Update on Therapeutic Suprachoroidal Injections

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Angiogenesis
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Disclosures: Clearside, Bausch and Regenxbio (Consultant)

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Suprachoroidal delivery
Setting the stage for posterior segment therapies

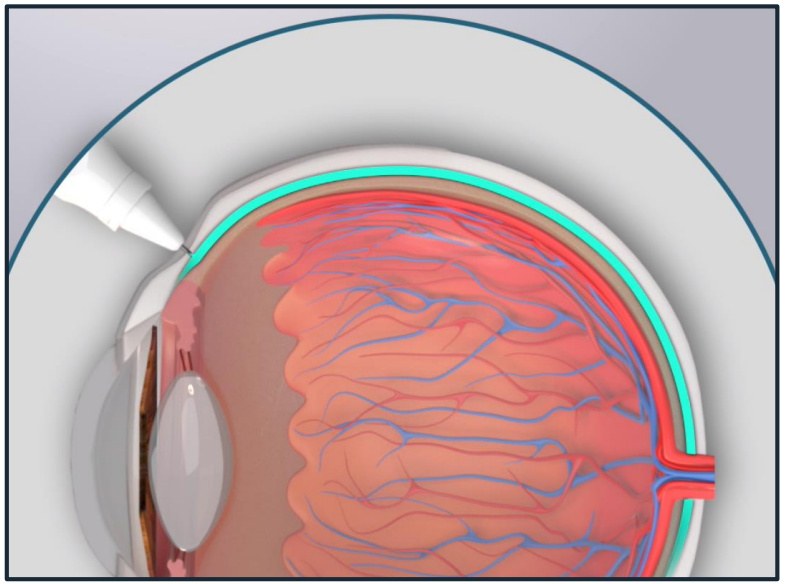
- 1. Small molecule suspension suprachoroidal delivery shows durability.
  - Triamcinolone, TKI, and complement inhibitor
- 2. Suprachoroidal compartmentalization has potential for safety benefits
  - Triamcinolone – favorable clinical safety data
- 3. Unique ocular distribution creates path forward for other therapies
  - Office-based gene therapy
  - Choroidal disease, e.g. melanoma

Suprachoroidal Delivery

- Triamcinolone [Xipere - Bausch & Lomb]
- Anti-Vegf (tyrosine kinase inhibitor)
- Complement Inhibition
- Gene therapy (NAV AAV-8) [Regenxbio]
- Gene Therapy (DNA nanoparticle)
- Treatment for choroidal tumors [Aura Pharmaceuticals]

Ocular Delivery Methods to Reach the Back of the Eye

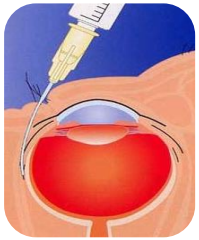
Suprachoroidal Injection



SCS Microinjector™ allows for
precise delivery into the suprachoroidal space

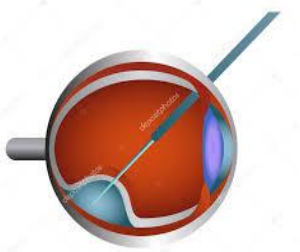
Intravitreal Injection

Broad diffusion to all areas of the eye including the anterior chamber and lens



Periocular Injection

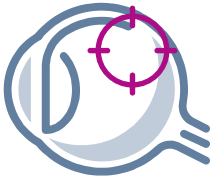
Highly variable drug diffusion across the sclera into the eye



Subretinal Injection

Invasive surgery with variable results

Core Advantages of Treating Via the Suprachoroidal Space



TARGETED

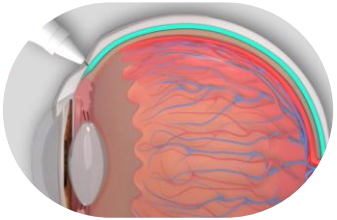
The back of the eye is the location of many irreversible and debilitating visual impairments[1]

for efficacy

COMPARTMENTALIZED

Drug is compartmentalized in the suprachoroidal space, which helps keep it away from non-diseased tissues[2]

for safety



BIOAVAILABLE PROLONGED PK

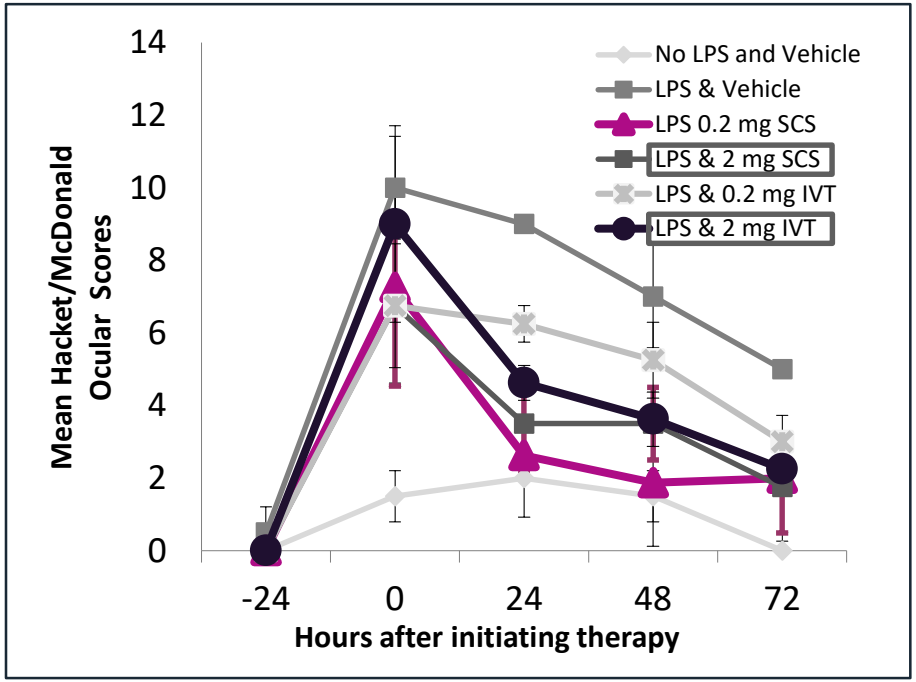
Fluid spreads circumferentially and posteriorly when injected within the suprachoroidal space, bathing the choroid and adjacent areas with drug[2]

for durability

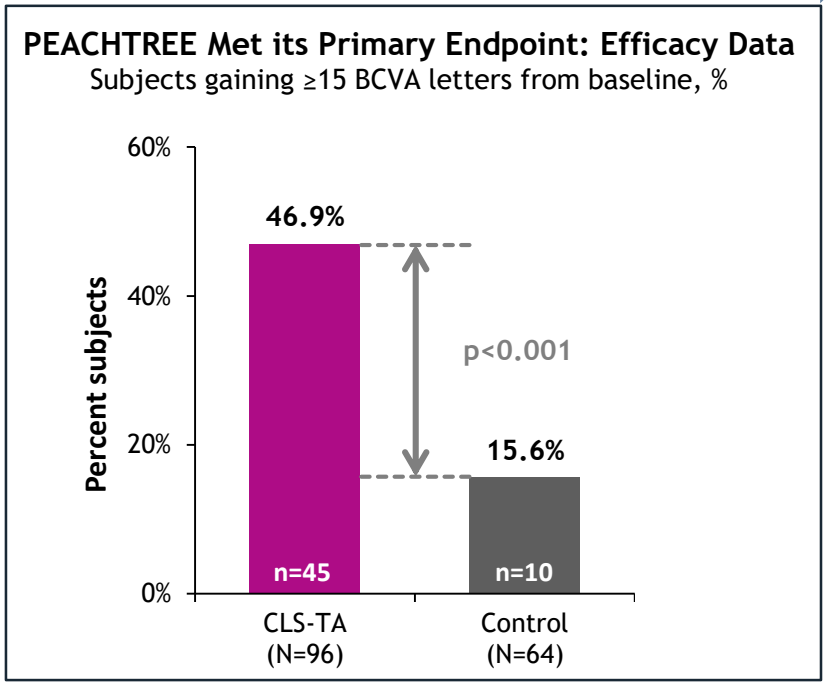
Sources: PK = pharmacokinetic | 1. Rai UDJ, Young SA, Thrimawithana TR, et al. The suprachoroidal pathway: a new drug delivery route to the back of the eye. Drug Discov Today. 2015;20(4):491-495. 3. Moisseiev E, Loewenstein A, Yiu G. The suprachoroidal space: from potential space to a space with potential. Clin Ophthalmol. 2016;10:173-178. 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.

The Suprachoroidal Space & Triamcinolone Acetonide *targeted for efficacy*

Preclinical



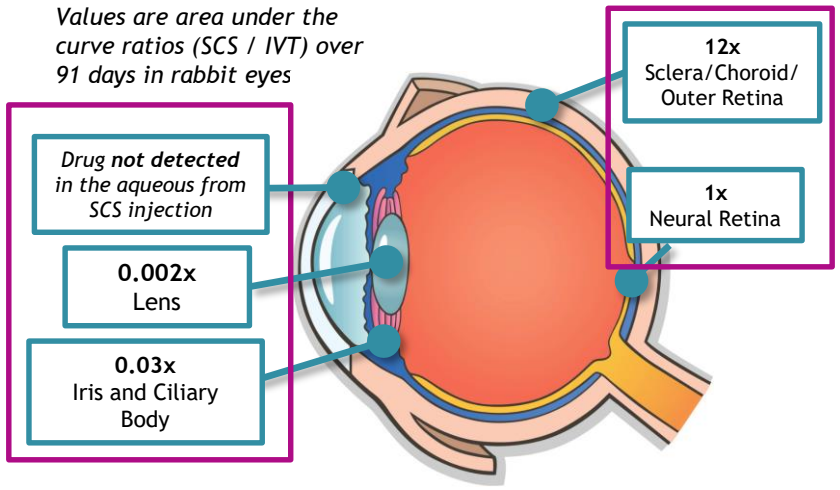
Clinical Trial



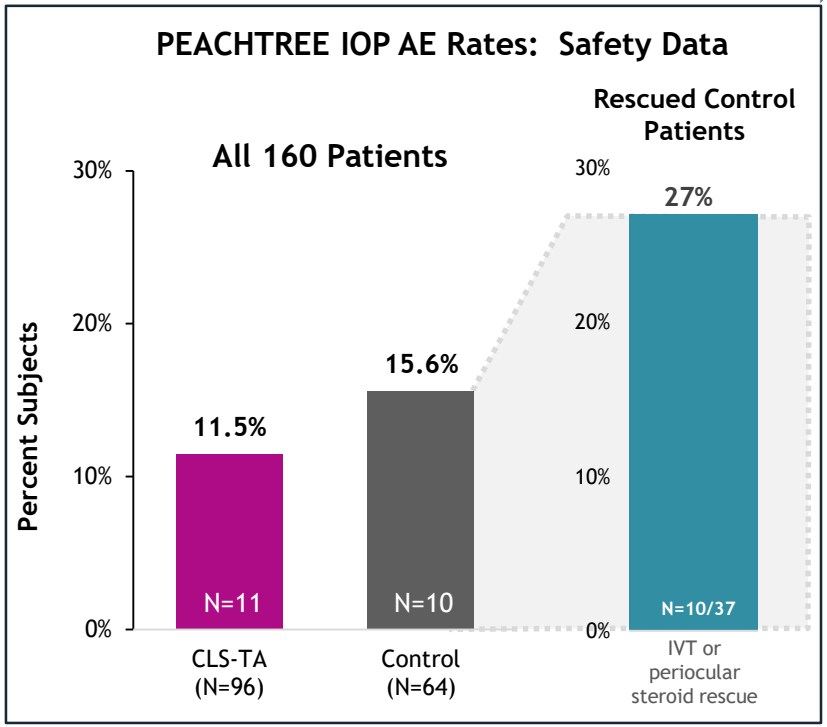
Source: Gilger, et al, *Treatment of Acute Posterior Uveitis in a Porcine Model by Injection of Triamcinolone Acetonide into the Suprachoroidal Space Using Microneedles*, Physiology and Pharmacology

The Suprachoroidal Space & Triamcinolone Acetonide *compartmentalized for safety*

Preclinical



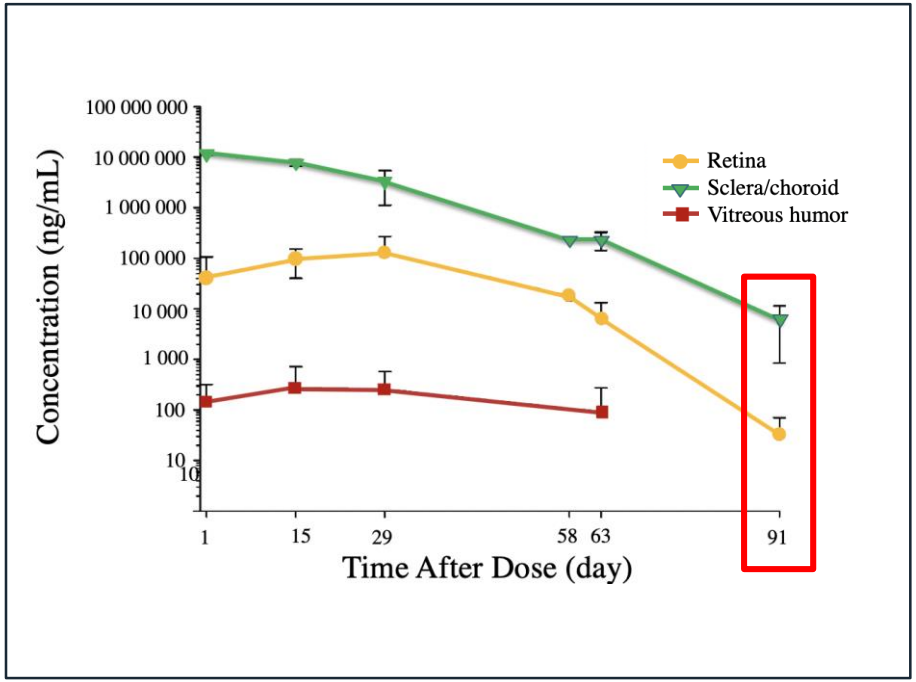
Clinical Trial



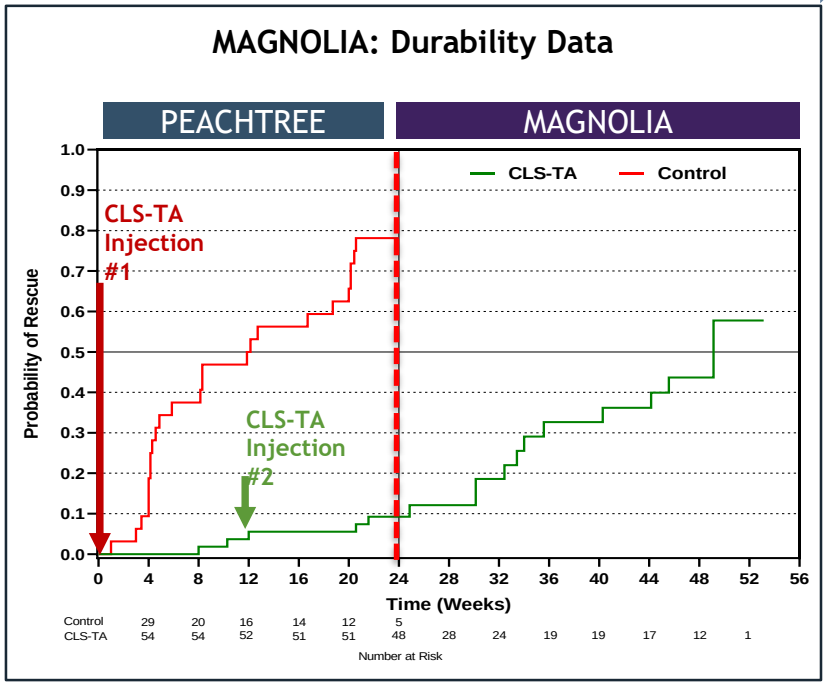
Source: Edelhauser HF, et al. ARVO Annual Meeting. 2013. | Phase 3 clinical trial data.

The Suprachoroidal Space & Triamcinolone Acetonide *prolonged PK for durability*

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

Bausch Health Licenses Clearside Biomedical's XIPERE™ (Triamcinolone Acetonide Suprachoroidal Injectable Suspension), An Investigational Treatment For Macular Edema Associated With Uveitis

October 23, 2019

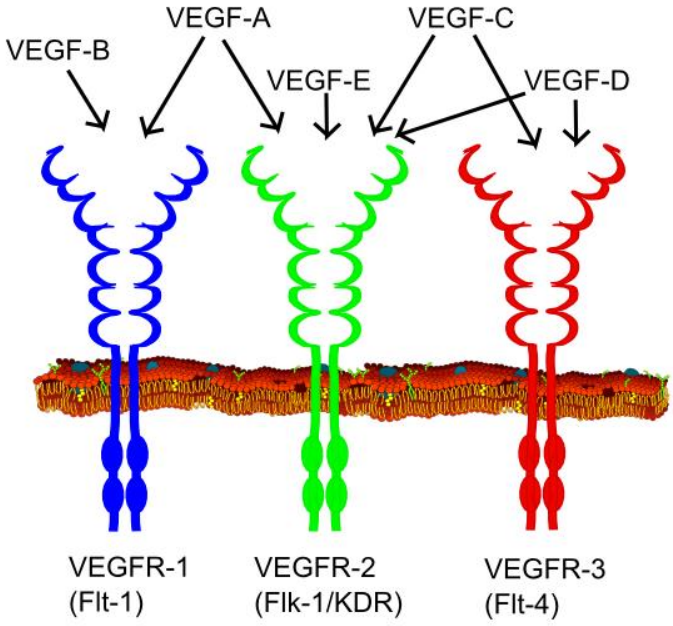
NDA Resubmission to the FDA Expected to Occur in the First Quarter of 2020

LAVAL, Quebec and ALPHARETTA, Ga., Oct. 23, 2019 /PRNewswire/ -- Bausch Health Companies Inc. (NYSE/TSX: BHC) ("Bausch Health") and Bausch + Lomb, its leading global eye health business, and Clearside Biomedical, Inc. (Nasdaq: CLSD) ("Clearside"), a biopharmaceutical company dedicated to developing and delivering treatments that can restore and preserve vision for people with serious back of the eye diseases, announced today that an affiliate of Bausch Health has acquired an exclusive license for the commercialization and development of XIPERE™ (triamcinolone acetonide suprachoroidal injectable suspension) in the United States and Canada.

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

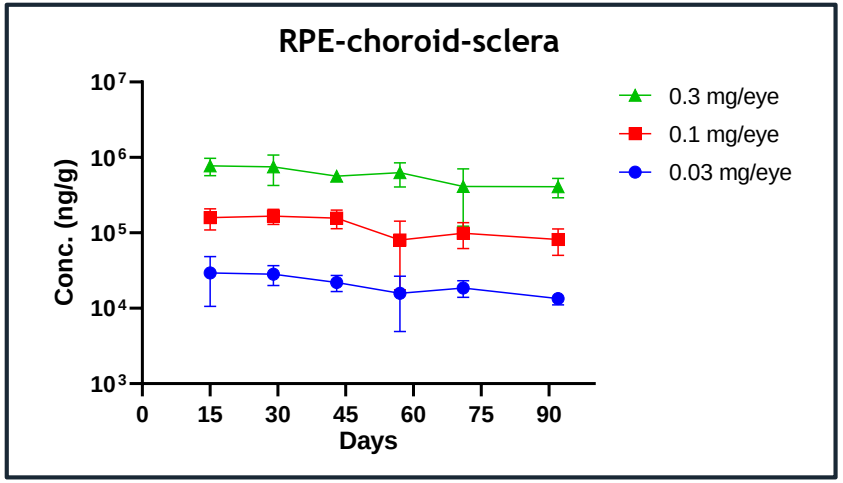
- Inhibits VEGFR-1, VEGFR-2, VEGFR-3
- Inhibited corneal, retinal, and choroidal angiogenesis in animal models[3-7]
- More effective than other TKIs for experimental corneal neovascularization in animal models
- Better ocular cell biocompatibility than other TKIs[8]

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

Complement Factor D Inhibitor and the Suprachoroidal Space Exploratory Preclinical PK Study

Suprachoroidal delivery of complement inhibitor small molecule suspension resulted in **targeted, compartmentalized,** and **sustained ocular levels** in rabbits

Dutch-Belted pigmented rabbits | n=4-6 eyes/ timepoint | Dose: 0.03, 0.1 and 0.3 mg/eye

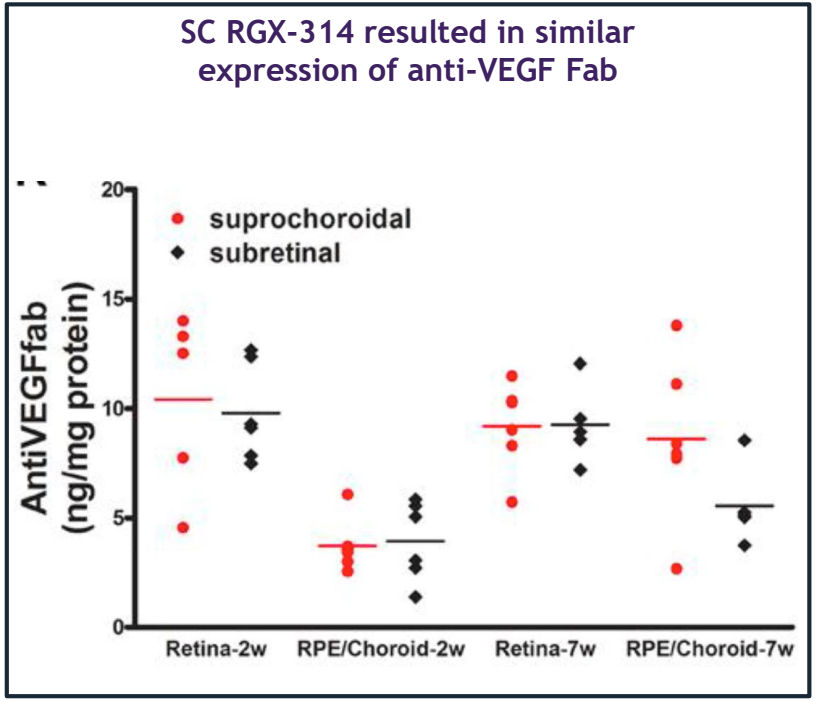


- **Targeted & Compartmentalized:** High exposure for 90+ days in RPE-choroid-sclera (RCS
- **Sustained:** Estimated half-life ($T_{1/2}$) of 66, 66, and 76 days at 0.03, 0.1, and 0.3 mg/eye level, respectively
- **Meaningful drug levels:** 3-5 orders of magnitude higher than the in-vitro (AP hemolysis assay) IC90 value (10nM)

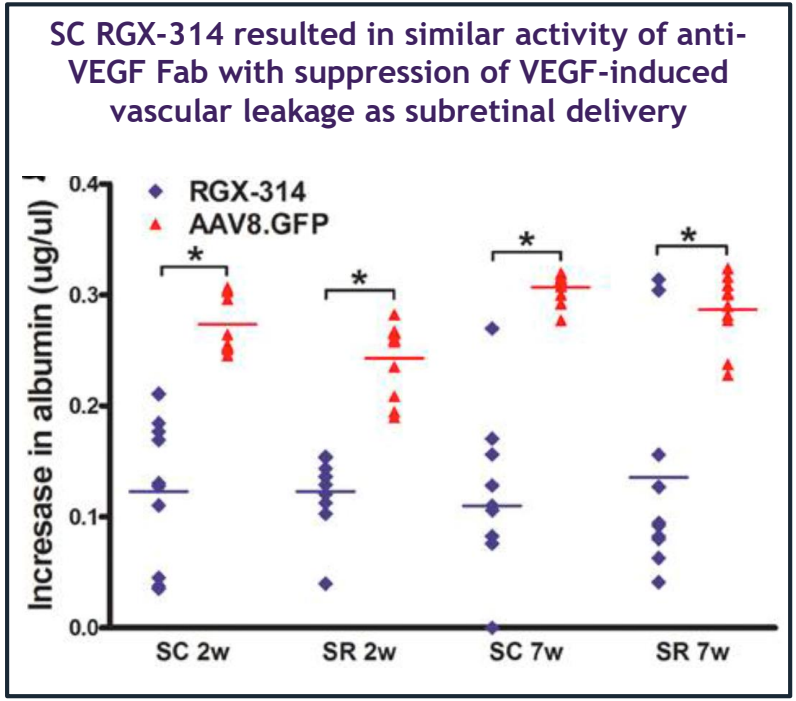
Viral Vectors and the Suprachoroidal Space Preclinical Activity

Suprachoroidal delivery of NAV AAV8-based gene therapy may avoid injected drug exposure to the vitreous and anterior segment of eye

SC RGX-314 resulted in similar expression of anti-VEGF Fab



SC RGX-314 resulted in similar activity of anti-VEGF Fab with suppression of VEGF-induced vascular leakage as subretinal delivery



Source: Ding, K., Shen, J., Hafiz, Z., Hackett, S. F., Silva, R. L. E., Khan, M., ... Campochiaro, P. A. (2019). AAV8-vectored suprachoroidal gene transfer produces widespread ocular transgene expression. *Journal of Clinical Investigation*. doi: 10.1172/jci129085

DNA Nanoparticle Gene Therapy and the Suprachoroidal Space

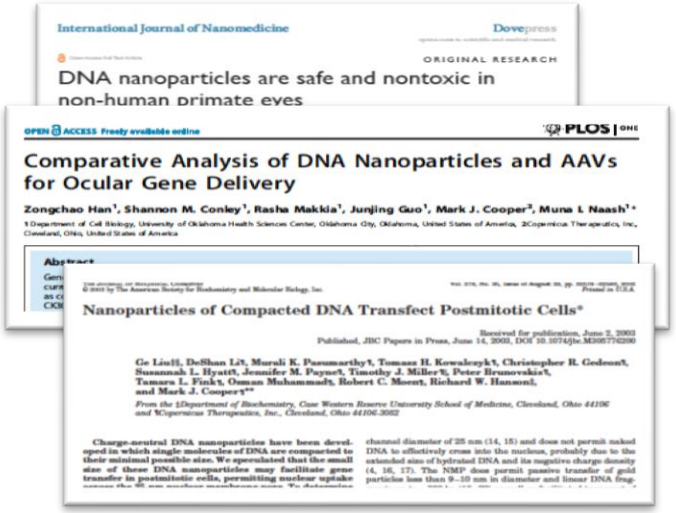
Potential advantages:

- 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

Potential synergies with suprachoroidal injection:

- In office, repeat dosing as needed
- Targeted circumferential compartmentalized spread to large surface areas
  - Potentially ideal distribution for inherited retinal disease treatment or biofactory approach

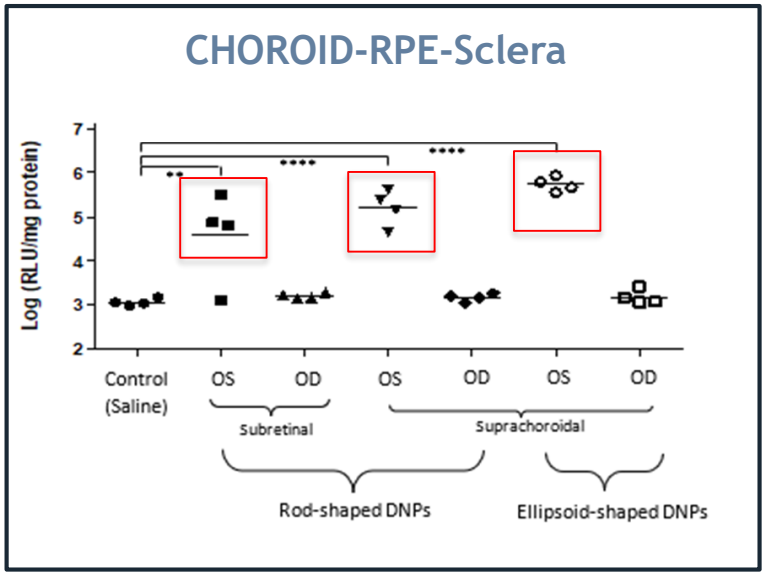
Well established literature on DNA nanoparticle gene therapy

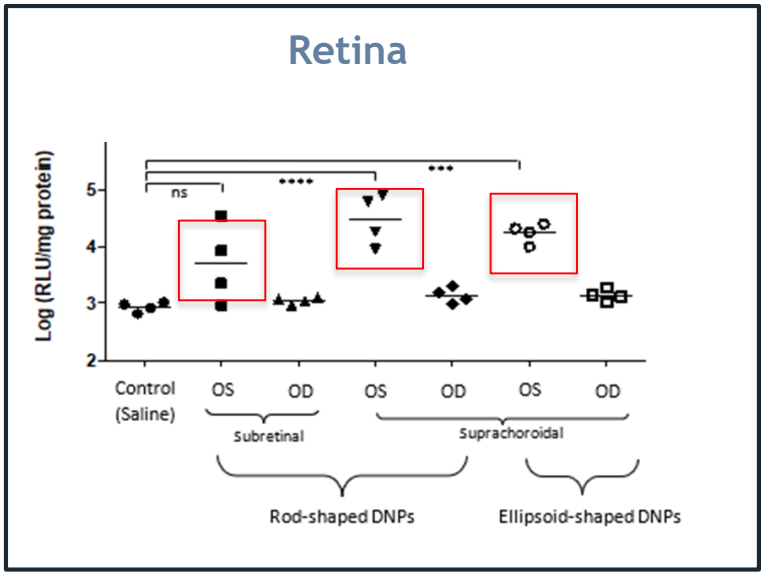


Preclinical studies demonstrate SC injections of DNA/polyethylene polylysine nanoparticles (DNPs) may offer the potential for a safe and efficient delivery method

Preclinical SCS and Subretinal Injections of DNA Nanoparticles Produced Comparable Luciferase Activity

Dose: 4mg DNPs/eye | Suprachoroidal injection (100 uL), Subretinal injection (50 uL)
DNPs consisted of a single copy of plasmid DNA with a polyubiquitin C/luciferase transcriptional cassette





DNA Nanoparticles Transfect Choroid and Retina

Source: Szilárd Kiss, MD, Macula Society Presentation February 2019

Ocular Oncology and the Suprachoroidal Space
Aura Biosciences: Press Release, 10/15/2019

Treatment: Proprietary viral-like particle bioconjugates (VPB), activated with an ophthalmic laser. VPBs bind selectively to unique receptors on cancer cells in the eye

Aura Biosciences Announces Updated Phase 1b/2 Clinical Data for AU-011 Presented at the American Academy of Ophthalmology 2019 Annual Meeting

October 15, 2019

Light-Activated AU-011 has the Potential to be the First FDA Approved Therapy for the Primary Treatment of Choroidal Melanoma

Exploring Suprachoroidal Delivery for AU-011

Amy C. Schefler, M.D., Weill Cornell Medical College and Retina Consultants of Houston, gave an oral presentation highlighting the data from the ongoing Phase 1b/2 study with intravitreal administration as well as new preclinical research demonstrating the potential advantages of delivering AU-011 using the suprachoroidal route of administration. Aura recently executed a licensing agreement with Clearside Biomedical for use of Clearside's suprachoroidal space (SCS) Microinjector™ for the treatment of intraocular cancers. Aura believes that by delivering AU-011 into the SCS, there is the potential for treating a larger number of patients with a good safety profile and a greater range of tumor sizes. Preliminary preclinical pharmacology data showed that AU-011 administered via the SCS Microinjector achieved full necrosis of tumor cells in all animals following laser activation. Further preclinical studies are currently ongoing and Aura expects to initiate clinical testing using suprachoroidal delivery for AU-011 during the first half of 2020.

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