Suprachoroidal Administration of Small Molecule and Nanoparticle Suspensions: Pre-Clinical Results Correlate to Clinical Trial Outcomes

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1. Illinois Retina Associates, S.C. and Rush University Medical Center; 2. Clearside Biomedical, Inc.

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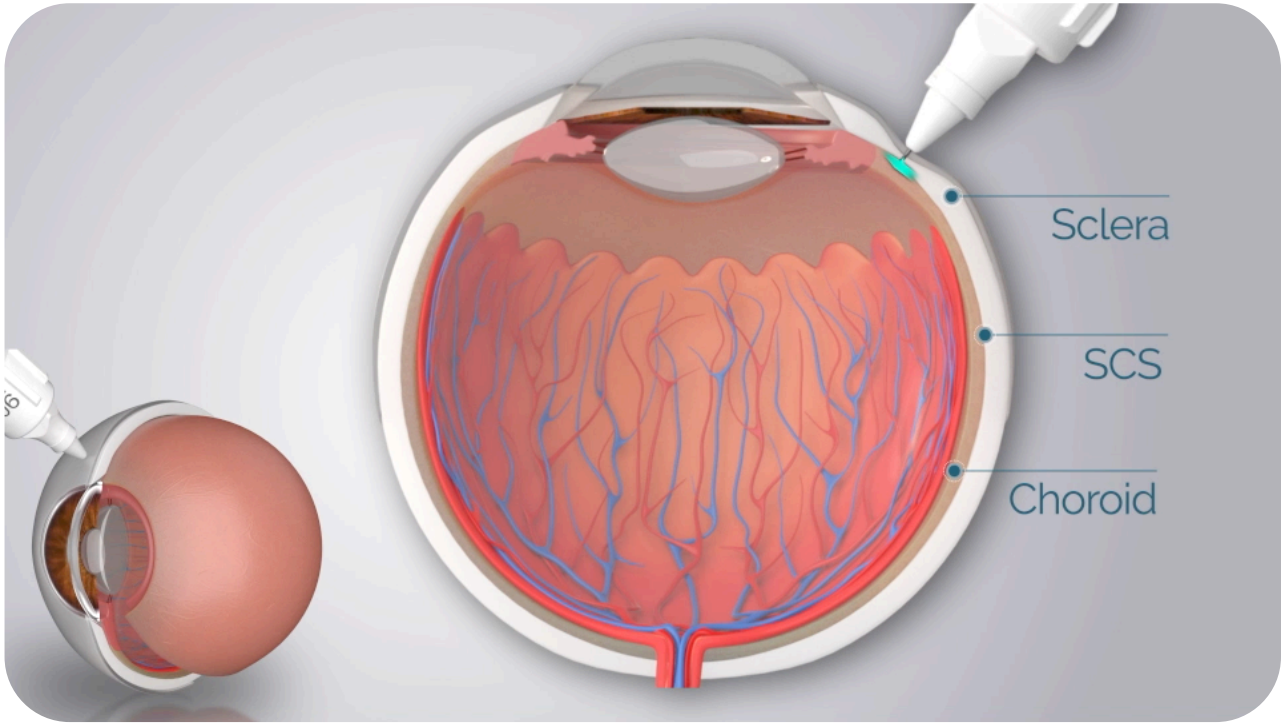
- TC: Clearside Biomedical - Employee & Shareholder
- VK: Clearside Biomedical - Employee & Shareholder

Injection into the Suprachoroidal Space (SCS)

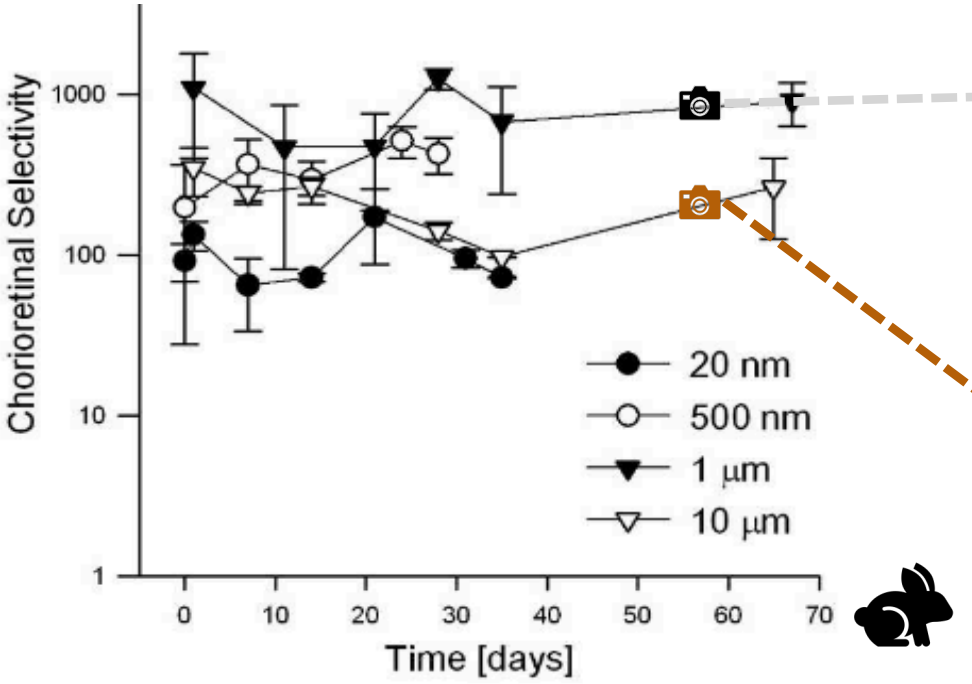


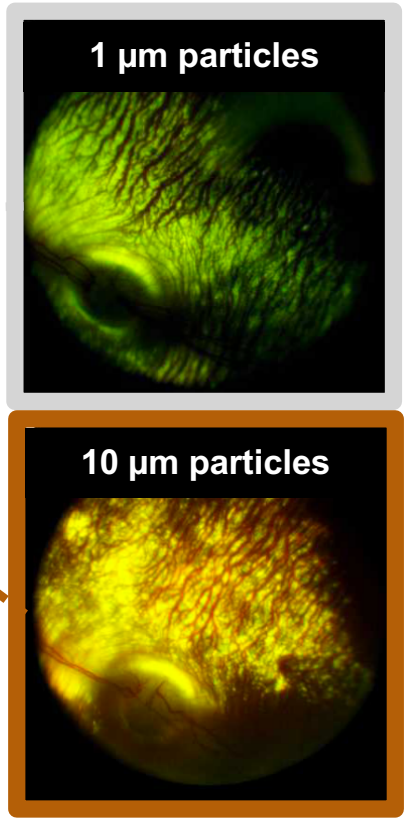
Suprachoroidal Injection (SCI)
with the SCS Microinjector®

Durability in the SCS for particles ranging from the size of small molecule suspensions, to DNA nanoparticles, to AAV

Fundus Images under Fluorescence
in vivo, 60 days post injection

Chorioretinal Selectivity of SCS Administration
SCS Administration of various particle sizes in rabbit model

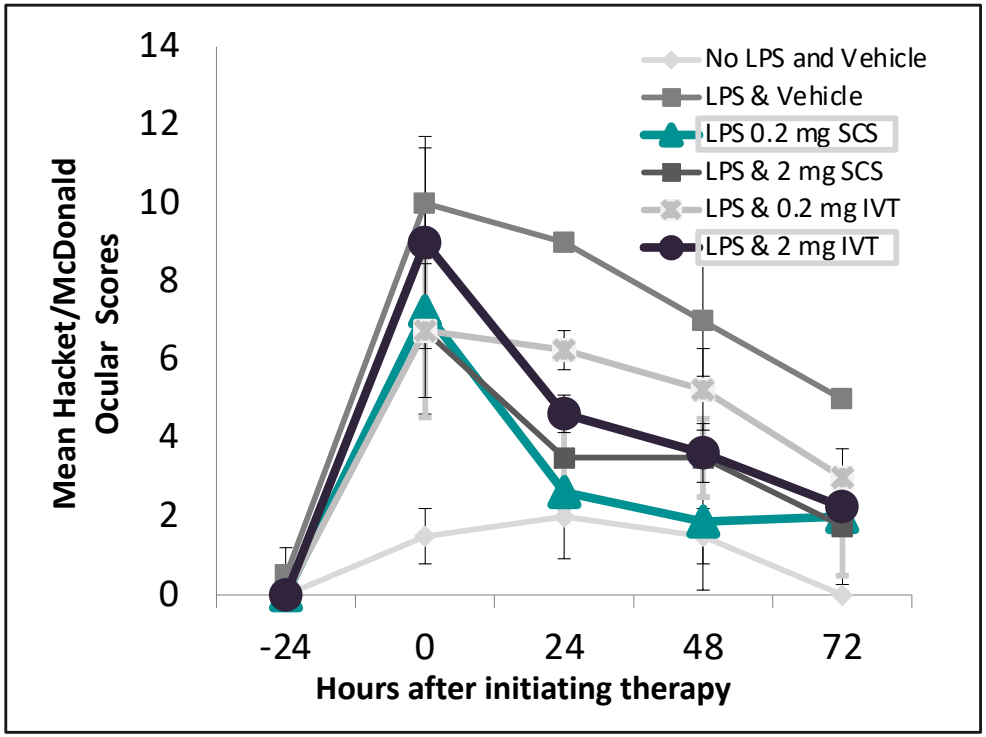


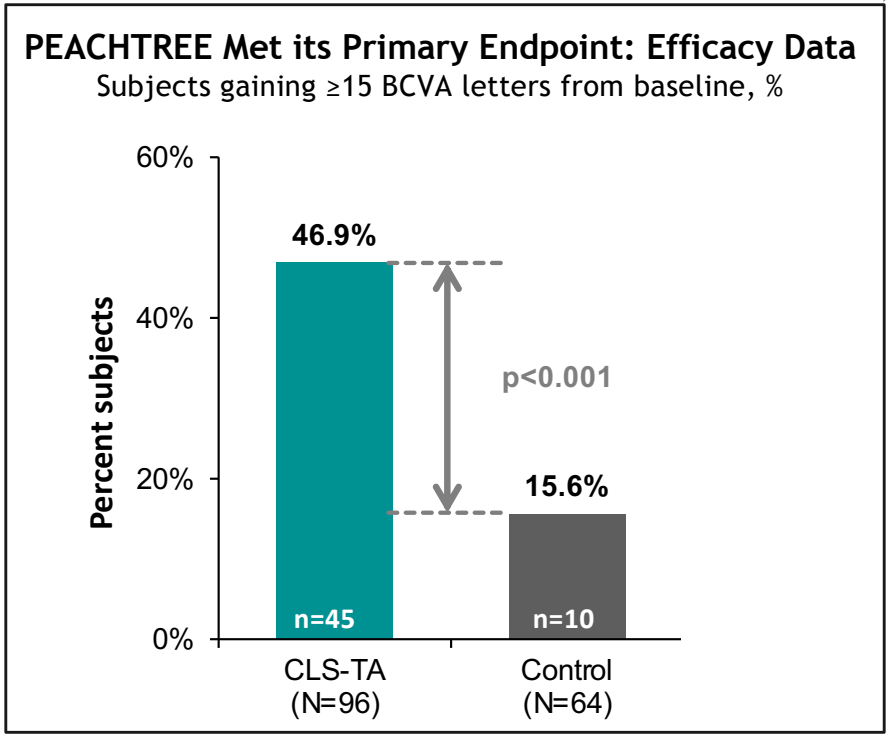


Patel SR, Berezovsky DE, McCarey BE, Zarnitsyn V, Edelhauser HF, Prausnitz MR. Targeted administration into the suprachoroidal space using a microneedle for drug delivery to the posterior segment of the eye. Invest Ophthalmol Vis Sci. 2012;53(8):4433-4441. Published 2012 Jul 1. doi:10.1167/iovs.12-9872

Preclinical efficacy corroborated in PEACHTREE Ph 3 trial for small molecule triamcinolone acetonide (TA)

Preclinical → **Clinical Trial**

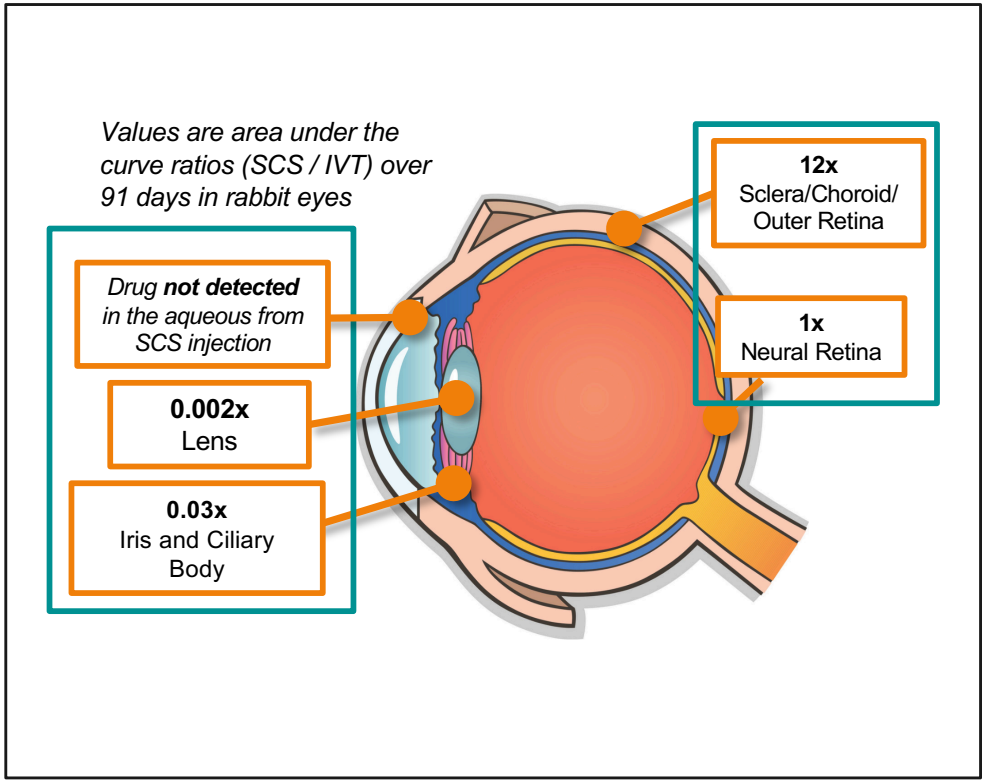




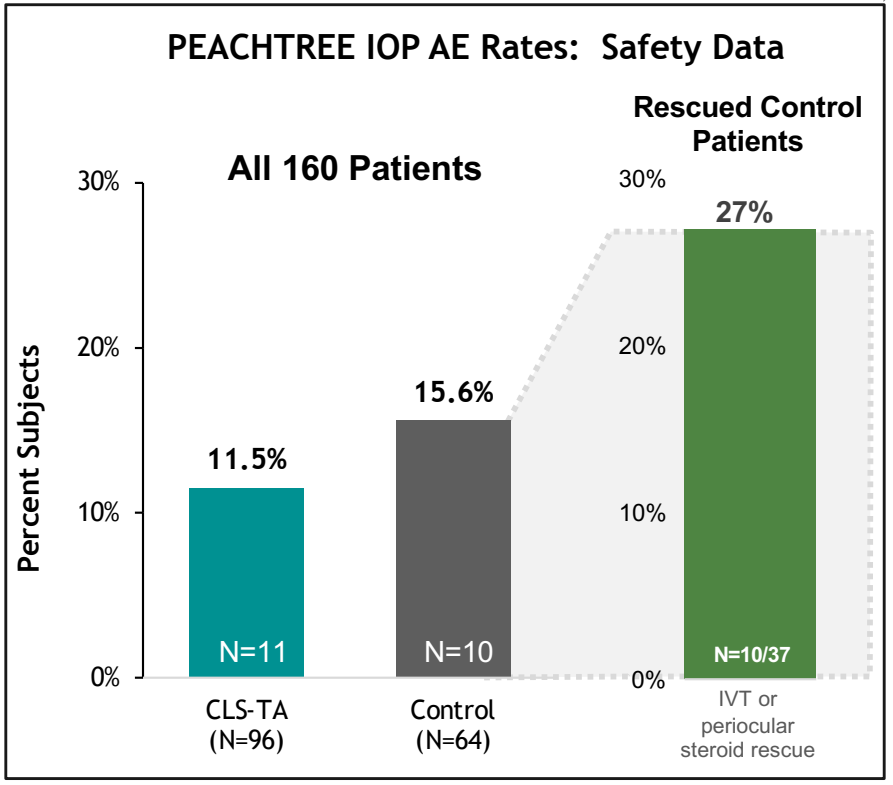
Source: Gilger, et al, *Treatment of Acute Posterior Uveitis in a Porcine Model by Injection of Triamcinolone Acetonide into the Suprachoroidal Space Using Microneedles*, Physiology and Pharmacology

Preclinical safety & compartmentalization corroborated in PEACHTREE Ph 3 trial for small molecule TA

Preclinical

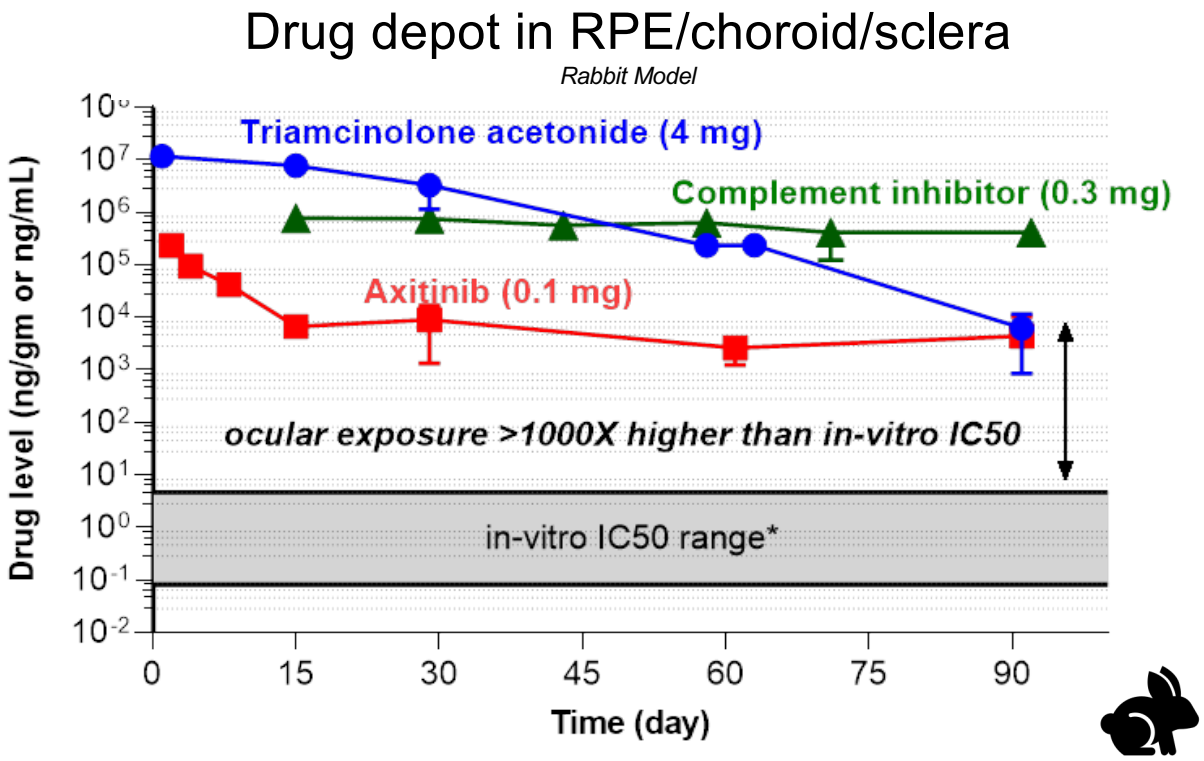


Clinical Trial



Source: Edelhauser HF, et al. ARVO Annual Meeting. 2013. | Phase 3 clinical trial data.

SCI of TKI (axitinib) and complement inhibitor yielded high and durable drug levels in RPE/choroid/sclera

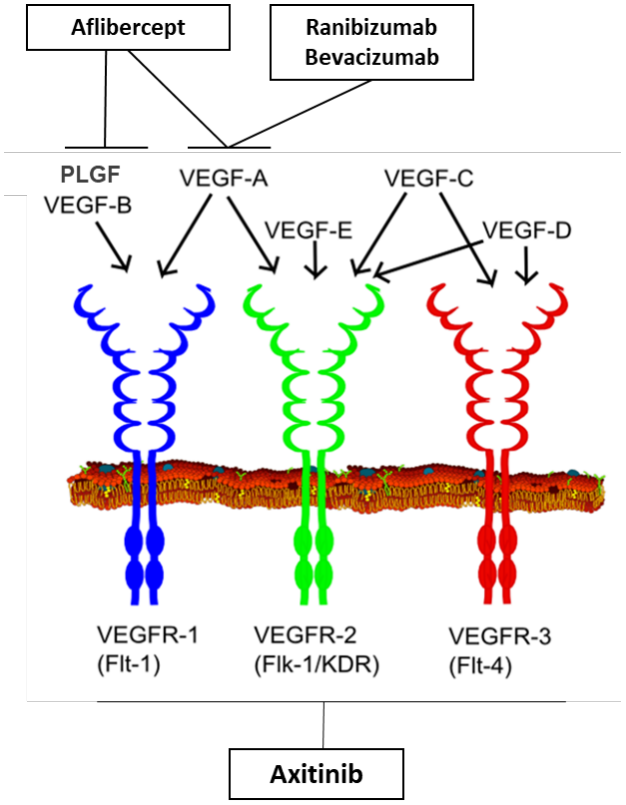


*References for in-vitro IC50 range:
Stellato et al. J Allergy Clin Immunol. 1999; volume 104, number 3, part 1
Yuan et al. Haematologica. 2017 Mar; 102(3): 466–475.
Inlyta, EMA. 2012 May; CHMP assessment report

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



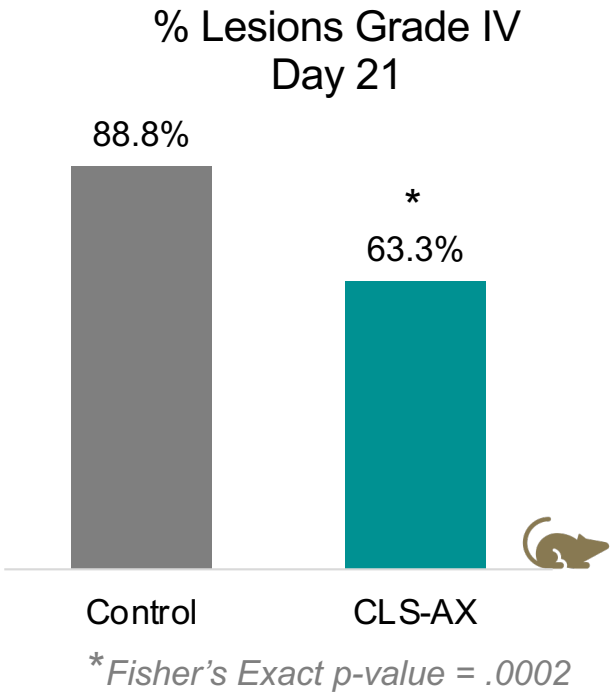
Axitinib Suprachoroidally Injected May Improve Outcomes with Its Broad VEGF Blockade

- 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 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.008. ISSN 2002-4436. Public Domain.

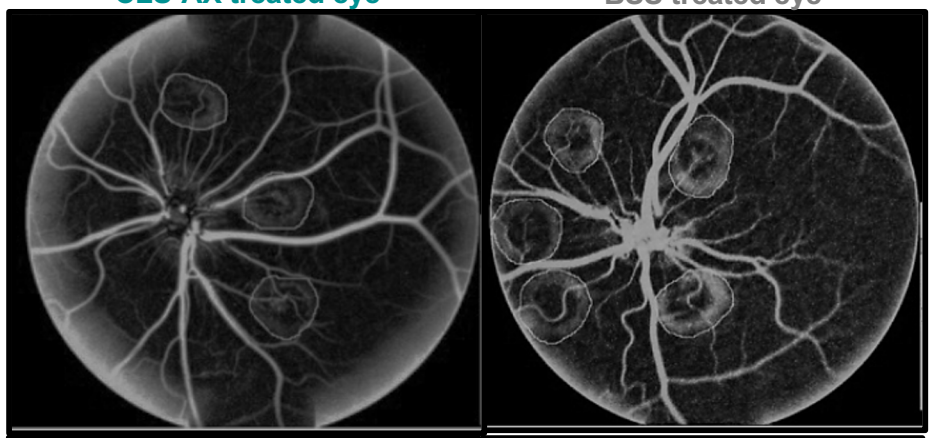
Preclinical models demonstrated signs of efficacy with TKI axitinib

In animal models, suprachoroidal axitinib (CLS-AX) treated groups experienced a reduction in severe lesions at Day 21, and significantly reduced vascular leakage



*Fisher's Exact p-value = .0002

NEOVASCIULARIZATION: Leakage



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

Increased vascular leakage
(marked region represents lesion area)

Phase 1/2A Trial Design: OASIS Clinical trial

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

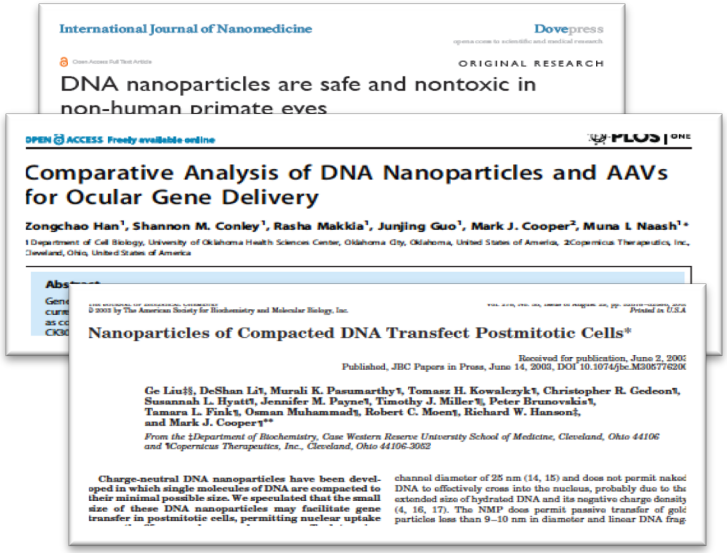
DNPs offer the potential for safe, efficacious, and repeat dosing ocular gene therapy

Potential Advantages

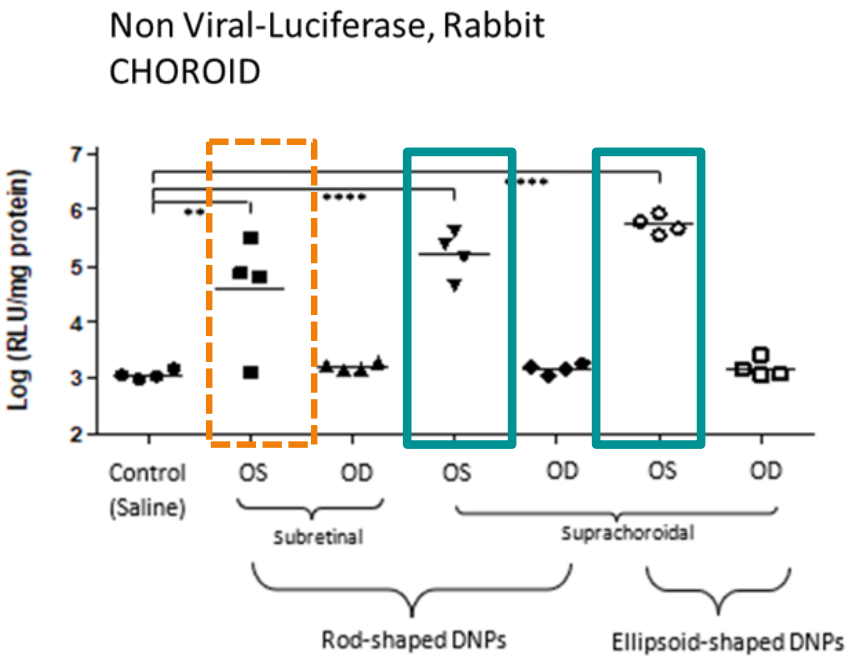
- Efficacy: Demonstrated in numerous ocular animal models
  - Transfer large genes (up to ~20 kb)

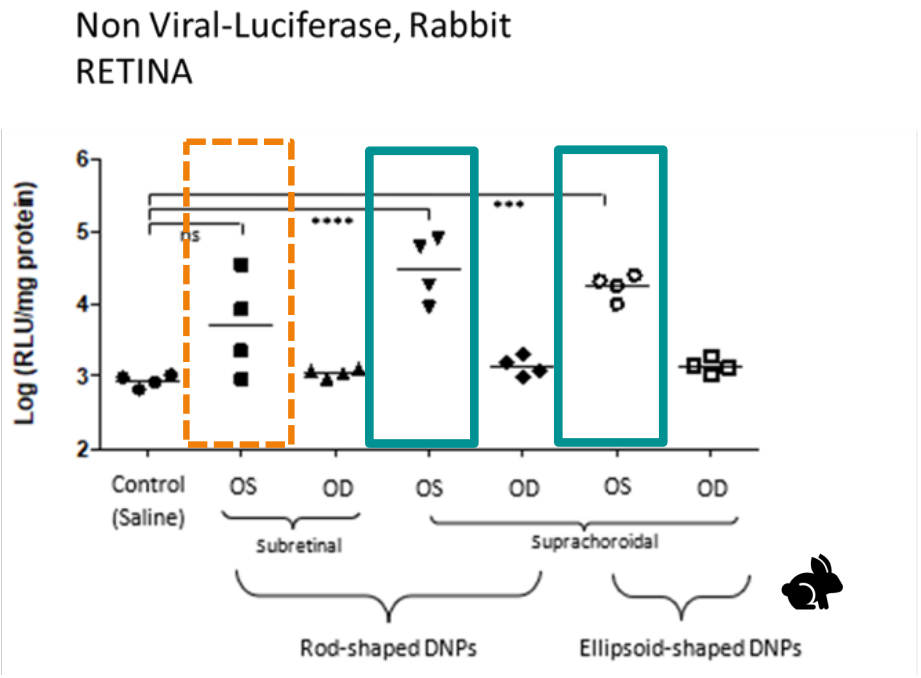
- Safety: Non-immunogenic, without viral capsid proteins or pre-existing immunity.
  - Potential for repeat dosing
  - Higher doses possible to enhance transfection

Well established literature on DNA nanoparticle gene therapy



Suprachoroidal DNPs demonstrated similar activity to subretinal DNPs





1-way ANOVA, $p<0.0001$.
Bonferroni's test: *$p<0.05$, ** $p<0.01$, ***$p<0.001$,

Two Phase 2 Trials Using SCS Microinjector® for delivery of viral vector RX-314

- RGX-314 for Treatment of wet AMD
  - **Phase 2 AAVIATE trial of suprachoroidal delivery of RGX-314 using SCS Microinjector is ongoing**.
  - Initial Safety Data from Cohort 1 expected in early 2021.
- RGX-314 for Treatment of Diabetic Retinopathy (DR)
  - Phase 2 ALTITUDE trial of suprachoroidal delivery of RGX-314 using SCS Microinjector is ongoing.
  - **First patient enrolled 12/2020** with interim data expected in 2021.

Suprachoroidal delivery of viral-like particle (VLP, AU-011) for choroidal melanoma in Phase 1B/2 Trial

- Suprachoroidal injection of AU-011* resulted in excellent distribution and duration in over 75% of the suprachoroidal space in preclinical models
- Drug exposure in the SC space lasted for at least 10 days
- Suprachoroidal injection of AU-011 followed by photoactivation resulted in a robust tumor response in an orthotopic rabbit choroidal melanoma model

Study results support further evaluation of AU-011 administration directly into the suprachoroidal space as a potential first line treatment for primary choroidal melanoma

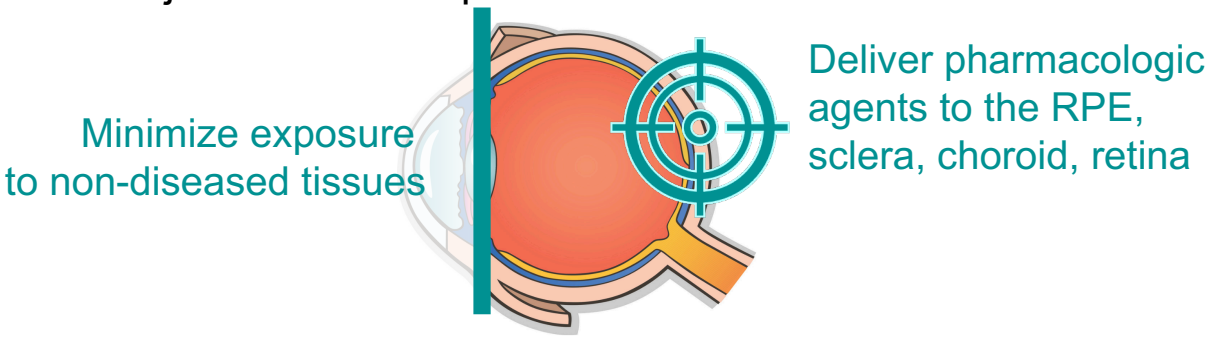
Clinical trial for suprachoroidal delivery of AU-011 ongoing

* VLP-488 has the same physicochemical characteristics as AU-011. VLP-488 is the same VLP as in AU-011 conjugated to AlexaFluor488

Savinainen et al, Ocular distribution and efficacy after suprachoroidal injection of AU-011 for treatment of ocular melanoma, ARVO 2020

Suprachoroidal Injection of Small Molecule Suspensions & Nanoparticles

- May provide an office-based method to target pharmacologic agents to the RPE, sclera, choroid, and retina
- Efficacy and safety results in preclinical models corroborated favorable clinical trial results for suprachoroidal delivery of triamcinolone acetonide for ME associated with NIU
- Four clinical trials are currently enrolling that utilize suprachoroidal injection with the SCS Microinjector®
  - Suprachoroidally injected Axitinib for wet AMD
  - Suprachoroidally injected viral vector RX-314 for wet AMD and DR
  - Suprachoroidal injected viral like particle AU-011 for choroidal melanoma



Thank you