Suprachoroidal Delivery of Small Molecule Suspensions and Nanoparticles

Judy E. Kim, MD[1]

Thomas Ciulla, MD, MBA[2]

Viral Kansara, PhD[2]

Retina Society
Virtual Annual Meeting
2020

1. Medical College of Wisconsin. 2. Clearside Biomedical, Inc.

Financial Disclosures

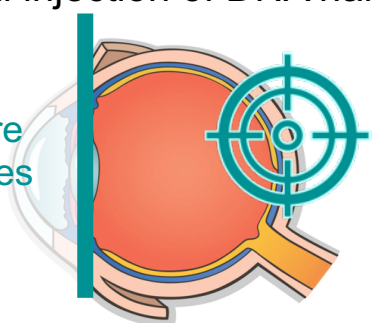
- JK: Advisory Boards – Adverum, Allergan, Clearside Biomedical, Genentech, Notal Vision, Novartis, Regeneron

  Data Safety Monitoring Boards – Gemini, Lineage
- TC: Employee & Shareholder – Clearside Biomedical
- VK: Employee & Shareholder – Clearside Biomedical

Suprachoroidal Injection of Small Molecule Suspensions and Nanoparticles

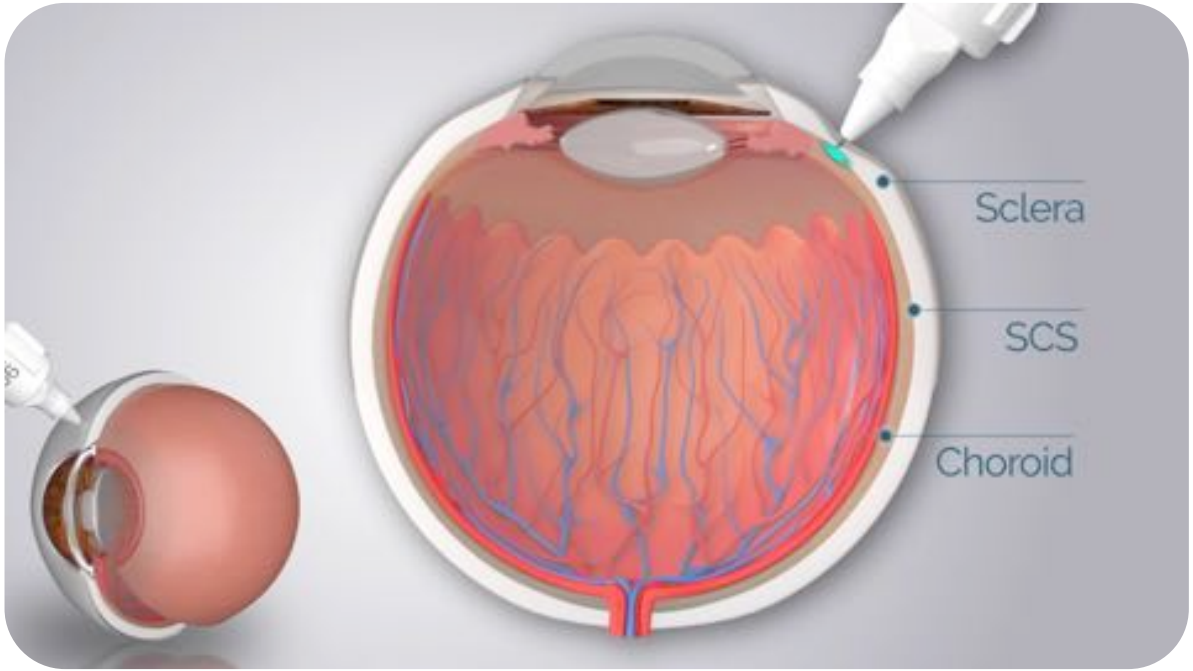
- May provide an office-based method to target pharmacologic agents to the RPE, sclera, choroid and retina
- Efficacy and safety results in preclinical models corroborated favorable clinical trial results for suprachoroidal delivery of triamcinolone acetonide for ME associated with NIU
- In preclinical models:
  - Tyrosine kinase inhibitor (TKI, axitinib) and complement inhibitor show promising results
  - Suprachoroidal and subretinal injection of DNA nanoparticles showed similar expression of a marker gene

Minimize exposure
to non-diseased tissues



Deliver pharmacologic
agents t the RPE,
sclera, choroid, retina

Injection into the Suprachoroidal Space (SCS)

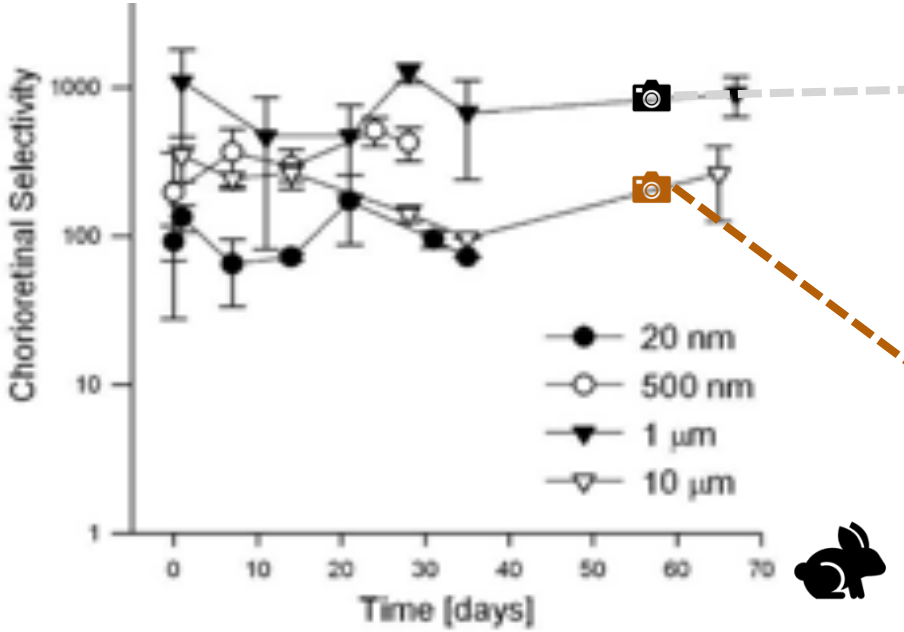


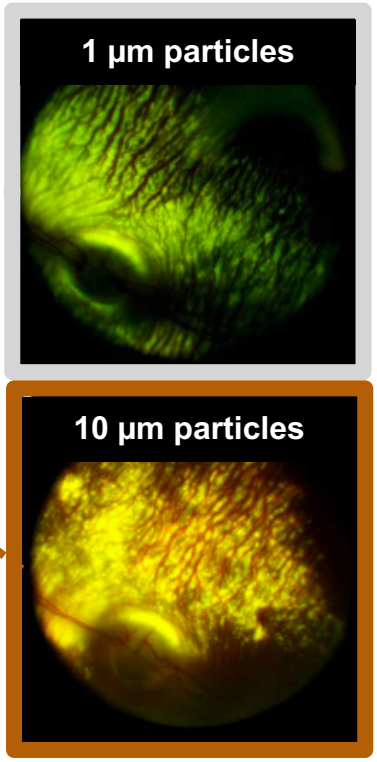
Suprachoroidal Injection (SCI)
with the SCS Microinjector®

Durability in the SCS for particles ranging from the size of small molecules 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



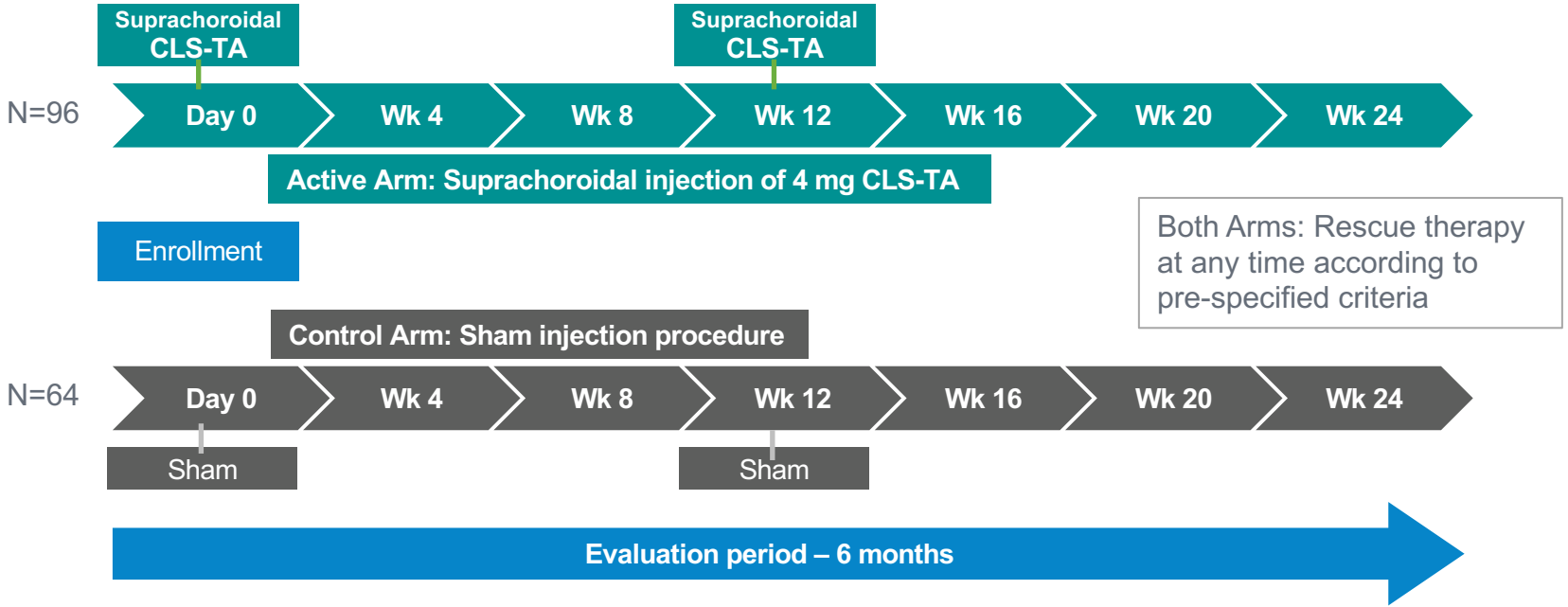


Patel SR, Berezovsky DE, McCarey BE, Zarnitsyn V, Edelhauser HF, Prausnitz MR. Targeted administration into the suprachoroidal space using a microneedle for drug delivery to the posterior segment of the eye. Invest Ophthalmol Vis Sci. 2012;53(8):4433-4441. Published 2012 Jul 1. doi:10.1167/iovs.12-9872

PEACHTREE: Phase 3, Randomized, Controlled, Double-Masked, Multicenter Trial

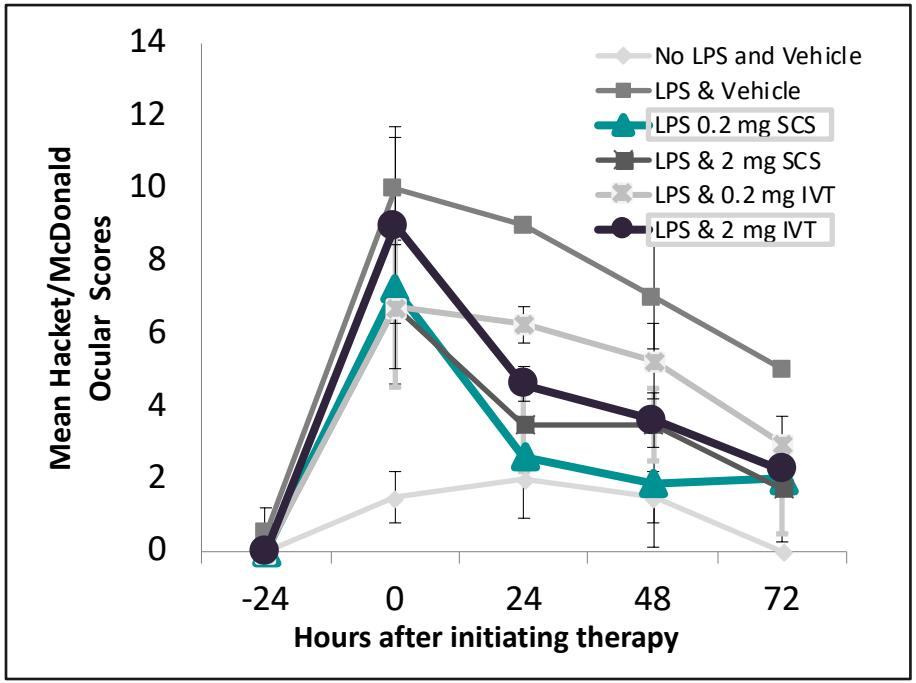
PEACHTREE

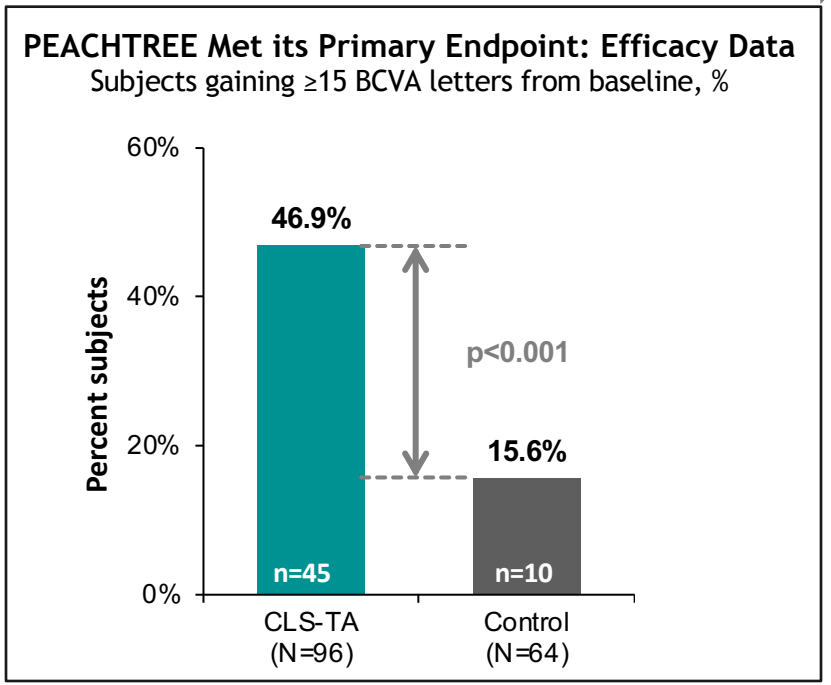
Primary Endpoint: Visual Acuity



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

Preclinical → **Clinical Trial**

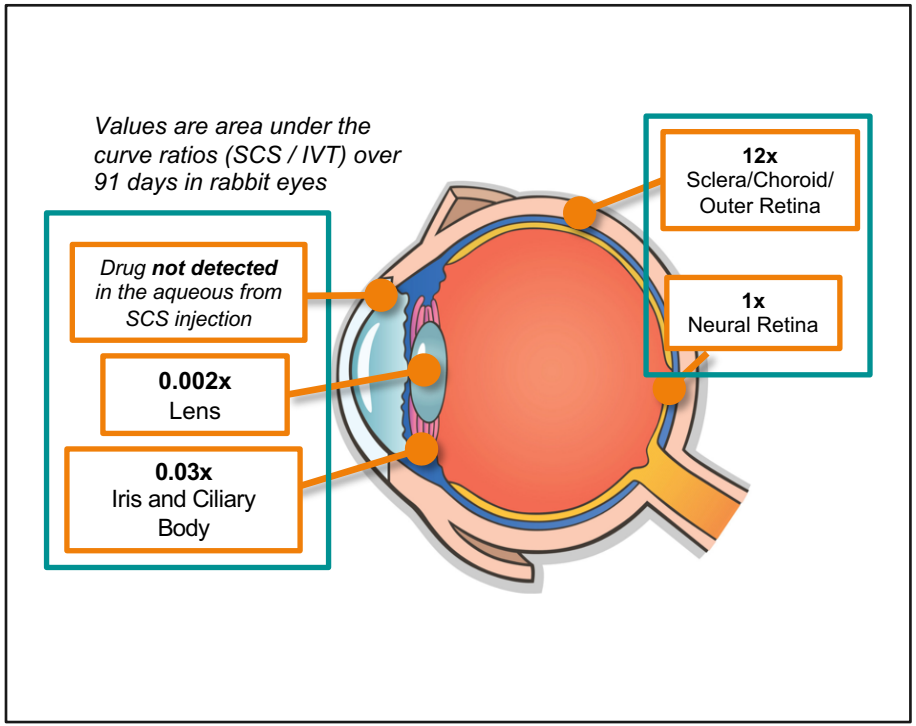




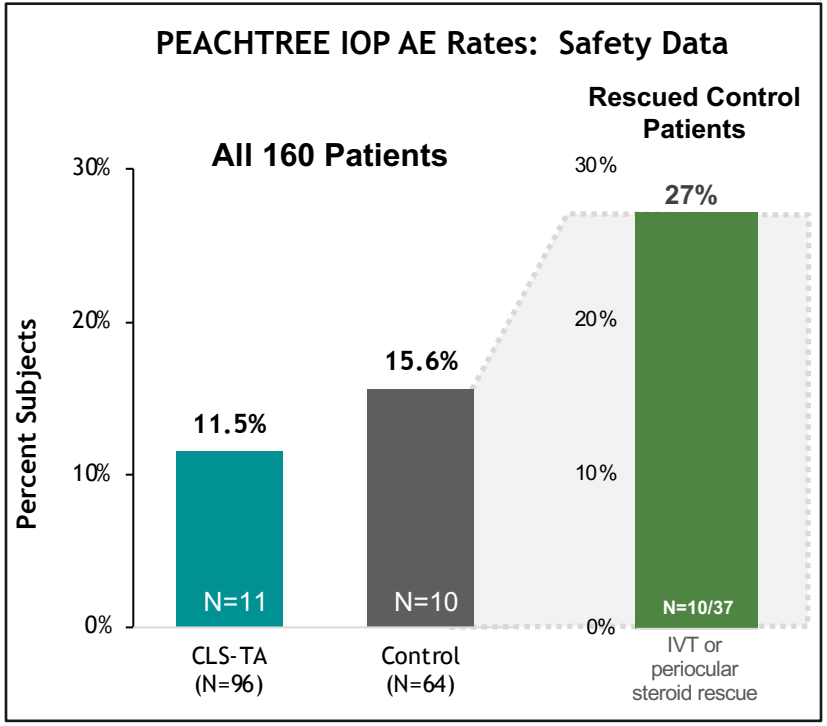
Source: Gilger, et al, *Treatment of Acute Posterior Uveitis in a Porcine Model by Injection of Triamcinolone Acetonide into the Suprachoroidal Space Using Microneedles*, Physiology and Pharmacology

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

Preclinical



Clinical Trial



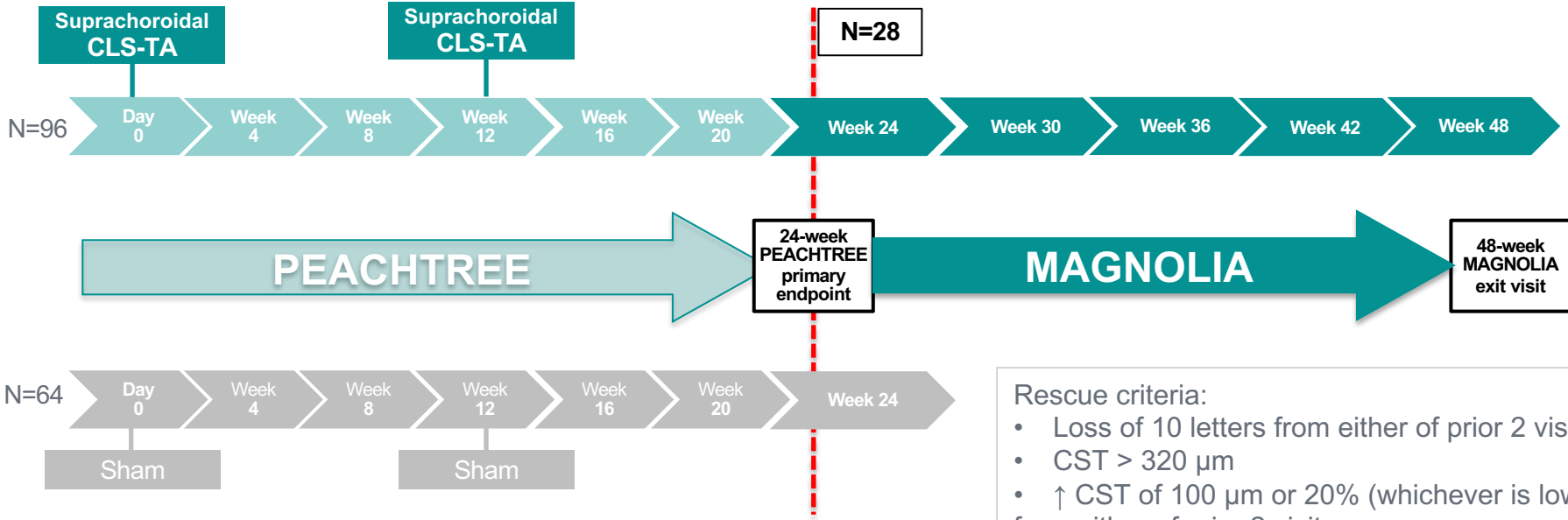
Source: Edelhauser HF, et al. ARVO Annual Meeting. 2013. | Phase 3 clinical trial data.

MAGNOLIA: Prospective, Non-interventional, Masked, Observational 24-week Extension Trial

MAGNOLIA

Primary Endpoint: Time to rescue therapy relative to Day 0 of PEACHTREE

*To be eligible for MAGNOLIA, subjects must have completed PEACHTREE and **NOT** have received rescue medication*

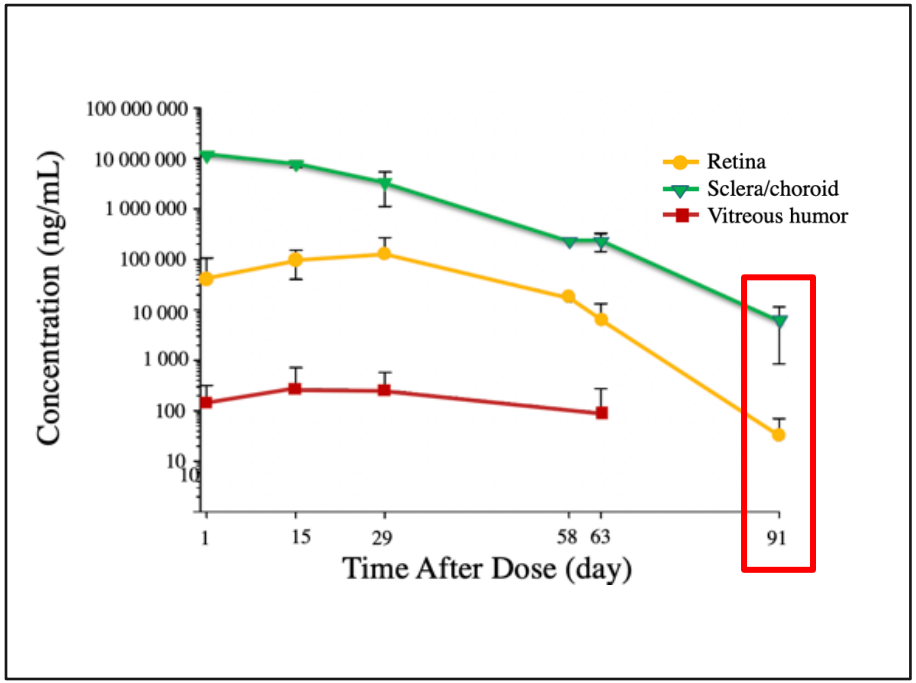


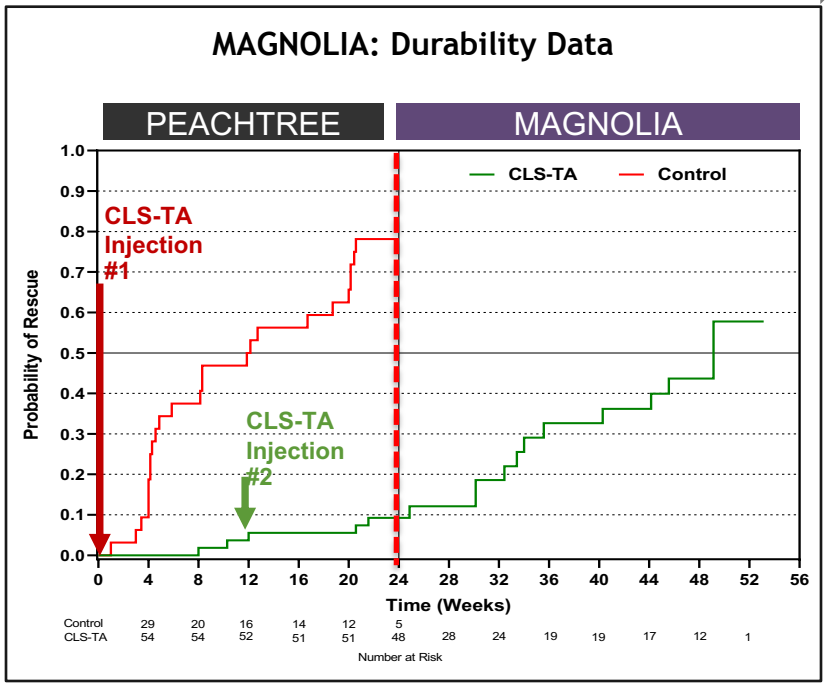
Rescue criteria:

- Loss of 10 letters from either of prior 2 visits
- CST > 320 µm
- ↑ CST of 100 µm or 20% (whichever is lower) from either of prior 2 visits
- Investigator discretion

Preclinical durability corroborated in PEACTHREE & MAGNOLIA trials for small TA

Preclinical → **Clinical Trial**



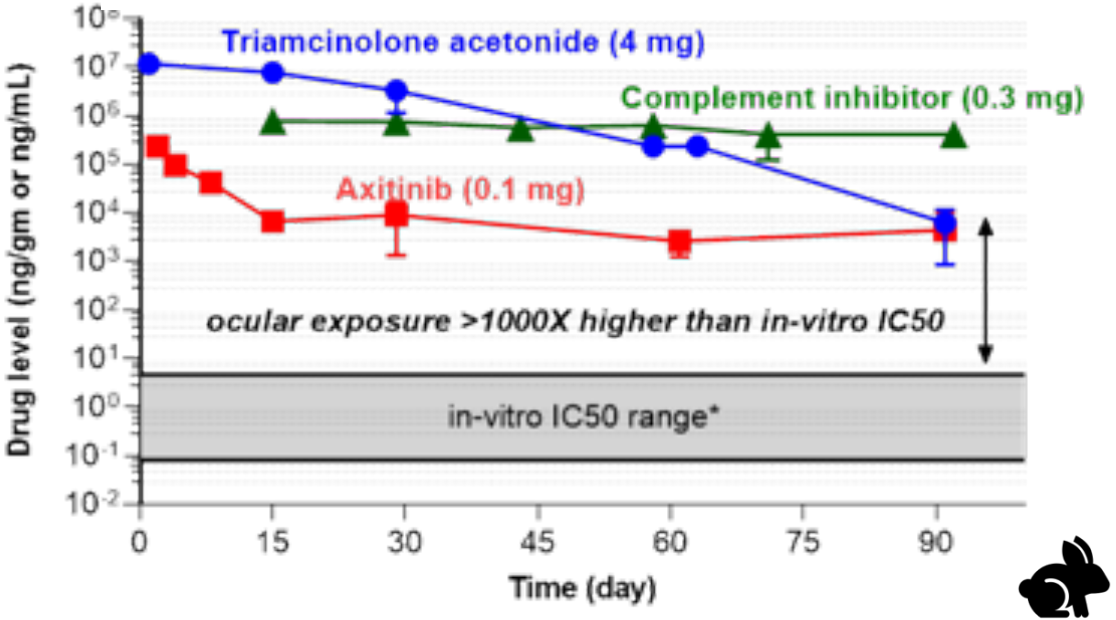


Sources: Gilger, et al, *Treatment of Acute Posterior Uveitis in a Porcine Model by Injection of Triamcinolone Acetonide into the Suprachoroidal Space Using Microneedles,* Physiology and Pharmacology | Phase 3 PEACHTREE data; MAGNOLIA data

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

Drug depot in RPE/choroid/sclera

Rabbit Model

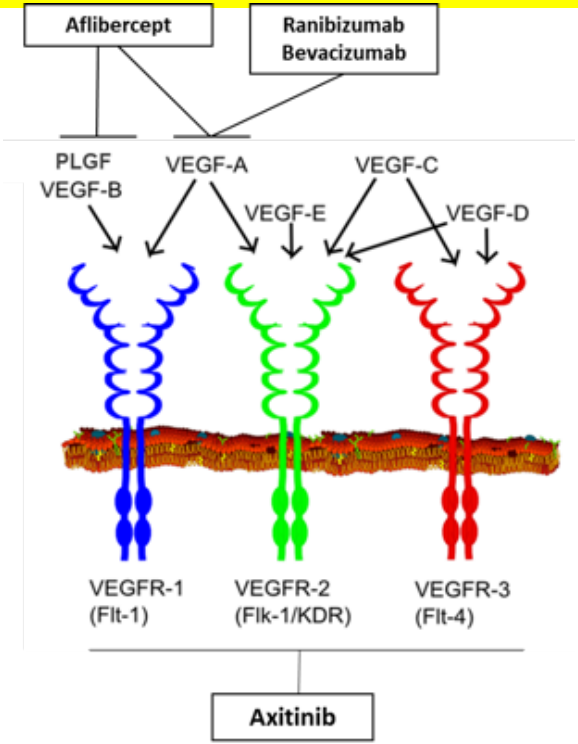


*References for in-vitro IC50 range:
Stellato et al. J Allergy Clin Immunol. 1999; volume 104, number 3, part 1
Yuan et al. Haematologica. 2017 Mar; 102(3): 466–475.
Inlyta, EMA. 2012 May; CHMP assessment report

Anti-Vascular Endothelial Growth Factor Treatment Approaches in AMD

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



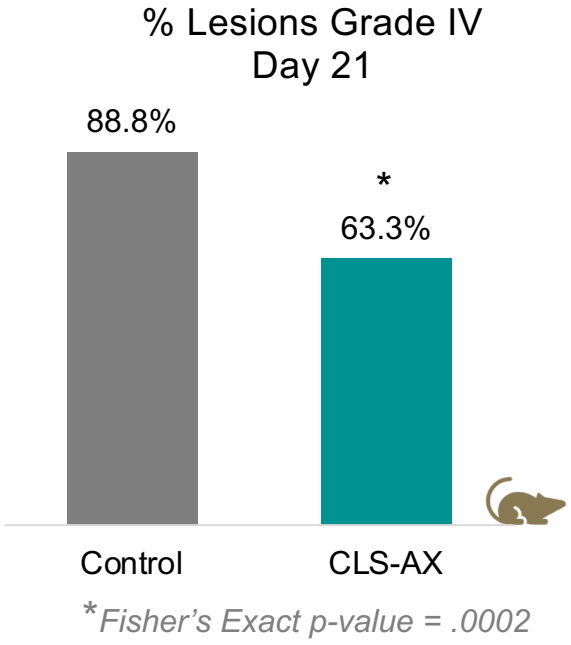
Axitinib Suprachoroidally Injected May Improve Outcomes with Its Broad VEGF Blockade

- 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.

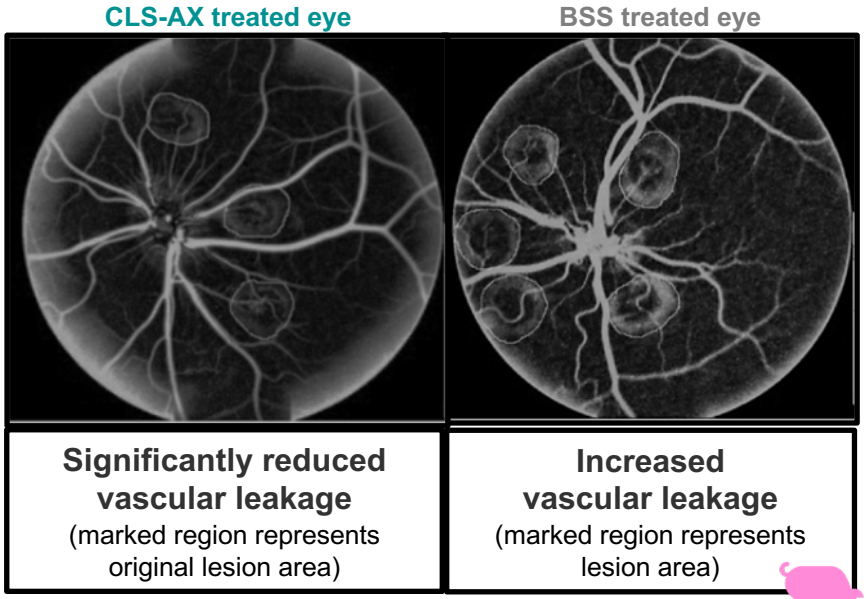
Preclinical models demonstrated signs of efficacy with TKI axitinib

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



*Fisher's Exact p-value = .0002

NEOVASCIULARIZATION: Leakage



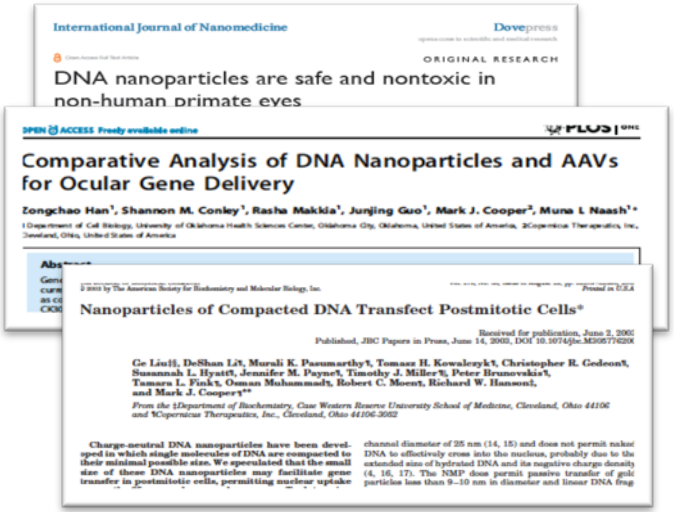
DNPs offer the potential for safe, efficacious, and repeat dosing ocular gene therapy

Potential Advantages

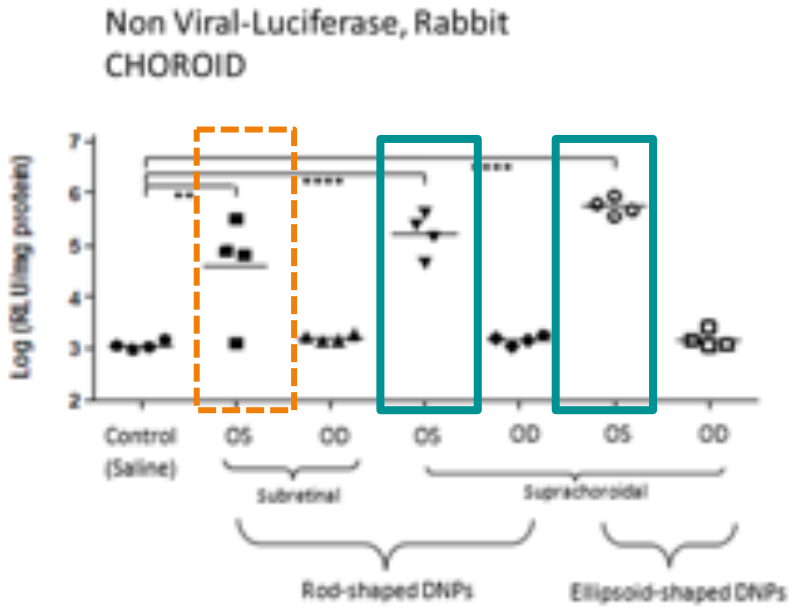
- Efficacy: Demonstrated in numerous ocular animal models
  - Transfer large genes (up to ~20 kb)

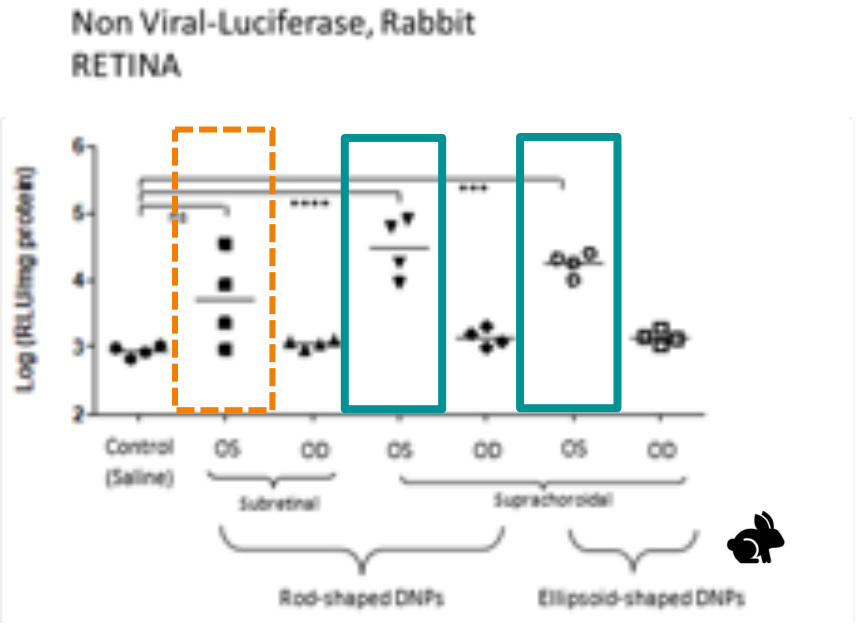
- Safety: Non-immunogenic, without viral capsid proteins or pre-existing immunity.
  - Potential for repeat dosing
  - Higher doses possible to enhance transfection

Well established literature on DNA nanoparticle gene therapy



Suprachoroidal DNPs demonstrated similar activity to subretinal DNPs



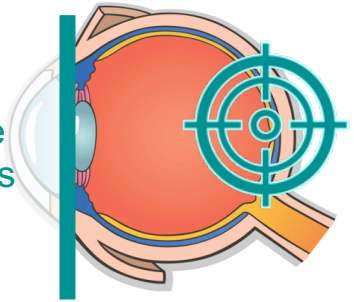


1-way ANOVA, $p<0.0001$.
Bonferroni's test: *$p<0.05$, ** $p<0.01$, ***$p<0.001$,

Suprachoroidal Injection of Small Molecule Suspensions and 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
- In preclinical models:
  - Tyrosine kinase inhibitor (TKI, axitinib) and complement inhibitor show promising results
  - Suprachoroidal injection of DNA nanoparticles showed similar expression of a marker genes subretinal administration

Minimize exposure to non-diseased tissues



Deliver pharmacologic agents t the RPE, sclera, choroid, retina