Axitinib: A Novel TKI Delivered by Suprachoroidal Injection for AMD

David Brown, MD, FACS

Director of Clinical Research
Retina Consultants of Texas
Houston, TX

Angiogenesis Virtual Meeting
February 12 – 13, 2021

Retina Consultants of Texas™

RETINA CONSULTANTS OF AMERICA

DB Financial Disclosures

Aerie (RG, C), **Alcon/Novartis** (RG, C), **Alexion** (C), **Allegro** (RG, C), **Allergan** (RG, C), **Apellis** (RG, C), **Astellas** (RG), **Boehringer-Ingelheim** (RG, C), **Carl Zeiss Meditec** (C), **Clearside Biomedical** (RG, E, C), **Coda Therapeutics** (C), **Envista** (C), **4D Molecular Therapeutics** (C), **Gemini Therapeutics** (RG, C), **Google/Verily** (C), **Genentech/Hoffman-La Roche** (RG, C), **Graybug** (RG, C), **Heidelberg Engineering** (RG, C), **Iconic** (C), **Irenix** (E, C), **Janssen** (C), **Johnson & Johnson** (C), **Kanghorn Pharma** (RG, C), **Kodiak Sciences** (RG, C), **Merck** (C), **NEI/NIH** (RG), **Nicox** (C), **Notal Vision** (RG, C), **Ohr** (RG, C), **Ophthotech, OPTOS/Nikon** (RG, C), **Optovue** (RG, C), **Pfizer** (RG, C), **PRN** (C), **Regeneron/Bayer** (RG, C), **RegenXbio** (RG, C), **Samsung Bioepsis** (RG, C), **Santen** (RG, C), **SciFlour Life Sciences** (C), **Second Sight** (RG, C), **Senju Pharmaceuticals** (RG, C), **Spark Bio** (RG, C), **Stealth Biotherapeutics** (RG, C), **Thrombogenics/Oxurion** (RG, C), **Tyrogenix** (RG, C), **Verseon** (C), **Wyle / NASA** (C),

R – Research Grant to Institution. E = Equity Options C = Consultant / Scientific Advisory Board

Intellectual Property: Co-patent hold OPTOS “dewarping” algorithms

Inventor: Sub-retinal Injection Micro-kit for Gene Therapy/ Stem Cell Application

Key Takeaways: Axitinib

Intrinsic high potency, pan-VEGF inhibition through receptor blockade

- **Pan-VEGF inhibition** versus focused VEGF-A inhibition
  - Axitinib is more effective than anti-VEGF-A in in-vitro angiogenesis model[1]
- **Highly potent TKI**
  - >10x more potent than Sunitib and other TKIs (IC50 table)
  - More effective than Sunitib and other TKIs in preclinical angiogenesis model[2]
- **Best biocompatibility** with ocular cells compared with other TKIs[3]

[1]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.2016.02.010c; [2]Yuan et al. Ocular Drug Delivery Nanowafer with Enhanced Therapeutic Efficacy. ACS Nano. 2015 Feb 24;9(2):1749-58. [3]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

Key Takeaways: Suprachoroidal Delivery of Axitinib

CLS-AX (axitinib injectable suspension) delivered via the SCS Microinjector® has potential as a durable therapy for nAMD

- **Targeted high levels in affected tissues via the suprachoroidal space (SCS)**
  - 11x higher in affected tissues than IVT
- **Compartmentalized** delivery to affected posterior tissues
  - Minimizes vitreous floaters, snow globe effect and corneal and anterior segment exposure
- **Pharmacodynamic effect** demonstrated in multiple animal models
- **Prolonged duration** observed in PK studies
- >1,000 suprachoroidal injections completed to date with the SCS Microinjector®
- Phase 1/2a clinical trial in nAMD currently enrolling

Sources: Clearside Biomedical preclinical and clinical studies

Axitinib for Suprachoroidal Injection (CLS-AX):

Primary Needs
Durable **maintenance of vision** and
reduced treatment burden in nAMD patients

TKIs = Tyrosine Kinase Inhibitors

Axitinib for Suprachoroidal Injection (CLS-AX):

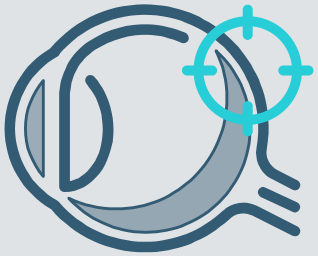
Primary Needs
Durable **maintenance of vision** and
reduced treatment burden in nAMD patients

The Opportunity

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

TKIs = Tyrosine Kinase Inhibitors

Core Advantages of Treating Via the Suprachoroidal Space



TARGETED

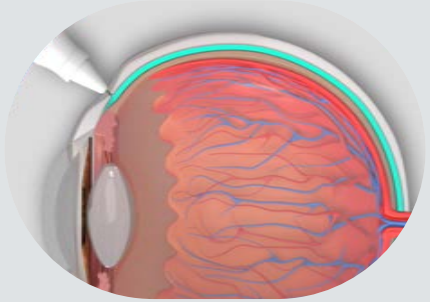
The back of the eye is the location of many irreversible and debilitating visual impairments[1]

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

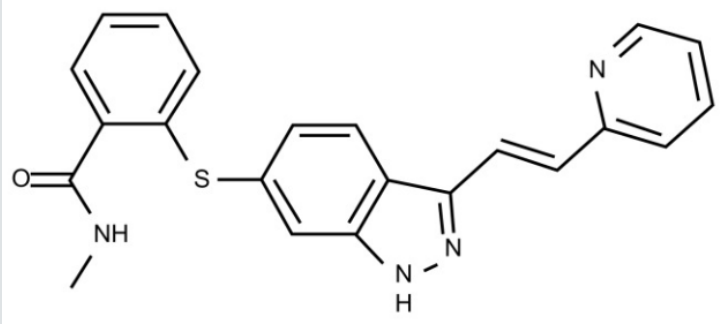
PK = pharmacokinetic

Sources: | 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.

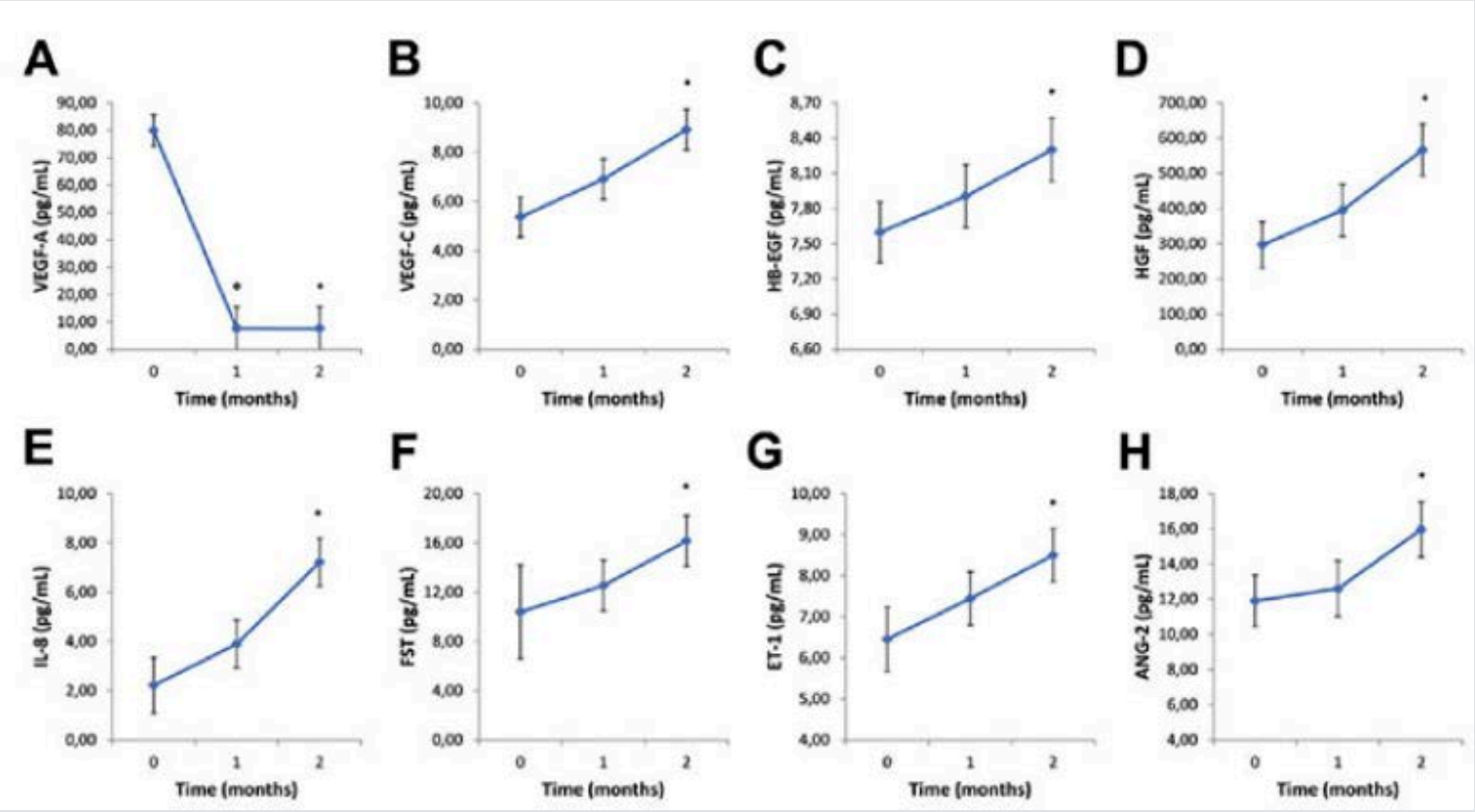
Suprachoroidal Injection Procedure

Axitinib inhibits angiogenesis in preclinical models

- Axitinib is a pan-VEGF inhibitor
  - 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 TKIs

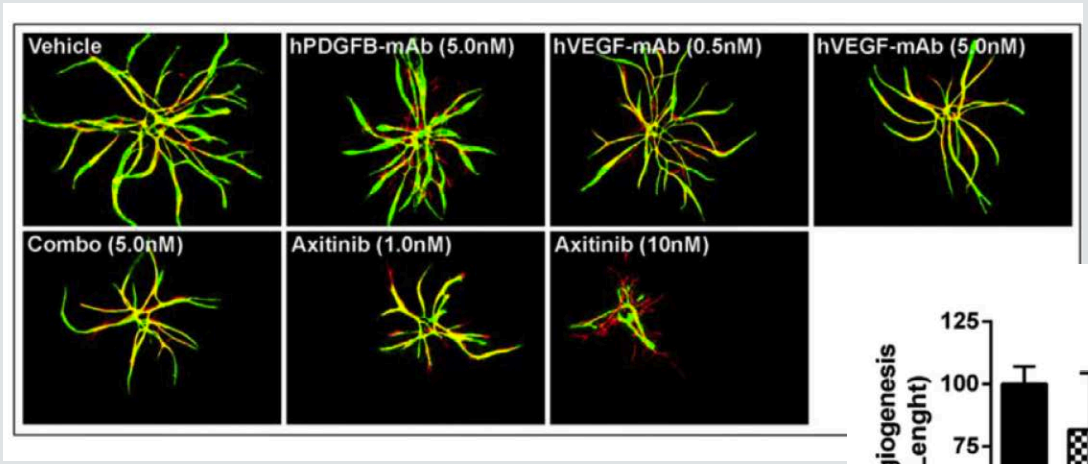


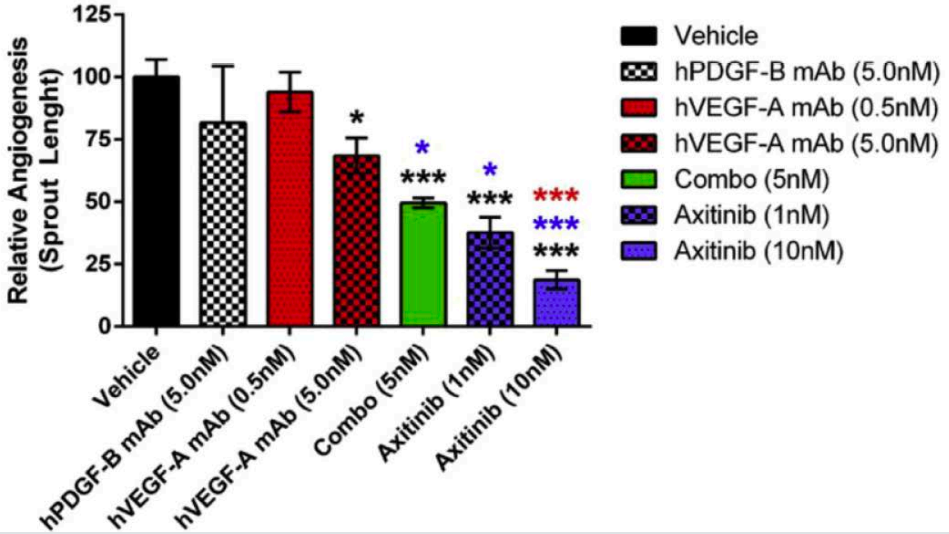
Bevacizumab increases angiogenic biomarkers in nAMD patients



Cabral et al. Bevacizumab Injection in Patients with Neovascular Age-Related Macular Degeneration Increases Angiogenic Biomarkers. Ophthalmol Retina. 2018 January ; 2(1): 31–37

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

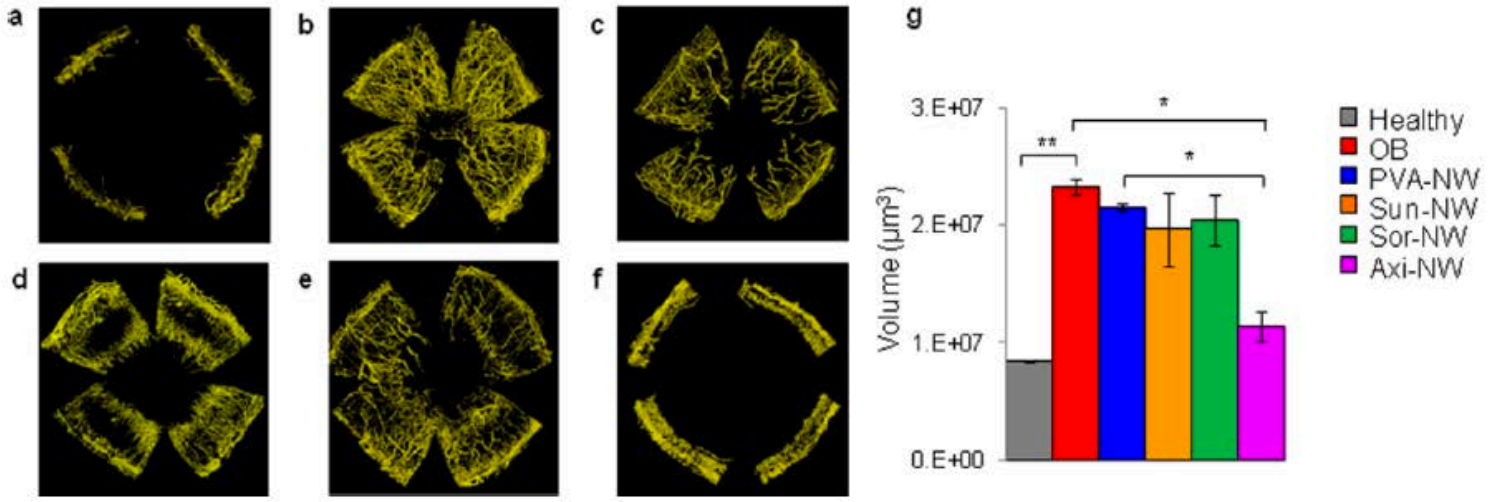
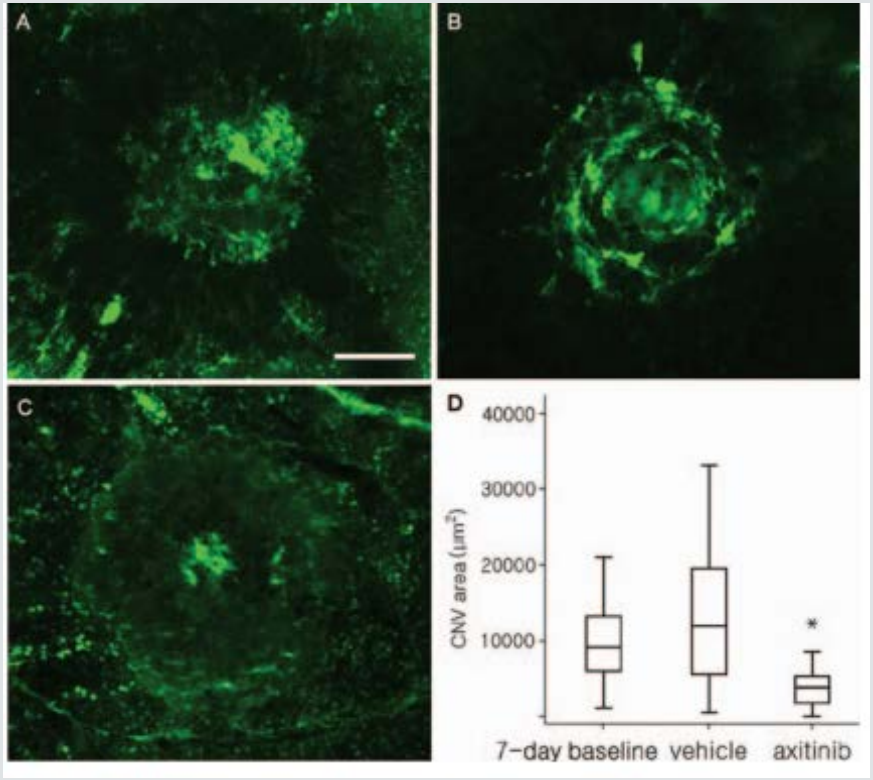


Figure 5. Selection of tyrosine kinase receptor inhibitor drugs. Screening of tyrosine kinase inhibitor drugs loaded nanowafers for their relative therapeutic efficacy in inhibiting corneal neovascularization after 10 days of treatment. Representative 3D reconstructed corneal images of fluorescence confocal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

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.

Axitinib is >10x more potent than other TKIs

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

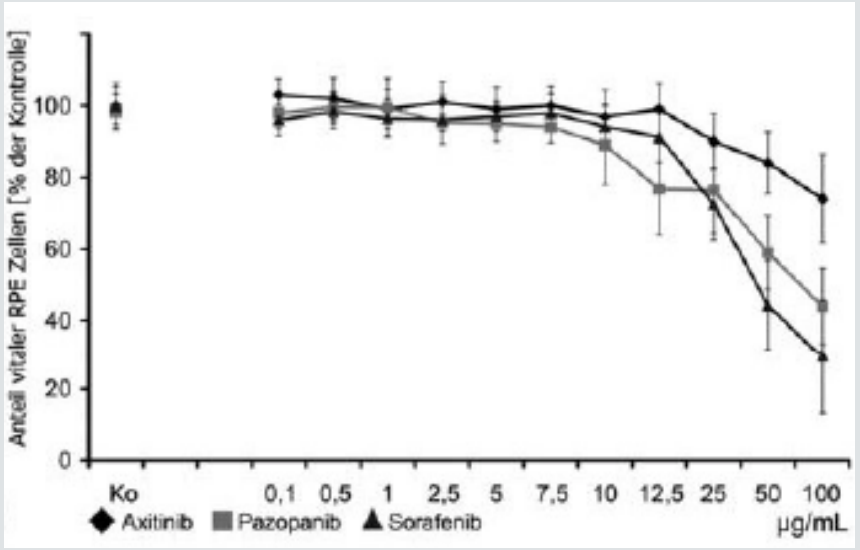
Gross-Goupil et al. (2013). Axitinib: a review of its safety and efficacy in the treatment of adults with advanced renal cell carcinoma. *Clinical Medicine Insights. Oncology*, 7, 269–277. doi:10.4137/CMO.S10594

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

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

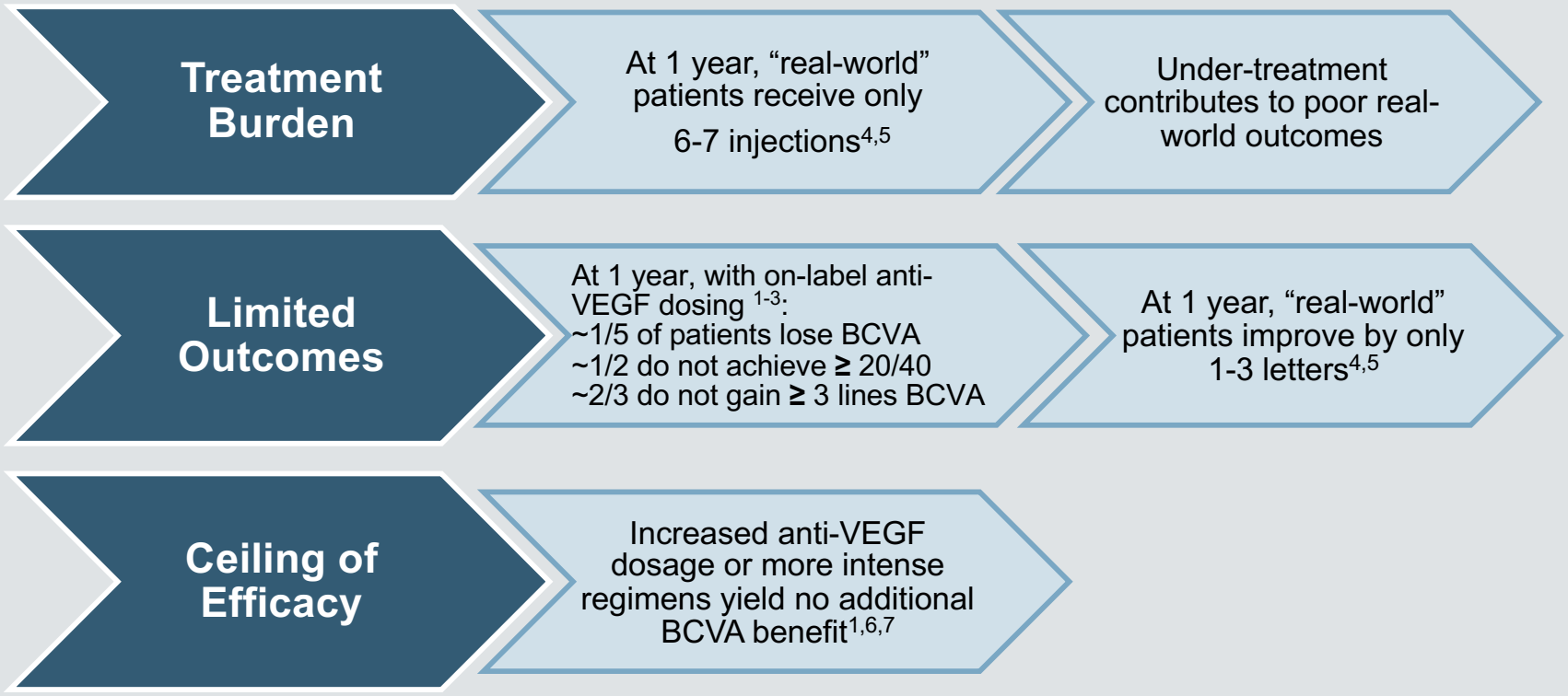
- Primary human optic nerve head astrocytes
- Trabecular meshwork cells
- Retinal pigment epithelium
- Human corneal endothelial & lens epithelial cells

Retinal pigment epithelium



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

CLS-AX May Address Unmet Needs in Neovascular AMD

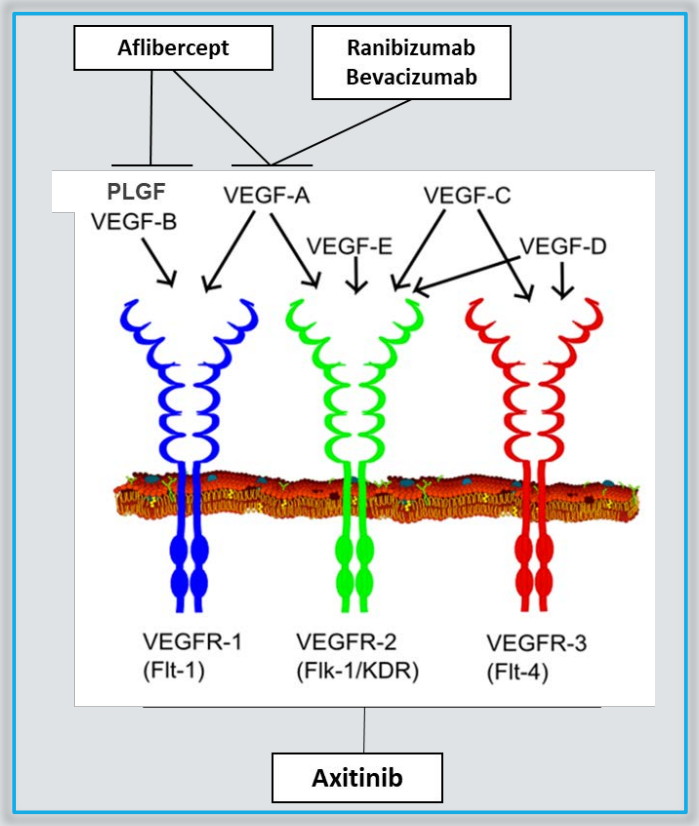


Sources: 1. Heier JS et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012;119:2537-2548. | 2. Brown DM et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. Ophthalmology. 2009;116:57-65.e5. | 3. Rosenfeld PJ et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1419-1431. | 4. Ciulla TA et al. Visual Acuity Outcomes and Anti-Vascular Endothelial Growth Factor Therapy Intensity in Neovascular Age-Related Macular Degeneration Patients: A Real-World Analysis of 49,485 Eyes. Ophthalmol Retina. 2019 May 25. pii: S2468-6530(19)30280-5. | 5. Rao P, Lum F, Wood K, et al. Real-world vision in age-related macular degeneration patients treated with single anti-VEGF drug type for 1 year in the IRIS Registry. Ophthalmology. 2018;125:522e528. | 6. Busbee BG et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology. 2013;120:1046-1056. | 7. Schmidt-Erfurth U et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology. 2014;121:193-201.

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

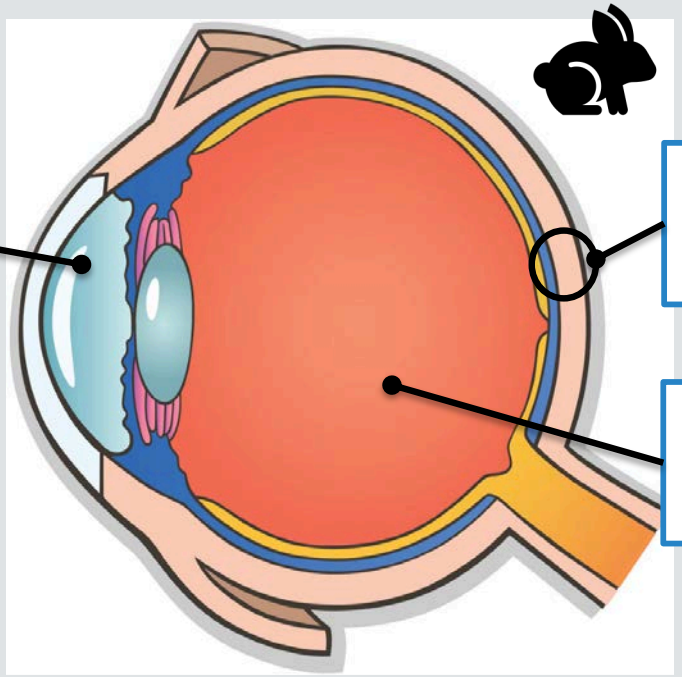


Suprachoroidal Axitinib May Improve Outcomes with Its Broad VEGF Blockade

- 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 prematurity-like abnormal vascular growth in neonatal Rats. Exp Eye Res. 2016. 143: 120-131. | 7. 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. | 8. 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

Suprachoroidal injection of axitinib provides targeted delivery relative to IVT injection of equivalent dose



- -

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

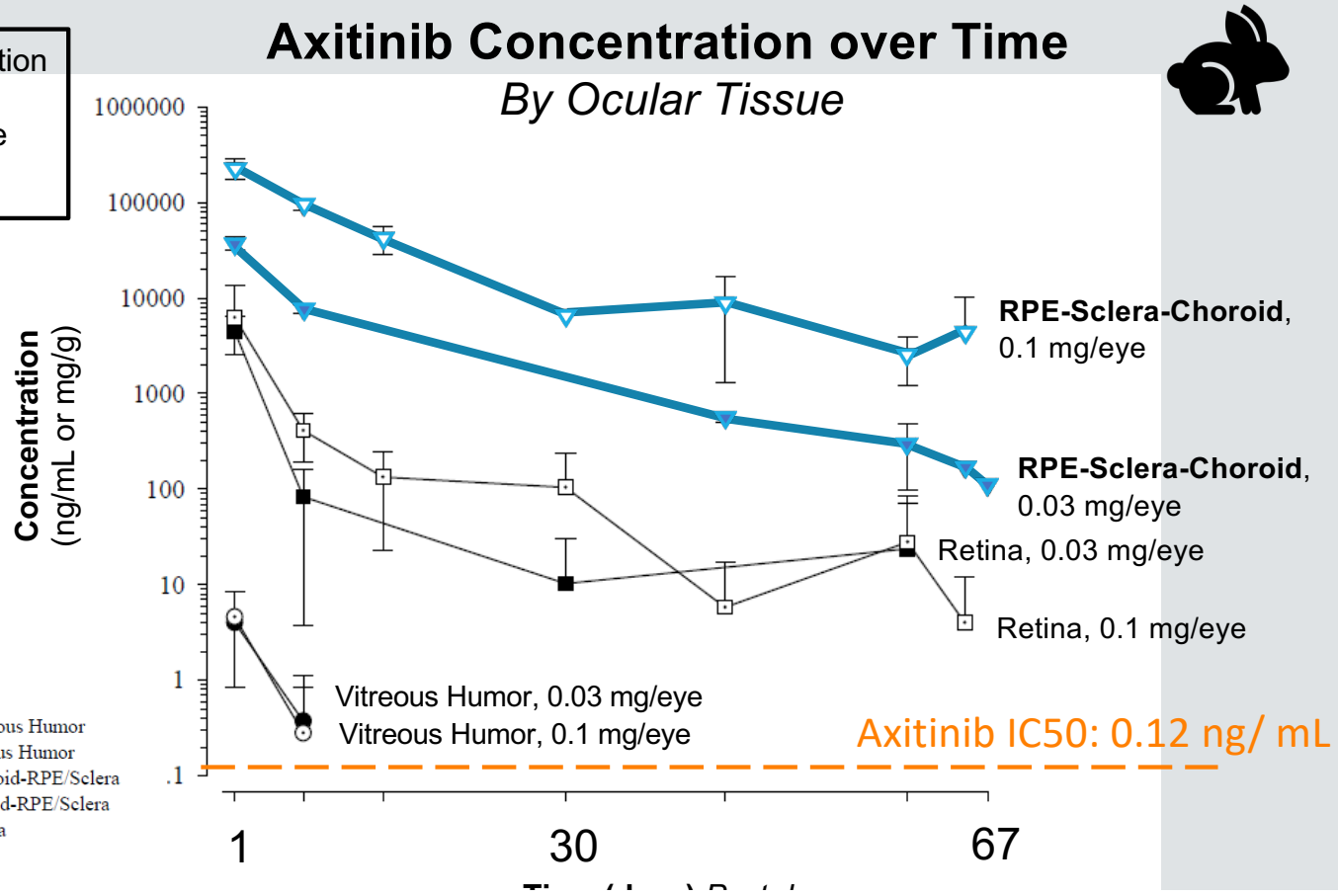
IVT: 1 mg/eye, 25 µL

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

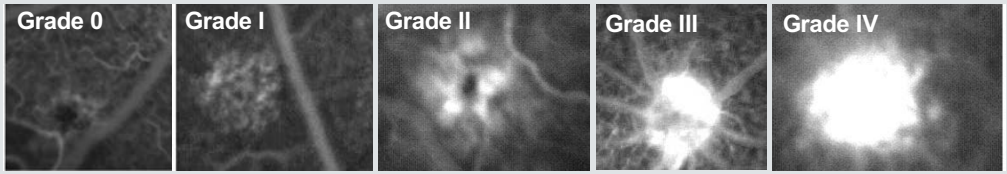
Single bilateral SC injection
0.1 mL/ eye
Group 1: 0.03 mg/eye
Group 2: 0.1 mg/eye



Suprachoroidal injection of axitinib reduces CNV lesion severity versus control in rat model

METHOD

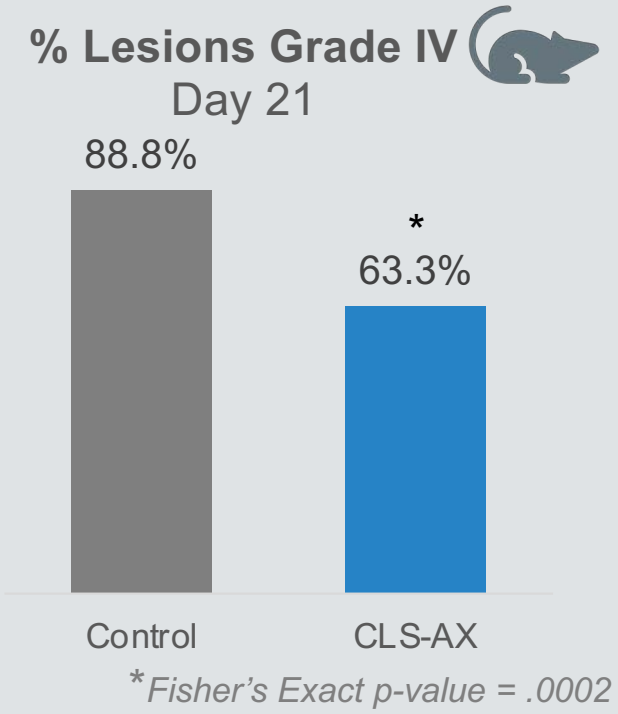
- Laser CNV: 4 lesions per eye
- N=20 eyes (n=10 specimens, bilateral SC injections)
- Two (2) doses, days 1 & 8, 0.4 mg/eye/dose



FLUOROSCEIN ANGIOGRAPHY GRADING SCALE

RESULTS

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



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

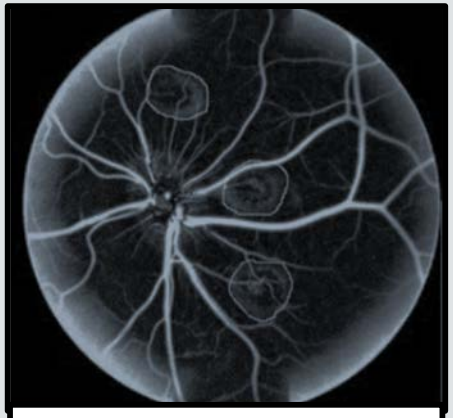
METHOD

- 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

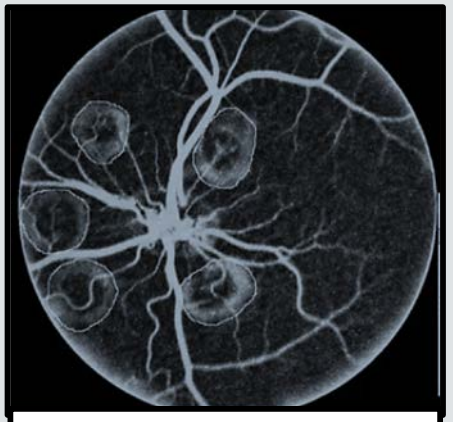
- SC CLS-AX significantly reduced fluorescein leakage
  - 10.5% @ week 1 (p=0.009)
  - 16.0% @ week 2 (p=0.0015)
- SC CLS-AX significantly reduced growth of new blood vessels
  - 18% reduction vs. saline treatment (p=0.03)

CLS-AX treated eye

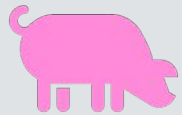


Significantly reduced vascular leakage
(marked region represents original lesion area)

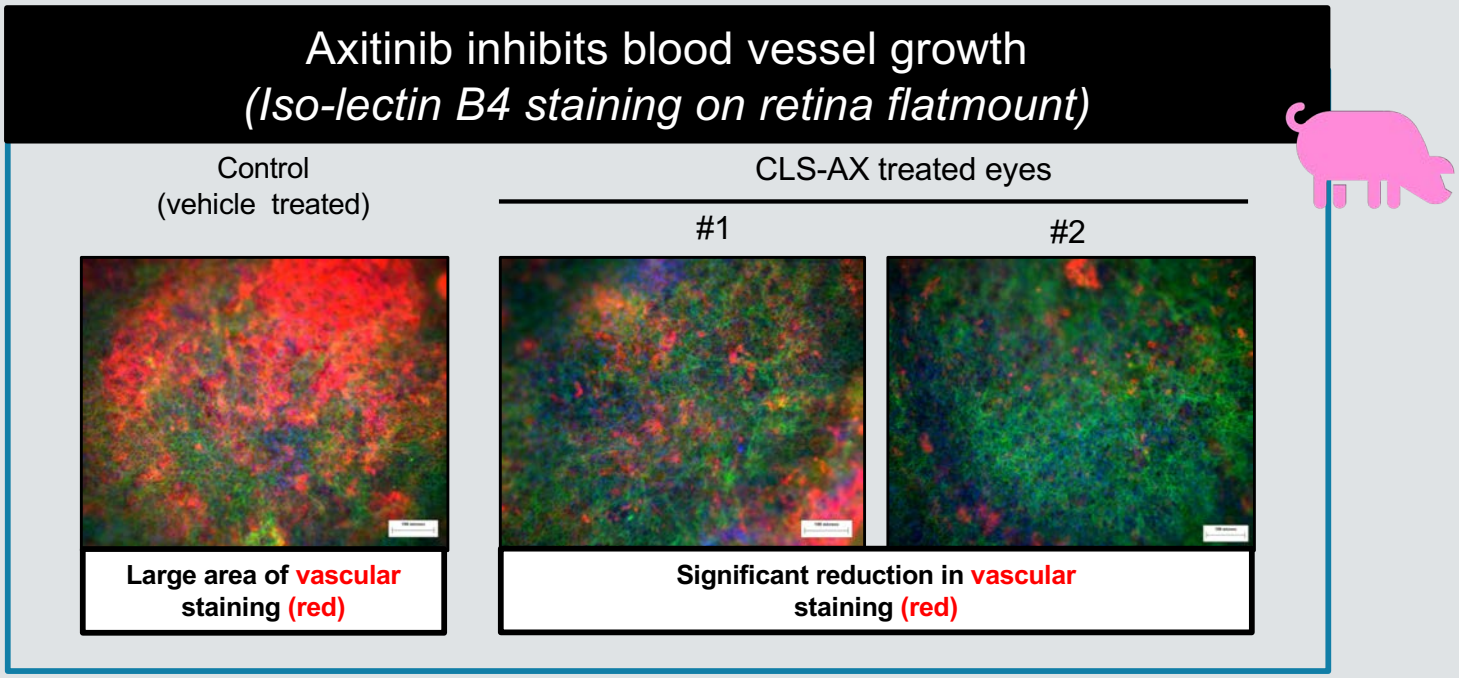
BSS treated eye



Increased vascular leakage
(marked region represents lesion area)



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



Suprachoroidal injection of axitinib was well tolerated in animals

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

OASIS: Phase 1/2A clinical study to evaluate safety and tolerability of CLS-AX in nAMD

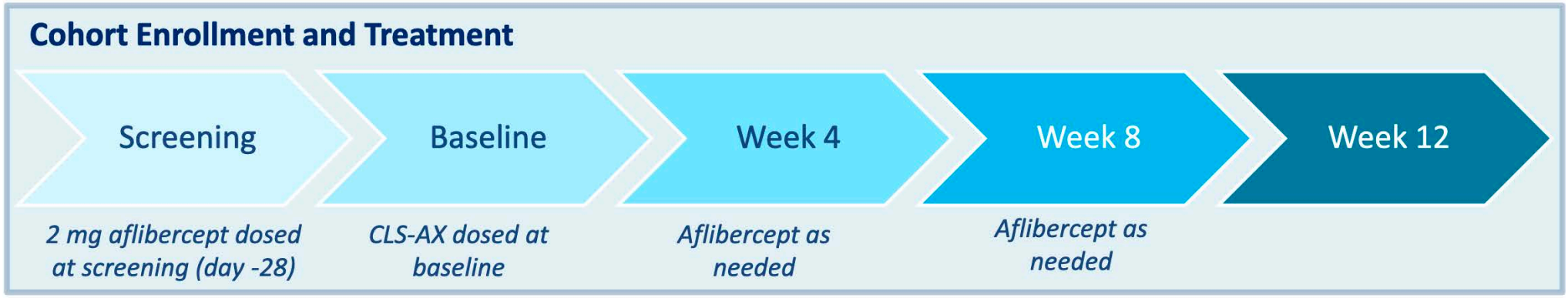
OASIS

Primary Endpoint	Evaluate **safety and tolerability** over 3 months of a single dose of CLS-AX given via suprachoroidal injection following IVT aflibercept

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

OASIS: Phase 1/2A clinical study to evaluate safety and tolerability of CLS-AX in nAMD

- Open-label study to assess the safety and tolerability of a single dose of CLS-AX administered through suprachoroidal injection
- 3 Cohorts with 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




Footage courtesy of Dr. Allen Hu

Suprachoroidal Administration of CLS-AX: Potential Impacts in nAMD

- Suprachoroidal injection of CLS-AX may have the potential to:
  - Reduce treatment burden via durability in the SCS with the customized CLS-AX formulation
  - Improve patient outcomes via targeted delivery to diseased tissues and via potency relative to other tyrosine kinase inhibitors (TKIs)
  - Optimize safety with compartmentalized delivery
  - Minimize the ceiling of efficacy via pan-VEGF inhibition
- Phase 1/2a OASIS clinical trial for nAMD currently enrolling