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

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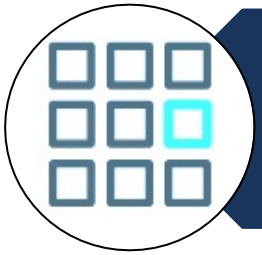
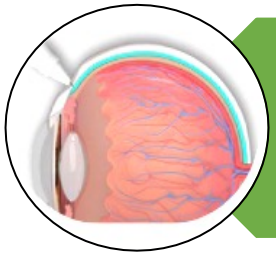
- TC: Clearside Biomedical - Employee & Shareholder
- VK: Clearside Biomedical - Employee & Shareholder

In-office access to posterior ocular tissues via the Suprachoroidal Space (SCS)

To understand the potential of the SCS



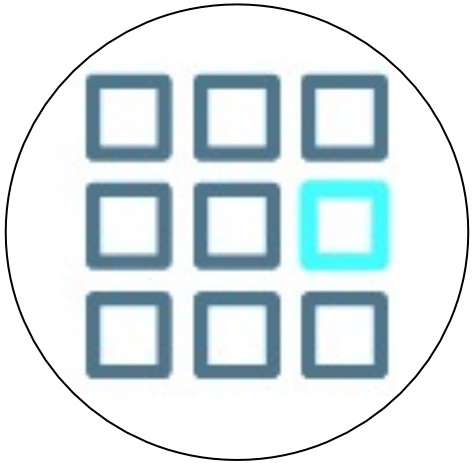
1. How do therapies **compartmentalize**?



2. What drives **durability**?

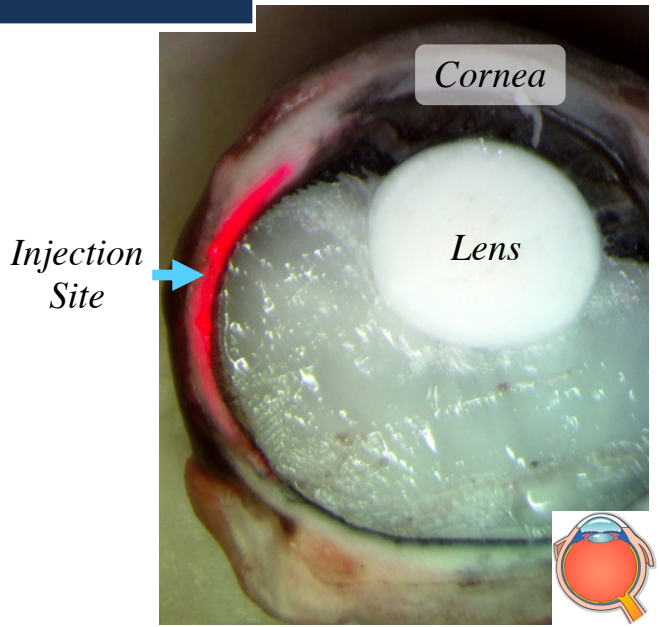
3. How do therapies **reach the macula**?

1. How do therapies compartmentalize?

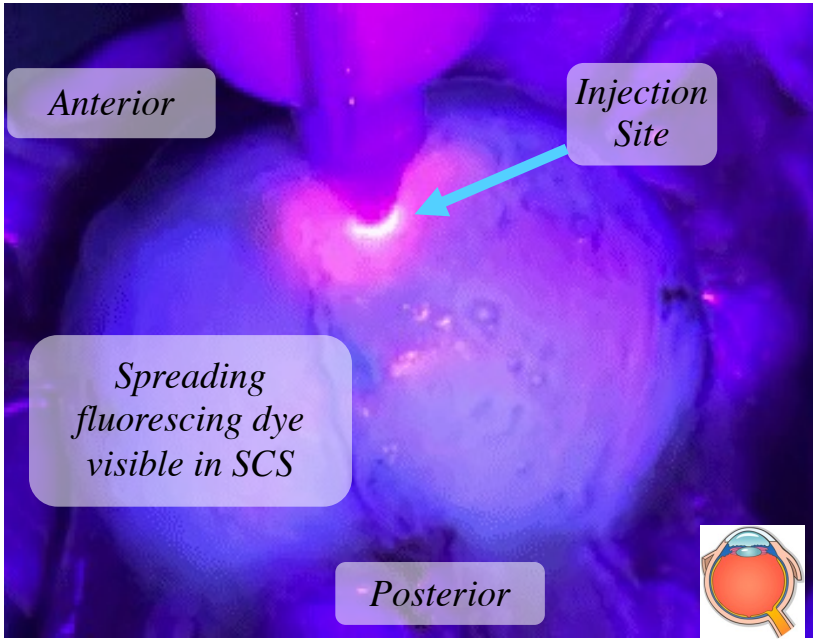


Suprachoroidal injection of dye shows posterior circumferential spread around the globe in porcine model

COMPARTMENTALIZED



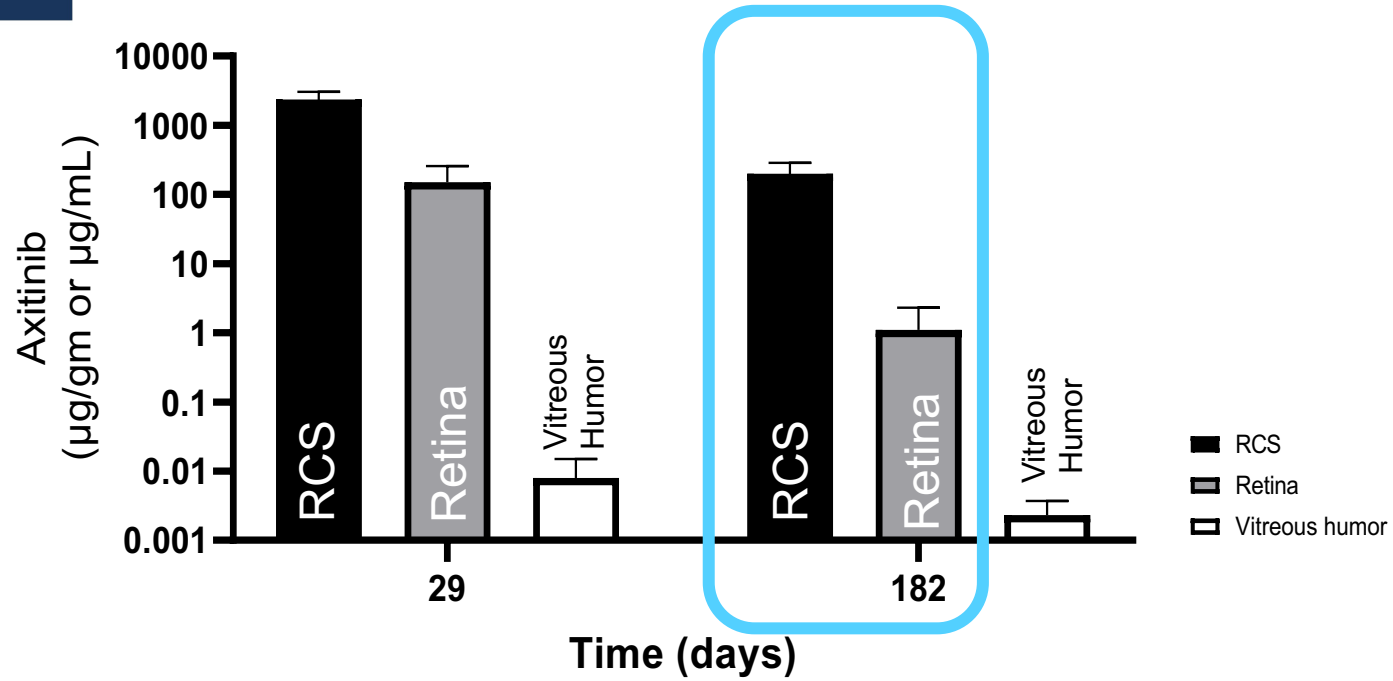
Cross-section: *Injectate spreads from scleral spur towards macula*



Top View: *Injectate immediately spreads from injection site to posterior tissues*

Suprachoroidally injected axitinib (CLS-AX) shows compartmentalization and durability in rabbit model

COMPARTMENTALIZED



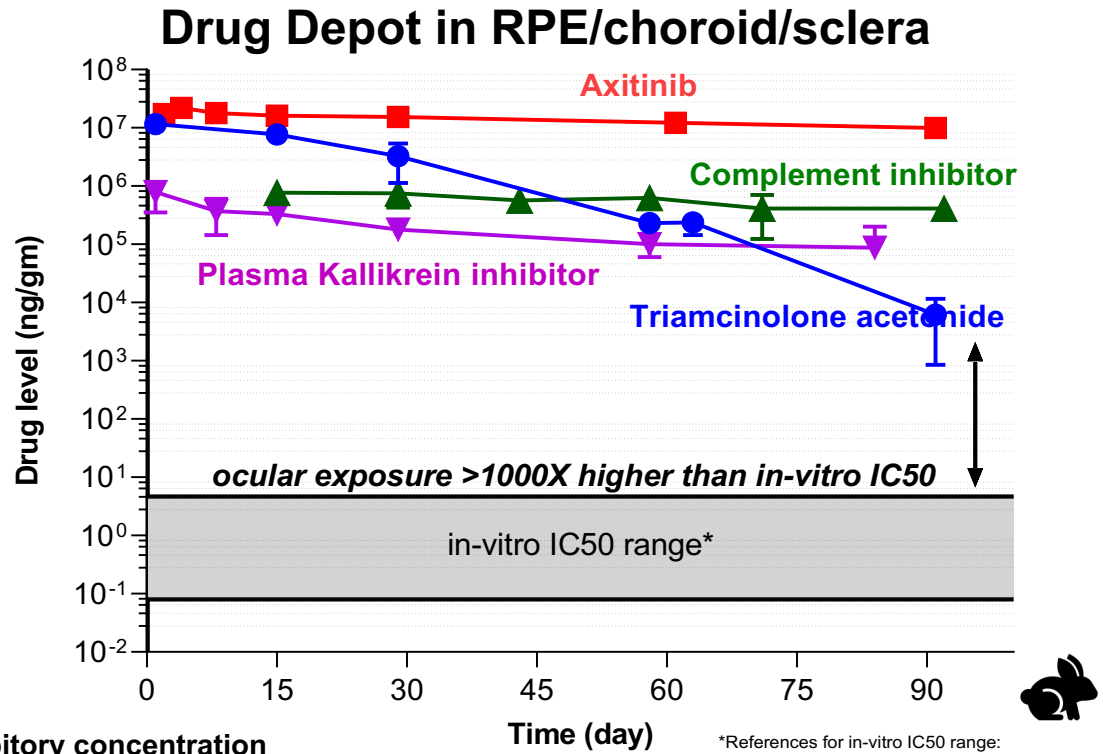
RCS: RPE / Choroid / Sclera

Source: *Translational Vision Science & Technology*, 2021, in press.

2. What drives durability?

Preclinical data of multiple small molecules support durability potential in the suprachoroidal space in rabbit models

DURABLE



IC50: **Half-maximal inhibitory concentration**
RCS: retinal pigment epithelium (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

3. How do therapies reach the macula?

IOP > Anterior SCS Pressure > Posterior SCS Pressure: Drives uveoscleral outflow
Also a driving force for macular distribution after SCS injection

TAGETED TOWARDS MACULA

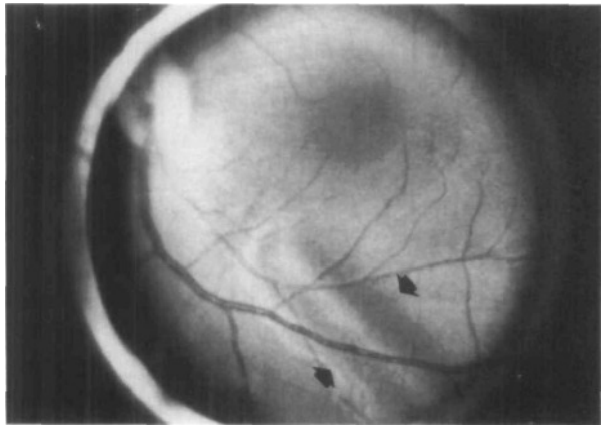


Table 1. Spontaneous pressure measurements (mm Hg)

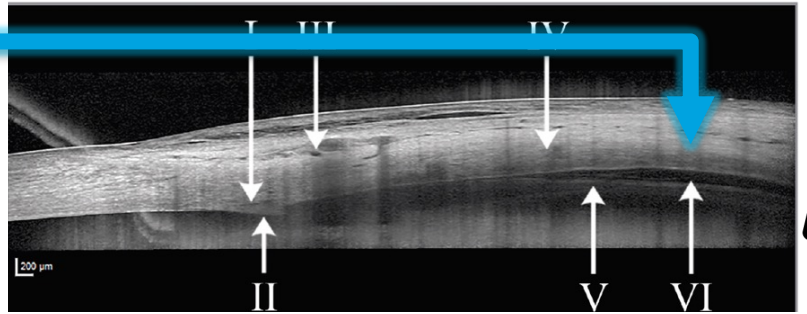
	Anterior cannula	*Posterior cannula*
IOP	9.4 ± 0.9 (9)*	9.2 ± 0.9 (10)†
SCSP	8.4 ± 0.9 (9)*	5.8 ± 0.5 (10)†
IOP-SCSP	0.9 ± 0.2 (9)§‖	3.5 ± 0.5 (10)§

Kozuyuki Emi, Jonathan E. Pederson, and Carol B. Tori.
Hydrostatic Pressure of the Suprachoroidal Space.
Investigative Ophthalmology & Visual Science, Vol. 30, No. 2, February 1989

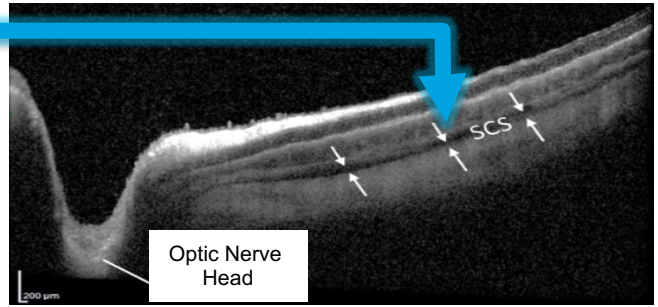
OCT show anterior and posterior expansion of the SCS post-injection

TAGETED TOWARDS MACULA

Anterior Expansion
Clinical Trial Subject



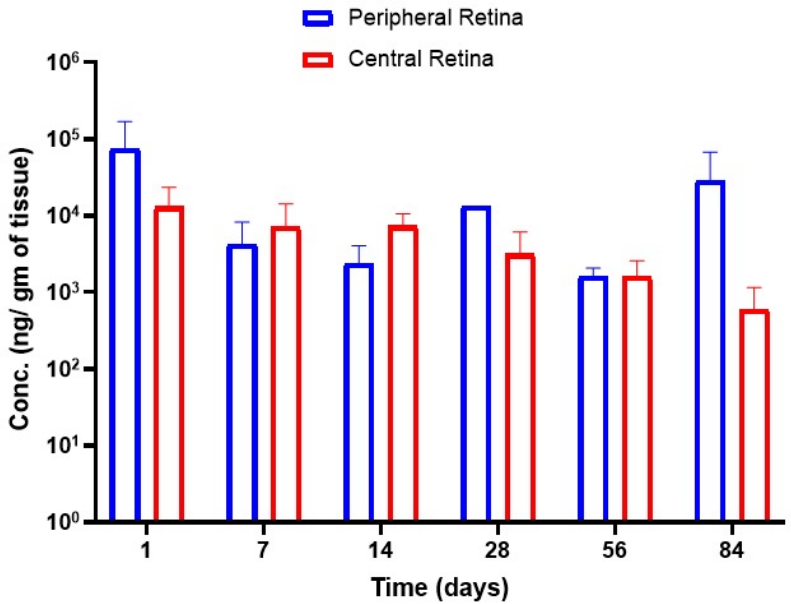
Posterior Expansion to Optic Nerve Head
Rabbit Model

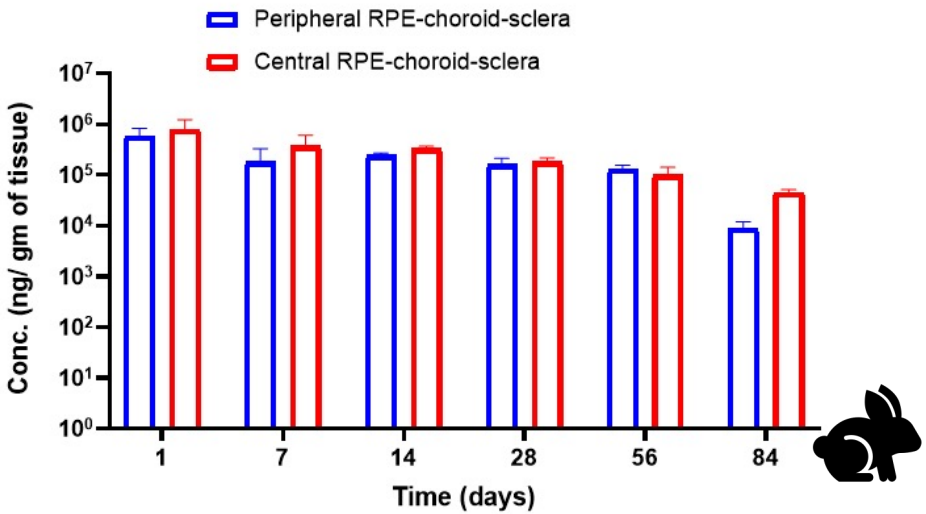


Sources: Lampen SIR, Khurana RN, Noronha G, Brown DM, Wykoff CC. Suprachoroidal Space Alterations Following Delivery of Triamcinolone Acetonide: Post-Hoc Analysis of the Phase 1/2 HULK Study of Patients With Diabetic Macular Edema. Ophthalmic Surg Lasers Imaging Retina. 2018;49(9):692-697. doi:10.3928/23258160-20180831-07, Add additional citation | Kansara VS, Cooper M, Sesenoglu-Laird O, Muya L, Moen R, Ciulla TA. Suprachoroidally Delivered DNA Nanoparticles Transfect Retina and Retinal Pigment Epithelium/Choroid in Rabbits. *Transl Vis Sci Technol*. 2020;9(13):21. Published 2020 Dec 15. doi:10.1167/tvst.9.13.21

Suprachoroidal injection of small molecule concentrations are similar in both retina and RPE / Choroid / sclera tissues

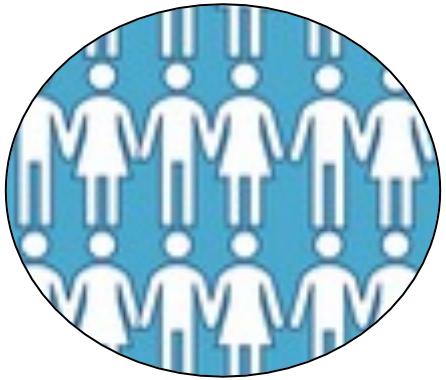
TAGETED TOWARDS MACULA





Leroy Muya, Yahya El-Kattan, Viral Kansara, Yarlagadda Babu, Thomas A Ciulla; Long-acting potential of suprachoroidally delivered BCX4161, a selective plasma kallikrein inhibitor, for diabetic macular edema. *Invest. Ophthalmol. Vis. Sci.* 2021;62(8):2194.

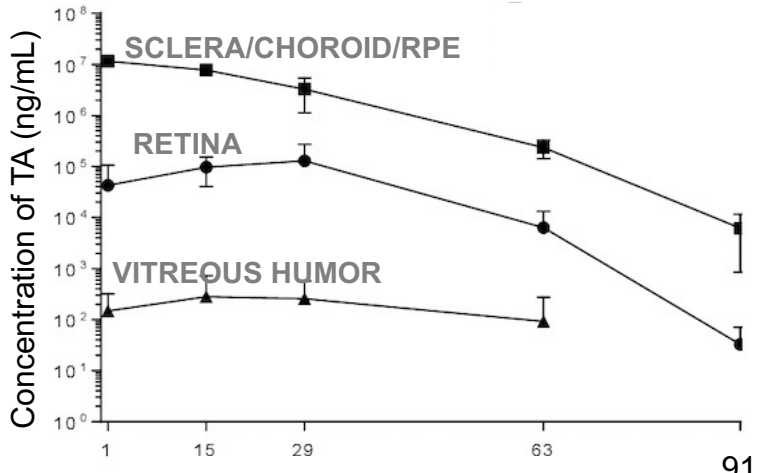
4. How do these concepts translate to clinical trials?



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

Preclinical

High TA levels in the Retina, Sclera/Choroid/RPE of rabbits post suprachoroidal administration of CLS-TA



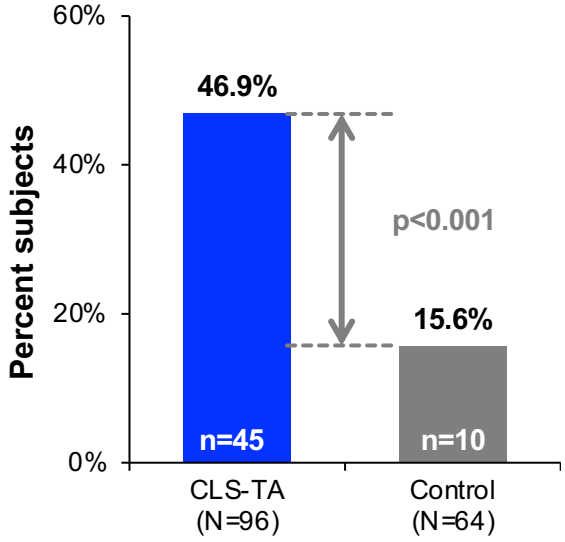
CLS-TA

3 months

Clinical Trial

PEACHTREE Met its Primary Endpoint:

Subjects gaining ≥15 BCVA letters from baseline, %



CLS-TA: Investigational formulation, triamcinolone acetonide for suprachoroidal injection

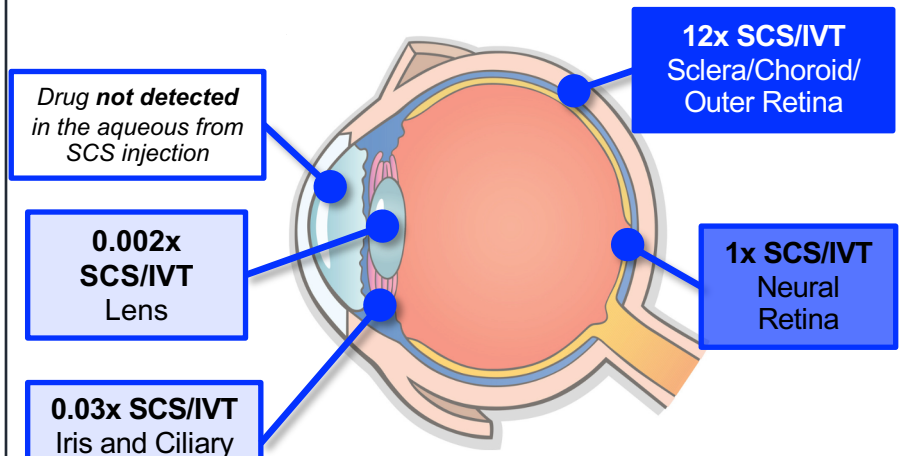
Source: Gilger, et al, *Treatment of Acute Posterior Uveitis in a Porcine Model by Injection of Triamcinolone Acetonide into the Suprachoroidal Space Using Microneedles*, Physiology and Pharmacology

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

Preclinical

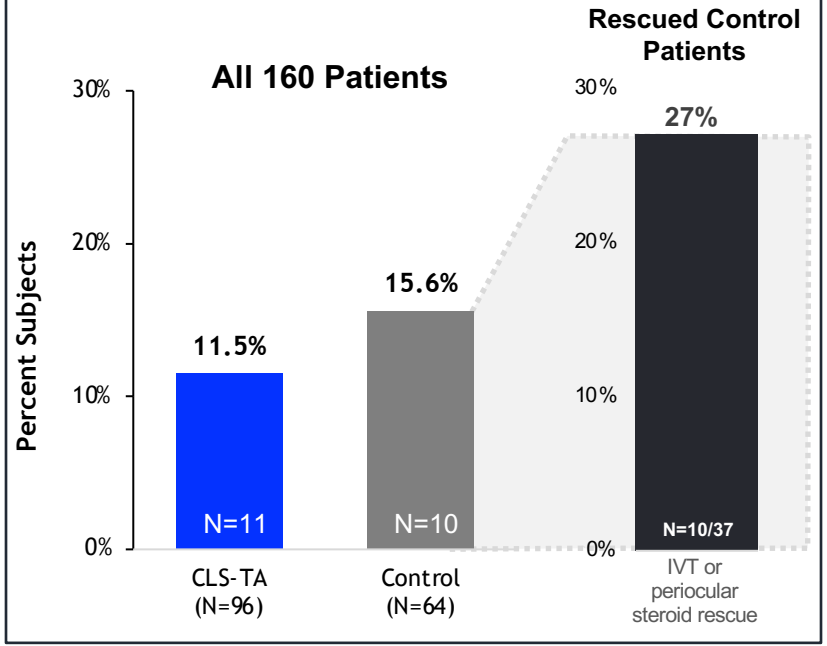
Clinical Trial

Low levels of suprachoroidal administered TA in the anterior spaces compared to intravitreal injection



Values are area under the curve ratios (SCS / IVT) over 91 days in rabbit eyes

PEACHTREE IOP AE Rates: Safety Data



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

Suprachoroidal TKI (CLS-AX) now in Phase 1/2 Clinical Trial

Clinical trial currently enrolling

OASIS

Dose-escalating, open label study to assess the safety and tolerability of CLS-AX in treatment experienced wAMD patients

Suprachoroidal Injection of Small Molecule Suspensions

- Suprachoroidal delivery of small molecule suspensions demonstrate
  - prolonged therapeutic levels with potential for sustained release
  - compartmentalization to posterior ocular tissues
  - high bioavailability
- Currently, 5 clinical trials evaluating 4 therapies:
  - CLS-AX for wAMD
  - RGX-314 for wAMD
  - RGX-314 for DR
  - AU-011 for Choroidal Melanoma
  - CLS-TA/ARVN001 for DME (China)