

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

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**The Macula Society
San Diego, CA
February 19-22, 2020**

Financial Disclosures

- Allergan C
- Clearside (this talk) none other
- Alimera C
- Regeneron G
- I CROWD C

Axitinib for Suprachoroidal Injection (CLS-AX): Rationale

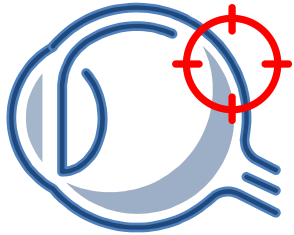
Primary Need

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

The Opportunity

- Pan-VEGF inhibition potentially more efficacious than current approaches
- Improve long-term, real-world visual outcomes for patients
- Reduce patient burden from monthly injections to every six months or longer
- Provide physicians with ability to titrate dose based on patient need
- Protect the anterior chamber from toxic exposure to TKIs

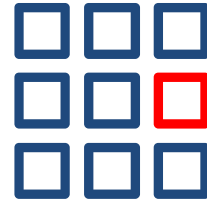
Core Advantages of Treating Via the Suprachoroidal Space



TARGETED

The back of the eye is the location of many irreversible and debilitating visual impairments¹

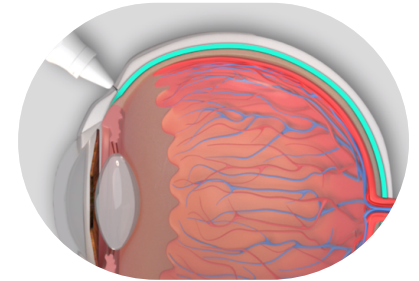
for efficacy



COMPARTMENTALIZED

Drug is compartmentalized in the suprachoroidal space, which helps keep it away from non-diseased tissues²

for safety



BIOAVAILABLE

Fluid spreads circumferentially and posteriorly when injected within the suprachoroidal space, bathing the choroid and adjacent areas with drug³

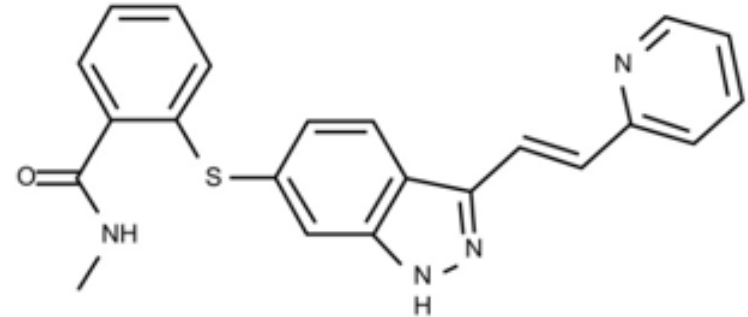
for durability

Suprachoroidal Injection Procedure

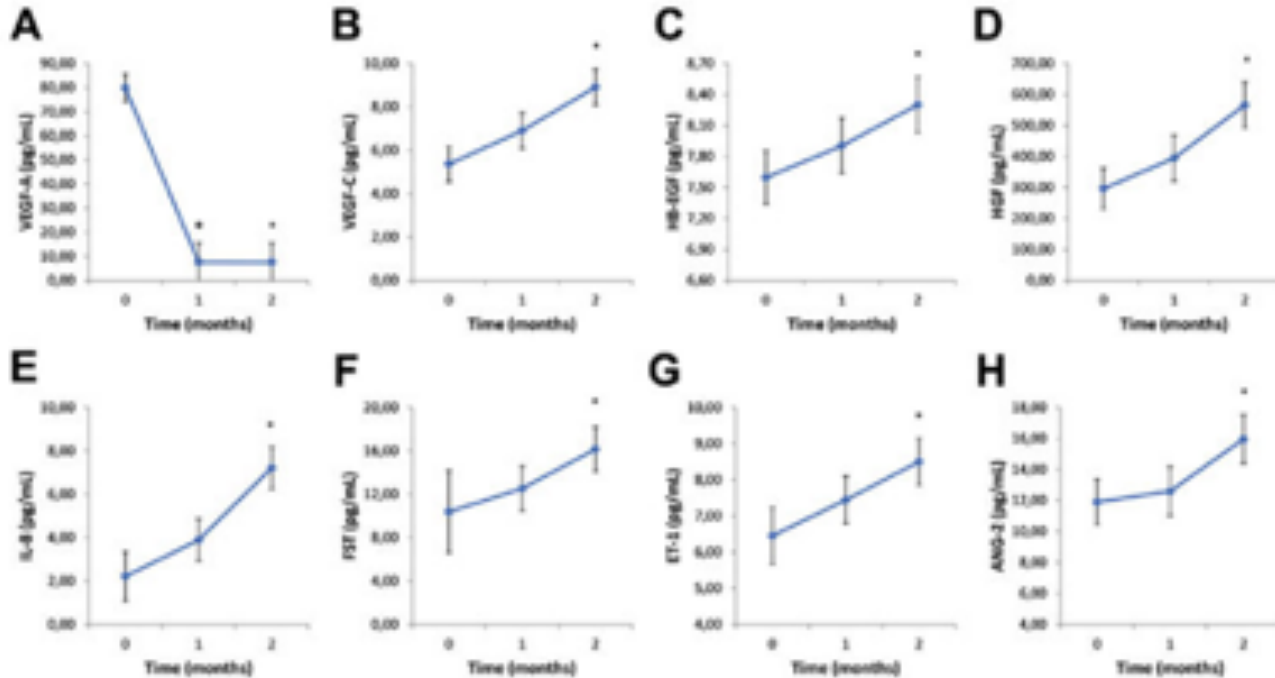


Axitinib: Literature Review

- Anti-VEGF-A upregulates VEGF-C & VEGF-D
- Axitinib effectively inhibits corneal, retinal and choroidal angiogenesis in multiple preclinical models
- Axitinib has better biocompatibility with ocular cells than other tyrosine kinase inhibitors

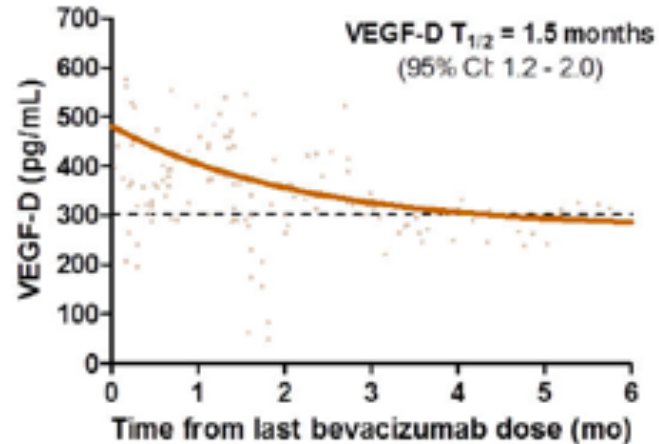
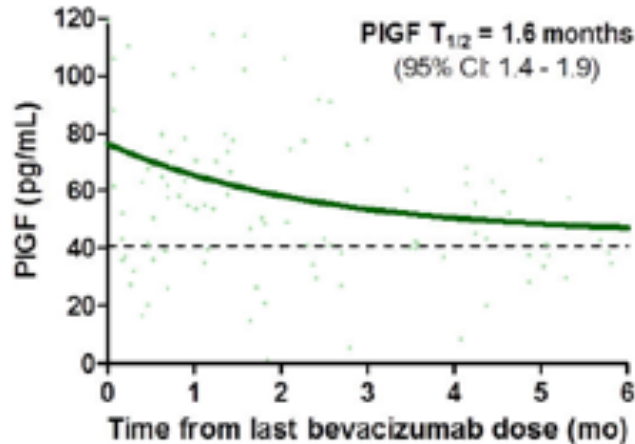


Bevacizumab Injection in Patients with Neovascular Age-Related Macular Degeneration Increases Angiogenic Biomarkers



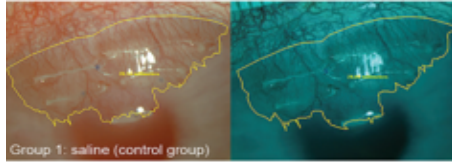
The Association of Alternate VEGF Ligands with Resistance to Anti-VEGF Therapy in Metastatic Colorectal Cancer

“Increases in PIGF and VEGF-D were observed after progression on chemotherapy with bevacizumab. These changes appear to be reversible after discontinuing therapy. These ligands are associated with resistance to bevacizumab-containing chemotherapy...”

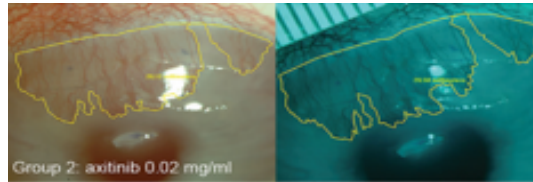


Topical Axitinib Inhibited Experimental Rabbit Corneal Neovascularization

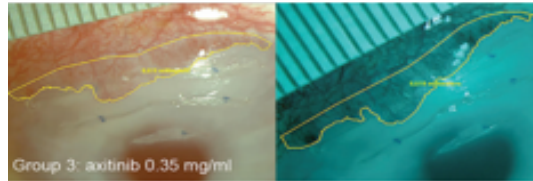
CONTROL (saline)



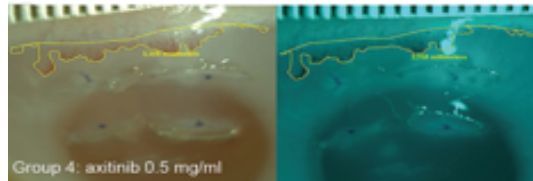
Axitinib



0.02 mg/mL = 39.04% Inhibition Rate



0.35 mg/mL = 71.96% Inhibition Rate



0.5 mg/mL = 83.74% Inhibition Rate

Table 1. Corneal neovascularization surface after 14 days of treatment (mean \pm SD)

	Group 1 Saline	Group 2 Axitinib 0.02 mg/mL	Group 3 Axitinib 0.35 mg/mL	Group 4 Axitinib 0.5 mg/mL	One-way ANOVA
Square mm	31.50 \pm 7.47	19.20 \pm 8.92	8.83 \pm 3.92	5.12 \pm 3.97	$P < 0.001$
Percentage of neovascularized area to corneal area covered by sutures	115.00 \pm 22.55	73.89 \pm 34.98	31.90 \pm 13.59	18.38 \pm 13.75	$P < 0.001$
Inhibition rate (%)	0	39.04	71.96	83.74	

ANOVA, analysis of variance.

Topical Axitinib More Effectively Inhibited Experimental Murine Corneal Neovascularization Than Sunitinib and Sorafenib (at same dose)

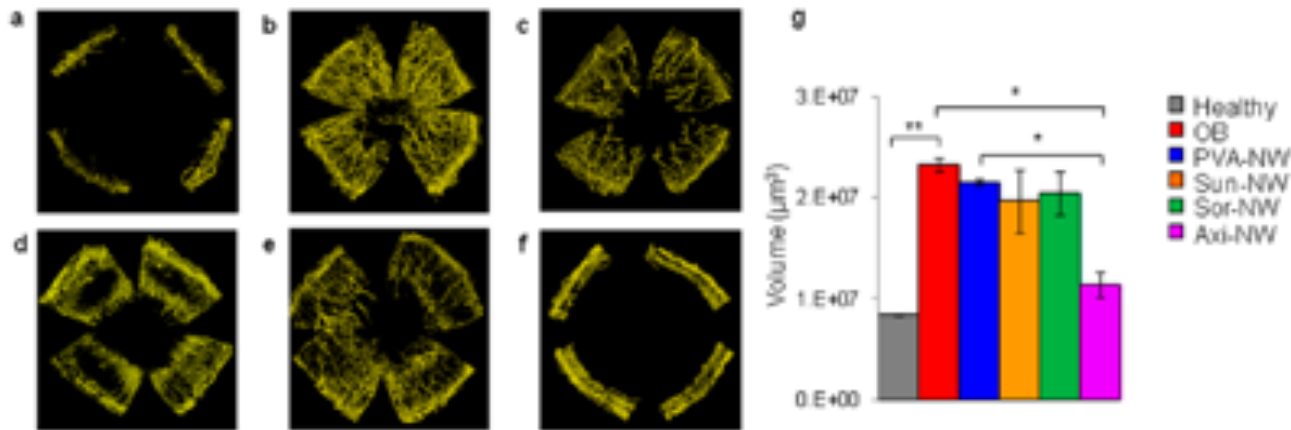
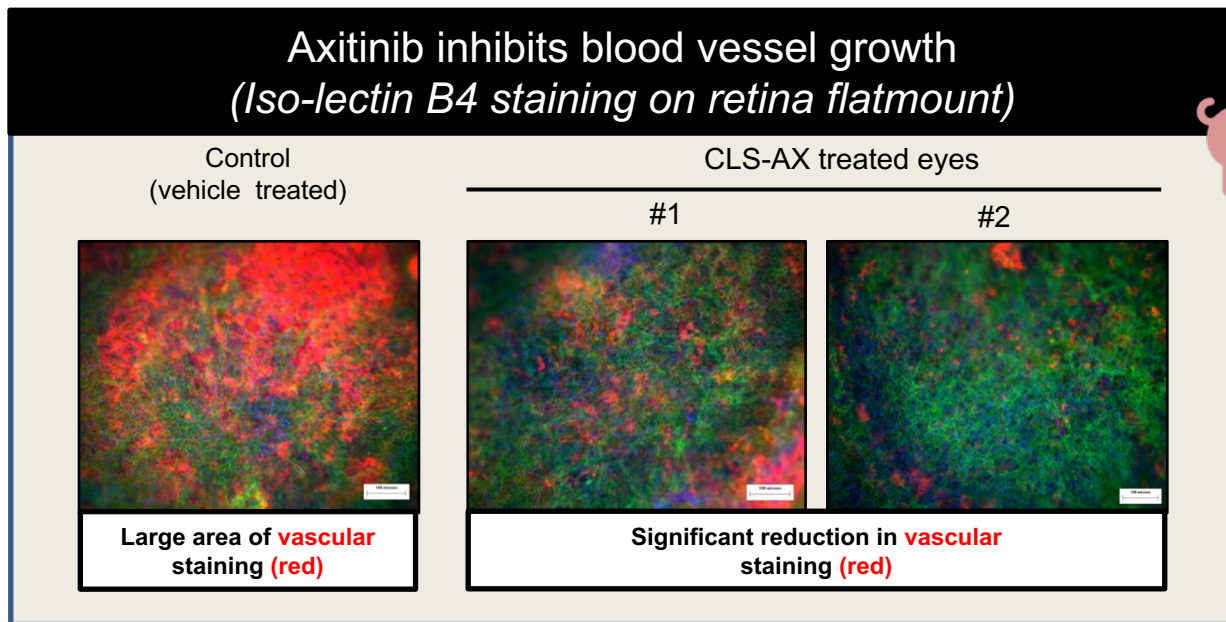
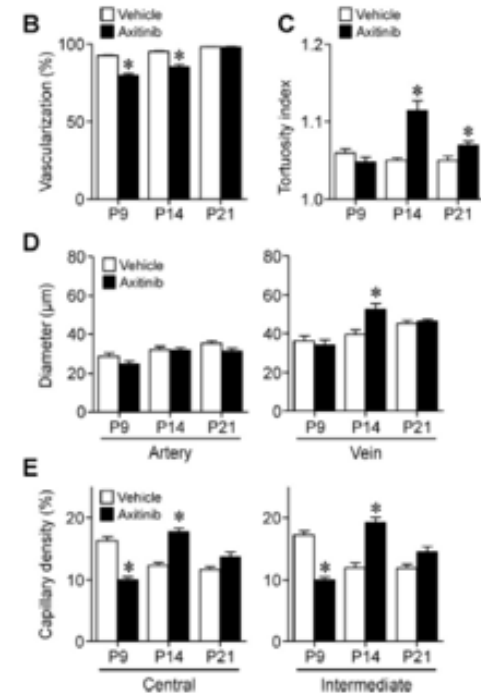
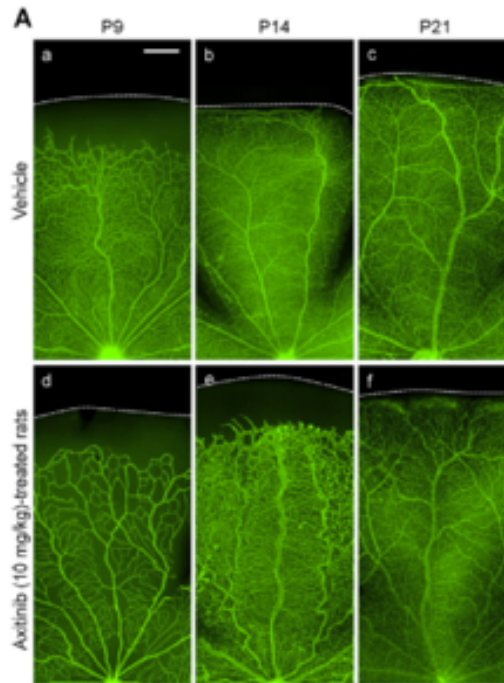
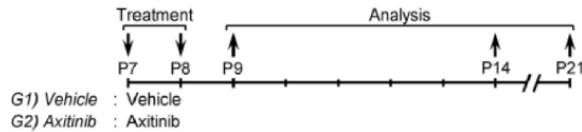


Figure 5. Selection of tyrosine kinase receptor inhibitor drugs. Screening of tyrosine kinase inhibitor drugs loaded nanowafers for their relative therapeutic efficacy in inhibiting corneal neovascularization after 10 days of treatment. Representative 3D reconstructed corneal images of fluorescence confocal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

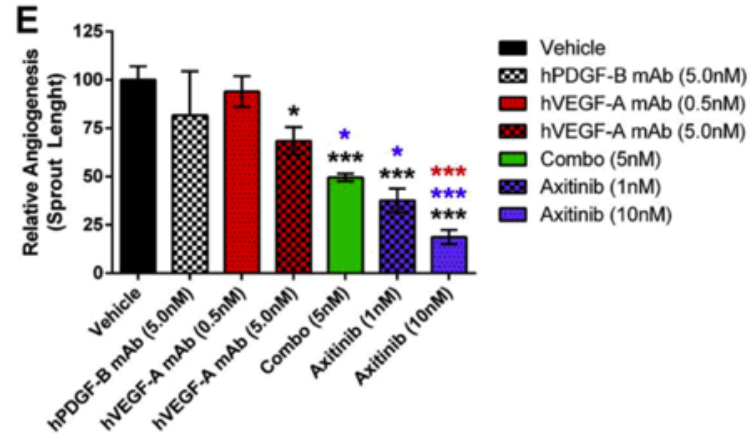
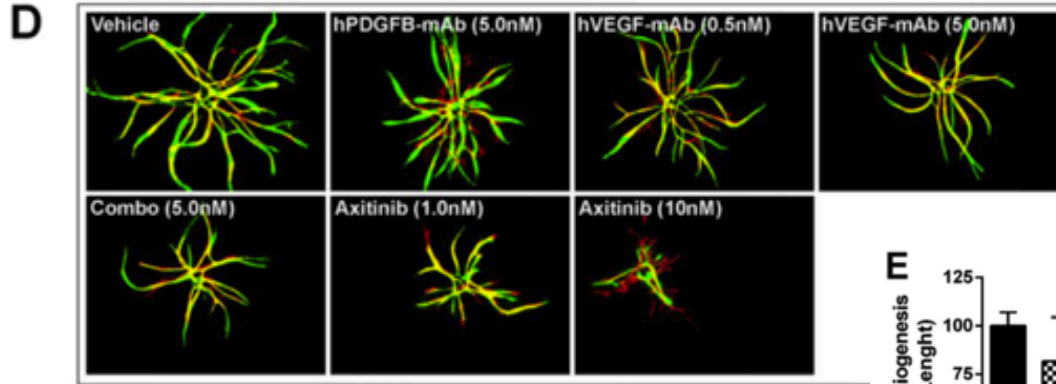
Suprachoroidal Axitinib: Iso-lectin B4 staining shows reduction in vascular staining in pigs



Short-Term Systemic Axitinib Inhibits Retinal Vascular Development Newborn Rats



Axitinib inhibits angiogenesis sprouts better than individual or combo anti-VEGFs

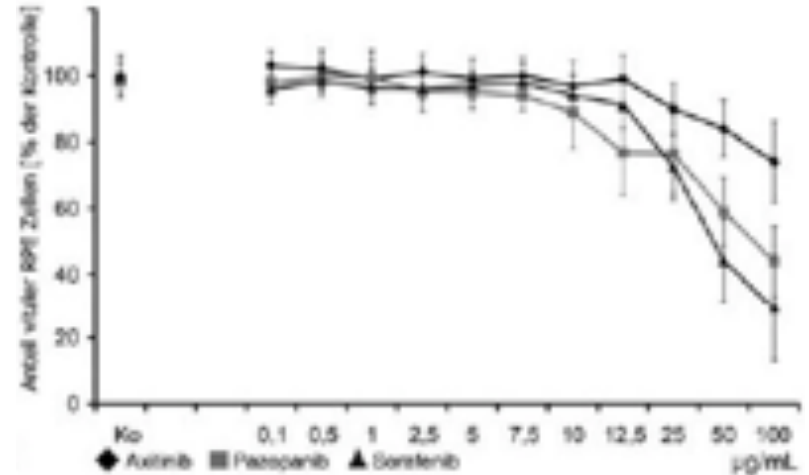


In Vitro Safety Evaluations of Axitinib, Pazopanib and Sorafenib for Intraocular Use

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



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

- **Targeted** therapy for affected tissue layers via suprachoroidal injection
- Intrinsic **high potency**, pan-VEGF inhibition through receptor blockade
- **Prolonged duration** observed in PK studies
- **Pharmacodynamic effect** demonstrated in multiple animal models