads circumferentially and posteriorly when injected within the suprachoroidal space, bathing the choroid and adjacent areas with drug[3]

for durability

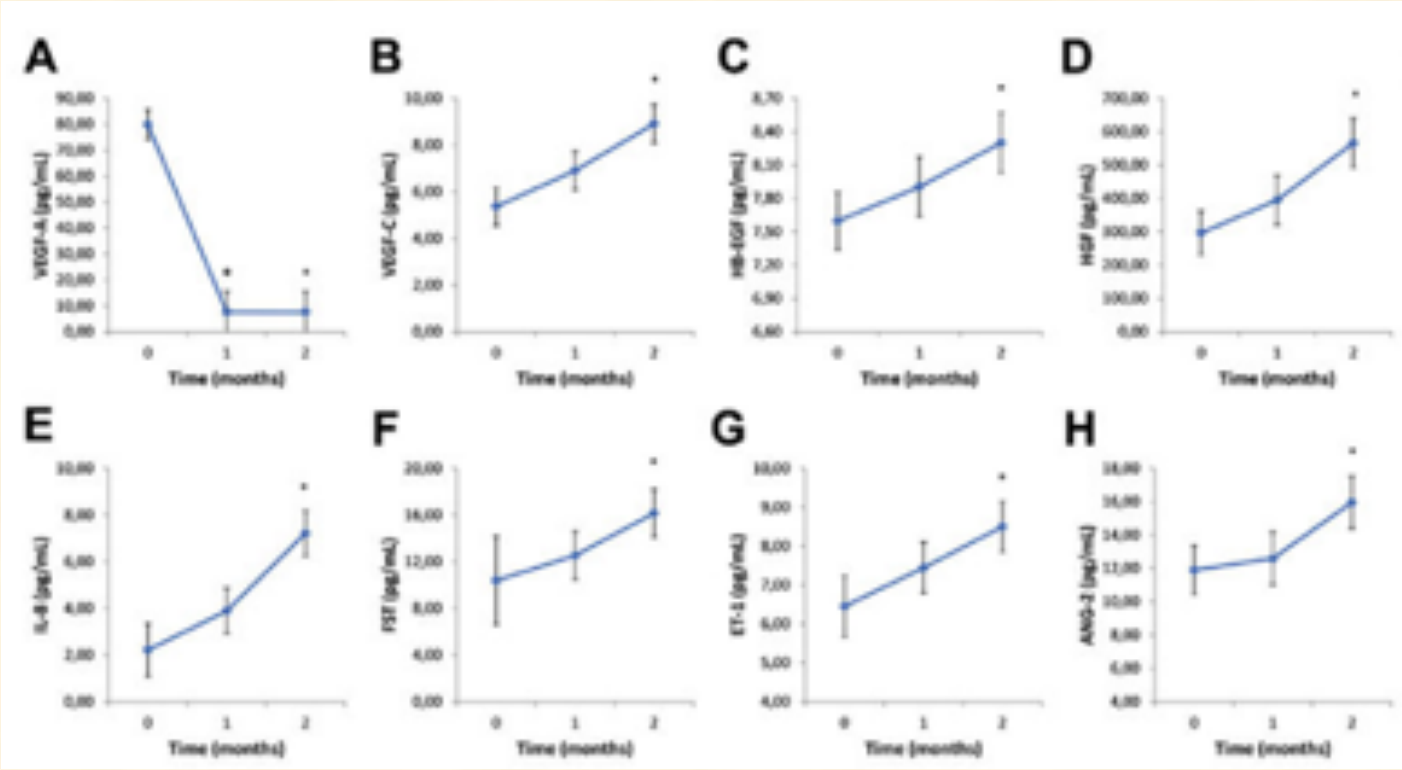
Sources: PK = pharmacokinetic | 1. Raj UDJ, Young SA, Thrimawithana TR, et al. The suprachoroidal pathway: a new drug delivery route to the back of the eye. Drug Discov

Axitinib: A Novel Tyrosine Kinase Inhibitor (TKI)

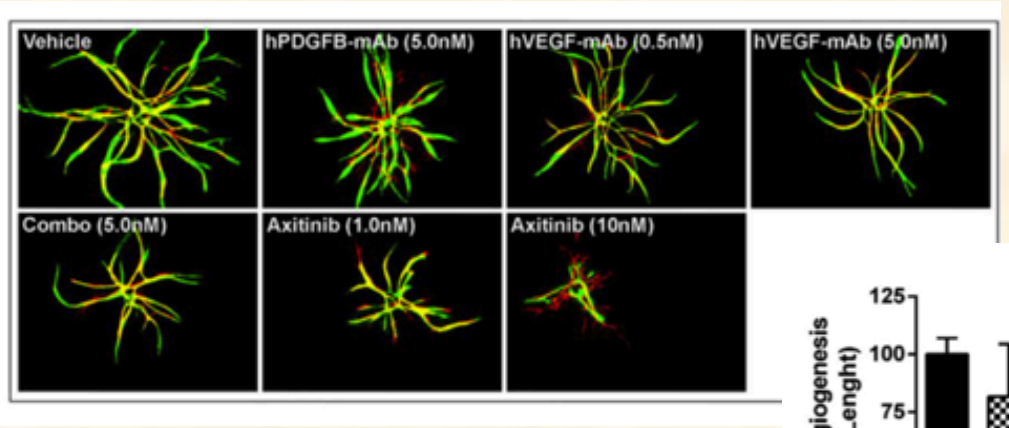
- Anti-VEGF-A upregulates VEGF-C & VEGF-D:TKIs block VEGF A/B/C
- Axitinib inhibits corneal, retinal and choroidal angiogenesis in multiple preclinical models
- Axitinib is more biocompatible with ocular cells than other TKIs

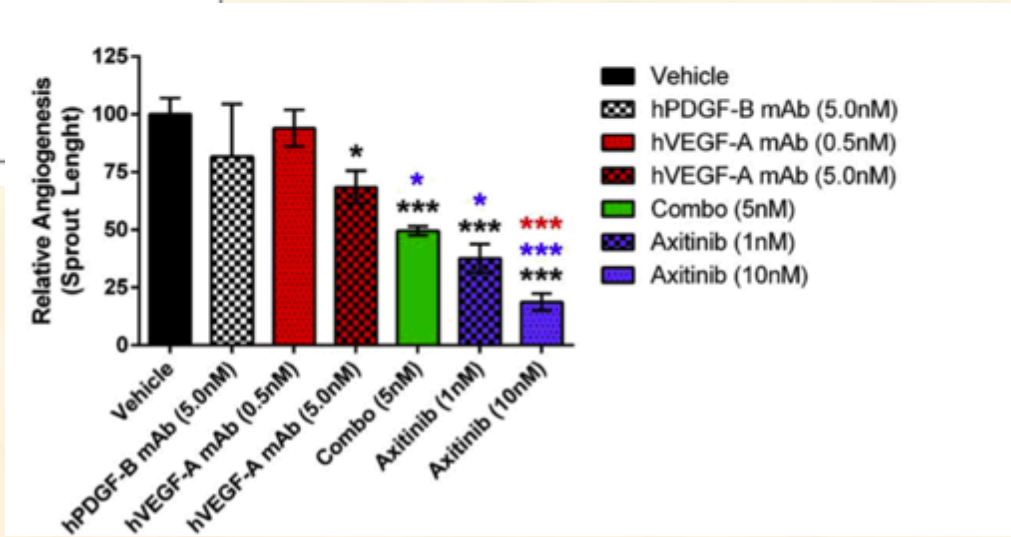


Bevacizumab injection increases angiogenic biomarkers in nAMD patients



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





Tyrosine Kinase Inhibitors: Potency

Inhibitory concentrations (IC50 in nmol) for targets with multitargeted TKIs.

Drug	VEGFR1	VEGFR2	VEGFR3	PDGFRα	PDGFRβ	c-Kit	RET	RAF	FLT3
Axitinib[9]	0.1	0.2	0.1–0.3	5	1.6	1.7	>1000	NA	>1000
Pazopanib[24]	10	30	47	71	84	74	>1000	NA	>1000
Sunitinib[25]	10	10	10	5–10	10	13	100–200	NA	1–10
Sorafenib[26]	NA	90	20	50–60	50–60	68	100–150	5–10	46

Gross-Goupil et al. (2013). Axitinib: a review of its safety and efficacy in the treatment of adults with advanced renal cell carcinoma. *Clinical Medicine Insights. Oncology*, *7*, 269–277. doi:10.4137/CMO.S10594

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

Figure 5

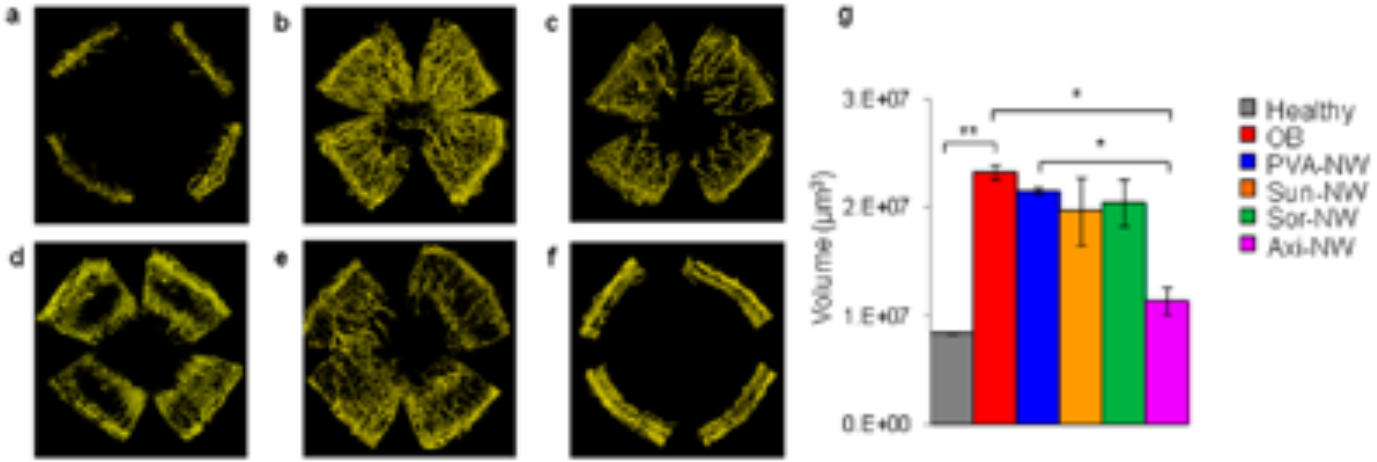
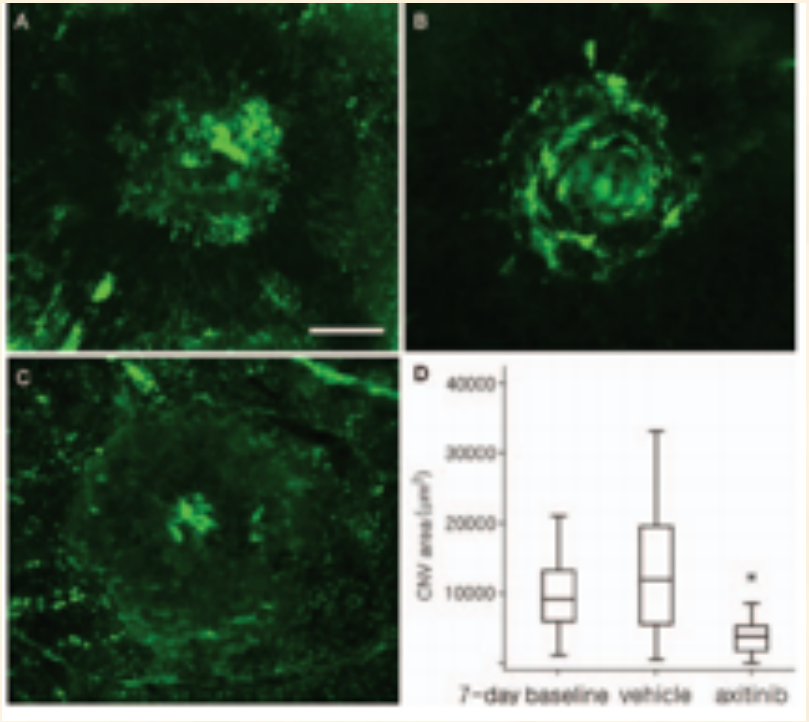


Figure 5. Selection of tyrosine kinase receptor inhibitor drugs. Screening of tyrosine kinase inhibitor drugs loaded nanowafers for their relative therapeutic efficacy in inhibiting corneal neovascularization after 10 days of treatment. Representative 3D reconstructed corneal images of fluorescence confocal 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.

Oral Axitinib caused 71% area regression of laser-induced CNV compared to vehicle-treatment ($p < 0.001$) in Mice



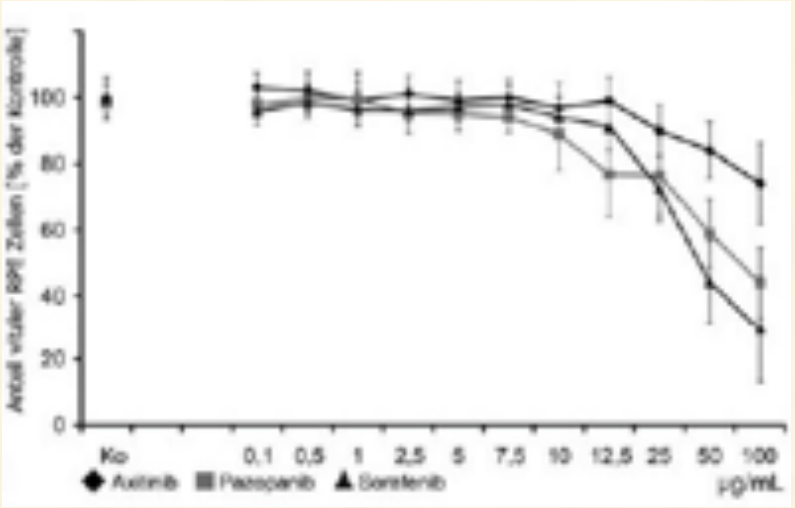
Kang et al. Antiangiogenic Effects of Axitinib, an Inhibitor of Vascular Endothelial Growth Factor Receptor Tyrosine Kinase, on Laser-Induced Choroidal Neovascularization in Mice. Curr Eye Res. 2012. 38: 119-127.

In vitro safety evaluations of axitinib, pazopanib and sorafenib for intraocular use

Axitinib, pazopanib, or sorafenib (0.1 to 100 µg/mL)

- Primary human optic nerve head astrocytes
- Trabecular meshwork cells
- Retinal pigment epithelium
- Human corneal endothelial & lens epithelial cells

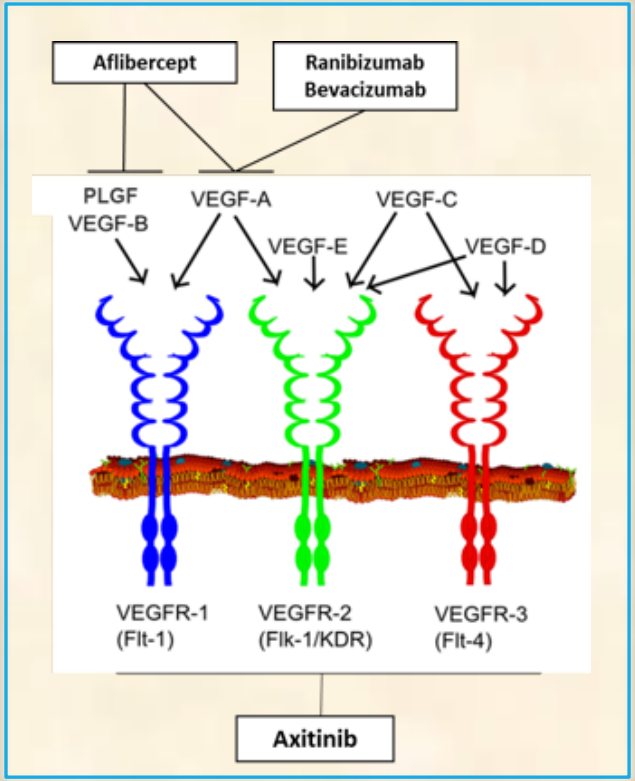
Retinal pigment epithelium



AMD Vascular Endothelial Growth Factor Treatment Approaches

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

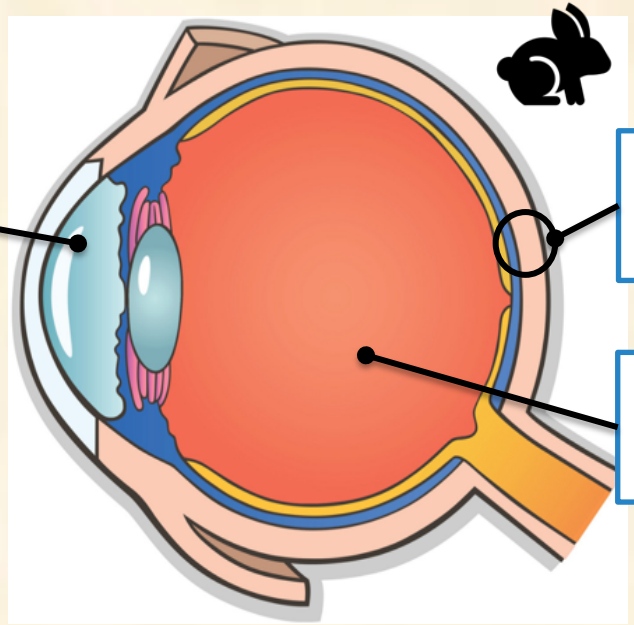


Suprachoroidal Axitinib May Improve Outcomes with Its Broad VEGF Blockade

- Inhibits VEGFR-1, VEGFR-2, VEGFR-3
- Inhibited corneal, retinal, and choroidal angiogenesis in animal models[3-7]
- More effective than other TKIs for experimental corneal neovascularization in animal models
- Better ocular cell biocompatibility than other TKIs[8]

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. Riquelme et al. Topical axitinib is a potent inhibitor of corneal neovascularization. Clinical and Experimental Ophthalmology 2018; 46: 1063–1074 | 4. Yuan et al. Ocular Drug Delivery Nanowafer with Enhanced Therapeutic Efficacy. ACS Nano. 2015 Feb 24;9(2):1749-58. | 5. Giddabasappa et al. Axitinib inhibits retinal and choroidal neovascularization in in-vitro and in-vivo models. Exp Eye Res. 2016, 145: 373-379. | 6. Nakano et al. Short-term treatment with VEGF receptor inhibitors induces retinopathy of

Suprachoroidal injection of axitinib (CLS-AX) provides targeted delivery relative to IVT injection at same dose



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Aqueous Humor

SCS CLS-AX at or below level of detection

11x SCS vs IVT

Retina / RPE-choroid-sclera

0.003X SCS vs IVT

Vitreous humor

- -

Plasma

SCS CLS-AX at or below level of detection

Values: area under the curve ratios, SCS / IVT

SCS : 1 mg/eye, 100 µL

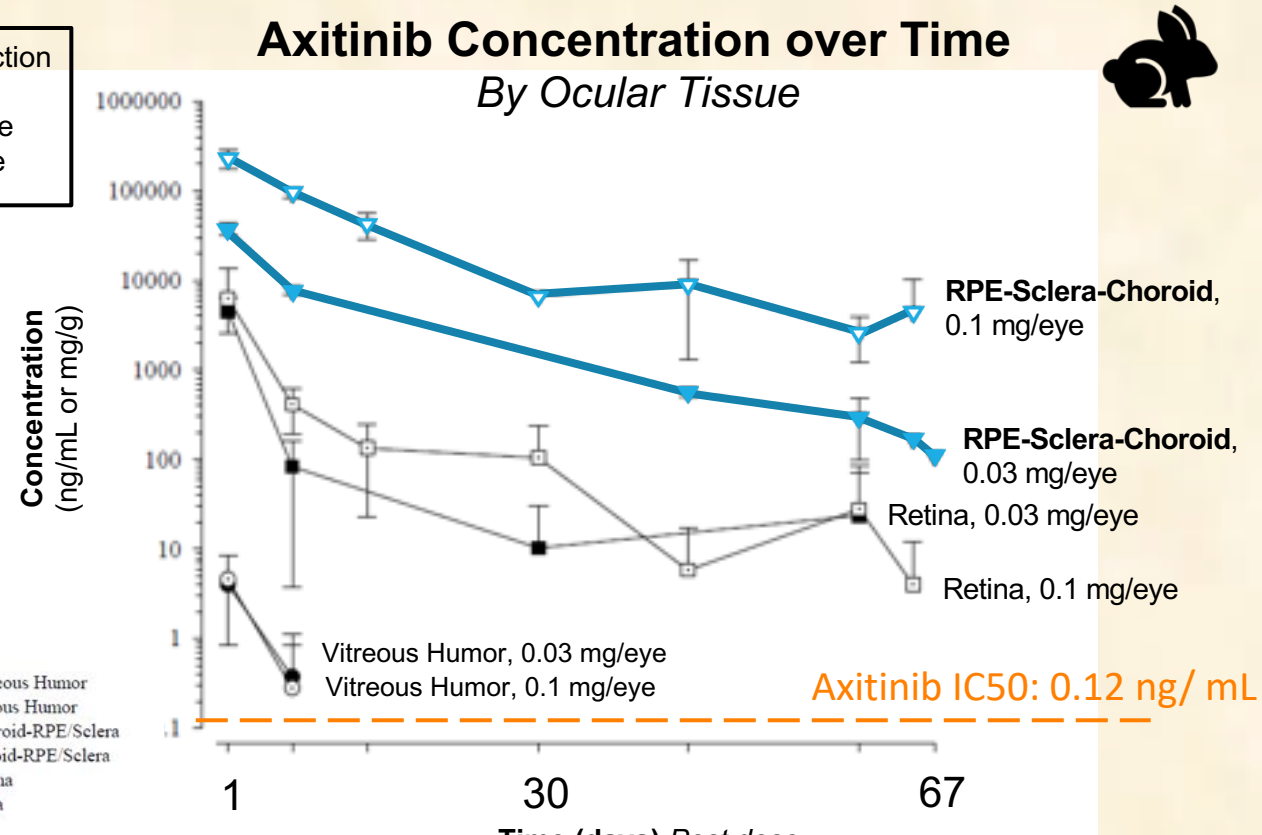
IVT: 1 mg/eye, 25 µL

Single bilateral injection, 1-wk rabbit PK studies

SCS: Suprachoroidal Injection
IVT: Intravitreal Injection
PK: Pharmacokinetic
CLS-AX: axitinib injectable suspension
LLOQ: lower limit of quantification, 0.15 mg/ml

Suprachoroidal axitinib maintains levels above IC50 for 60+ days in rabbit model

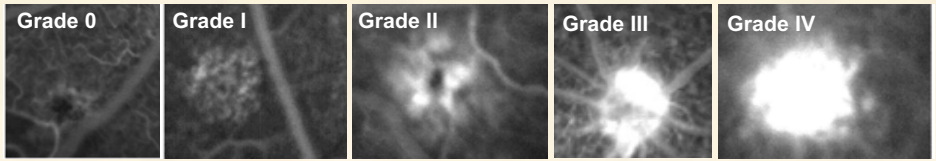
Single bilateral SC injection
0.1 mL/ eye
Group 1: 0.03 mg/eye
Group 2: 0.1 mg/eye



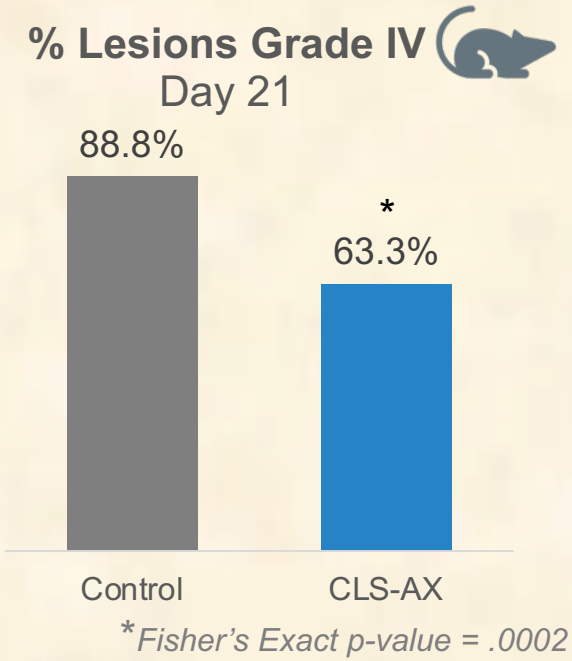
Suprachoroidal axitinib reduces CNV lesion severity versus control in rat model

METHOD

- Laser CNV: 4 lesions per eye
- N=20 eyes (n=10 specimens, bilateral SC injections)
- Two (2) doses, days 1 & 8, 0.4 mg/eye/dose



FLUOROSCEIN ANGIOGRAPHY GRADING SCALE



RESULTS

- At Day 21: CLS-AX lesion reduction in severe (Grade IV) lesions versus control – see graph

Suprachoroidal axitinib reduces fluorescein leakage and new vessel growth in pig model

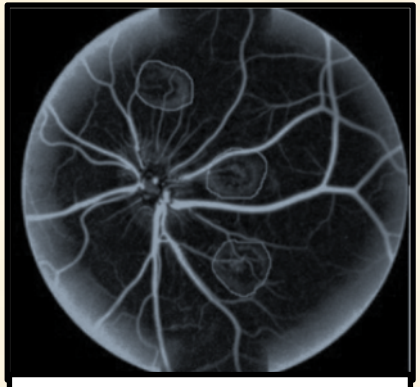
METHOD

- Laser CNV created 6 lesions per eye
- N=8 Weanling Pigs
  - OD: 4mg/ 0.1 mL Suprachoroidal CLS-AX
  - OS: 0.1 mL Saline
- Single dose followed by imaging at week 1 and week 2

RESULTS

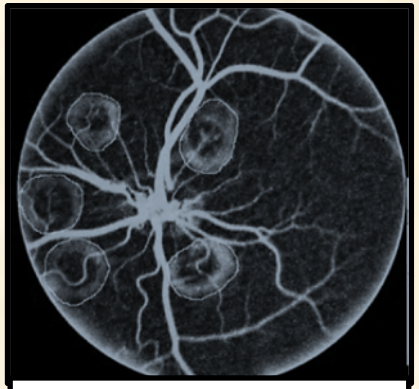
- SC CLS-AX significantly reduced fluorescein leakage
  - 10.5% @ week 1 (p=0.009)
  - 16.0% @ week 2 (p=0.0015)
- SC CLS-AX significantly reduced growth of new blood vessels
  - 18% reduction vs. saline treatment (p=0.03)

CLS-AX treated eye



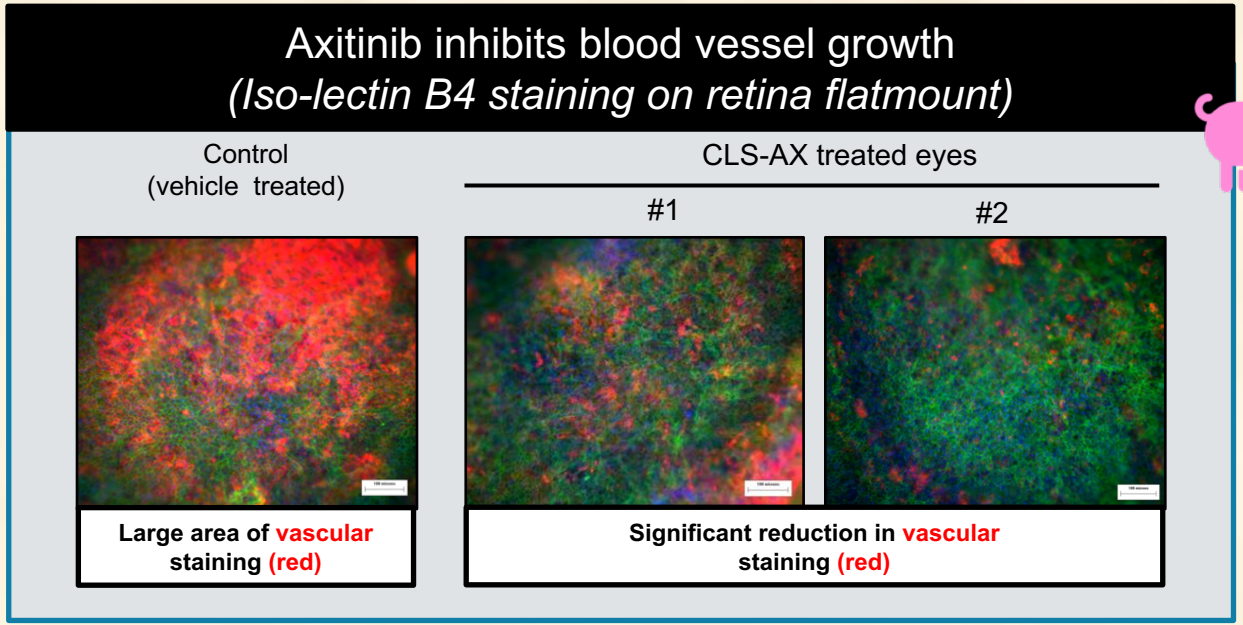
Significantly reduced vascular leakage
(marked region represents original lesion area)

BSS treated eye



Increased vascular leakage
(marked region represents lesion area)

Suprachoroidal axitinib: Iso-lectin B4 staining shows reduction in vascular staining in pigs



Suprachoroidal Axitinib in Animal Models

Across all animal models

- Suprachoroidal axitinib was well tolerated in all species
- No overt signs of toxicity
- Sustained, high exposure observed in ocular tissues through 10 weeks
  - Highest levels in the sclera/choroid/RPE > retina > vitreous
- No quantifiable axitinib detected in plasma or aqueous humor

Conclusion

- Suprachoroidal CLS-AX has potential as a bi-annual therapy for nAMD
- Intrinsic high potency, pan-VEGF inhibition through receptor blockade
- Prolonged duration observed in PK studies
- Pharmacodynamic effect demonstrated in multiple animal models
- Targeted therapy for affected tissue layers via suprachoroidal injection
- IND submission is planned this year, followed by a Phase 1/2a clinical trial in neovascular AMD