

CLEARSIDE®  
BIOMEDICAL

Corporate Presentation | August 2020

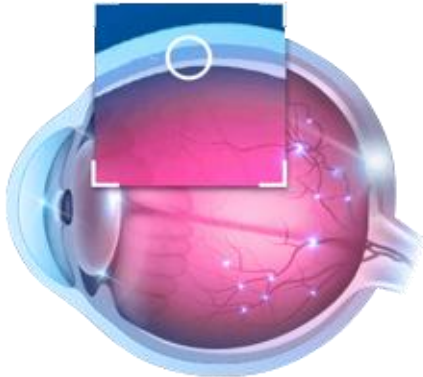
# Forward-Looking Statements

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. The words “may,” “will,” “could,” “would,” “should,” “expect,” “plan,” “anticipate,” “intend,” “believe,” “estimate,” “predict,” “project,” “potential,” “continue,” “target” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Clearside Biomedical, Inc.’s views as of the date of this presentation about future events and are subject to risks, uncertainties, assumptions, and changes in circumstances that may cause Clearside’s actual results, performance, or achievements to differ significantly from those expressed or implied in any forward-looking statement. Although Clearside believes that the expectations reflected in the forward-looking statements are reasonable, Clearside cannot guarantee future events, results, performance, or achievements. Some of the key factors that could cause actual results to differ from Clearside’s expectations include its plans to develop and potentially commercialize its product candidates; Clearside’s planned clinical trials and preclinical studies for its product candidates; the timing of and Clearside’s ability to obtain and maintain regulatory approvals for its product candidates; the extent of clinical trials potentially required for Clearside’s product candidates; the clinical utility and market acceptance of Clearside’s product candidates; Clearside’s commercialization, marketing and manufacturing capabilities and strategy; Clearside’s intellectual property position; and Clearside’s ability to identify additional product candidates with significant commercial potential that are consistent with its commercial objectives. For further information regarding these risks, uncertainties and other factors you should read the “Risk Factors” section of Clearside’s Annual Report on Form 10-K for the year ended December 31, 2019, filed with the SEC on March 13, 2020, Clearside’s Quarterly Report on Form 10-Q for the quarter ended June 30, 2020, filed with the SEC on August 10, 2020, and Clearside’s other Periodic Reports filed with the SEC. Clearside expressly disclaims any obligation to update or revise the information herein, including the forward-looking statements, except as required by law. This presentation also contains estimates and other statistical data made by independent parties and by Clearside relating to market size and growth and other data about its industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of Clearside’s future performance and the future performance of the markets in which Clearside operates are necessarily subject to a high degree of uncertainty and risk.

# Developing and Delivering Treatments that Restore and Preserve Vision for People with Serious Back of the Eye Diseases

## Versatile Therapeutic Platform

SCS Microinjector® with proprietary drug formulations target the Suprachoroidal Space



Proprietary Access to the Suprachoroidal Space (SCS®)

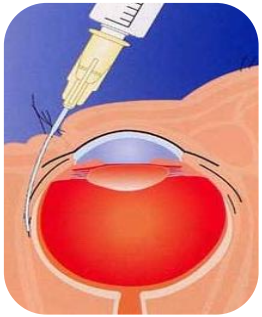
Utilization Across Small Molecules and Gene Therapy

Ability to Target Multiple Ocular Diseases

Internal Research & Development Pipeline

External Collaborations for Pipeline Expansion

# Evolution of Injection Procedures to Reach the Back of the Eye



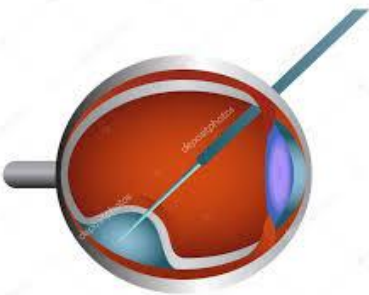
## Periocular Injection

Highly variable drug diffusion across the sclera into the eye



## Intravitreal Injection

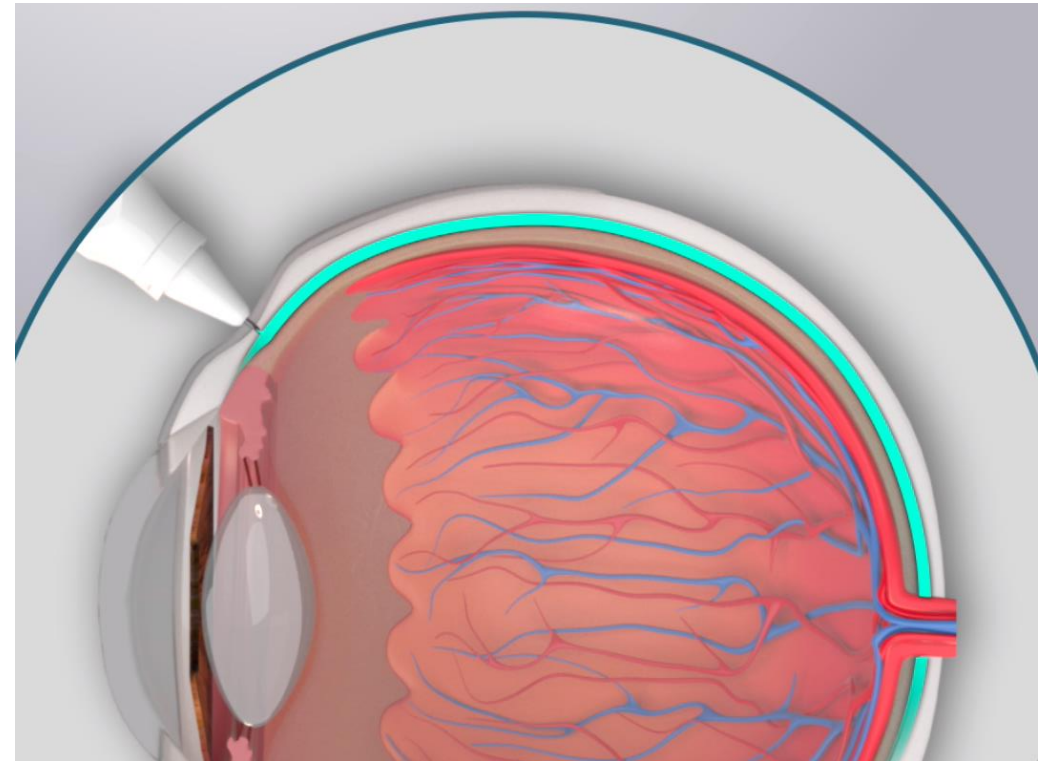
Broad diffusion to all areas of the eye including the anterior chamber and lens



## Subretinal Injection

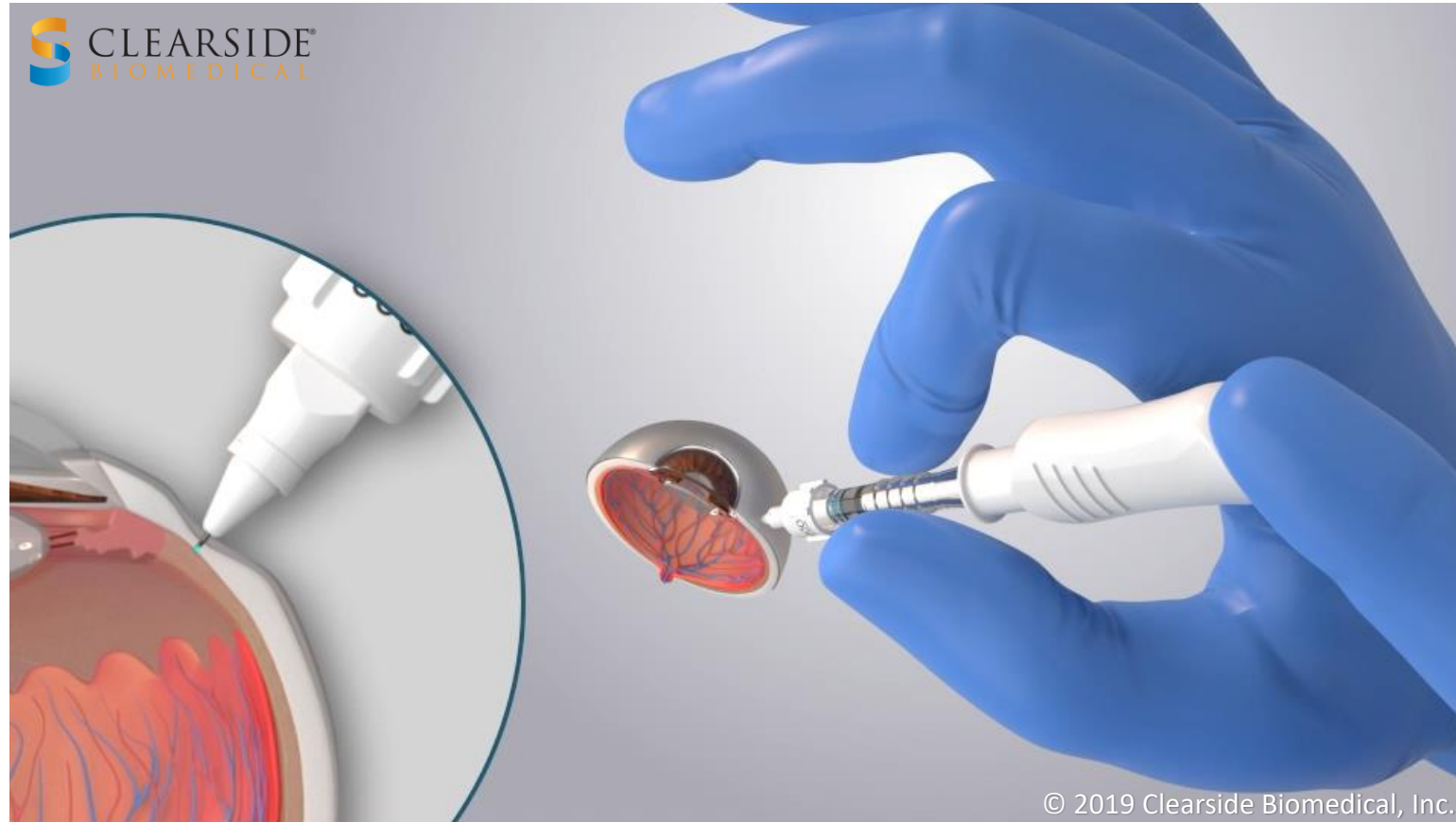
Invasive surgery with variable results

## Suprachoroidal Space Injection



Novel SCS Microinjector® allows for precise delivery into the suprachoroidal space

# Exclusive Access to the Back of the Eye Using Clearside's Proprietary SCS Microinjector®



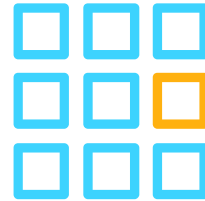
# Core Advantages of Treating Via the Suprachoroidal Space



## TARGETED

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

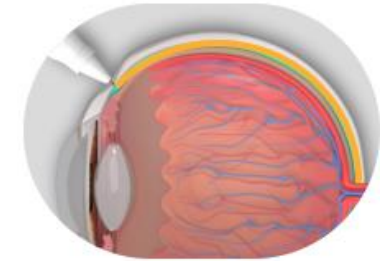
*for efficacy*



## COMPARTMENTALIZED

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

*for safety*



## BIOAVAILABLE PROLONGED PK

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

*for durability*

# Strong Intellectual Property Coverage of SCS Platform

21

U.S. Patents Total  
Expiring between  
2027 - 2037

2

Methods using  
loss-of-  
resistance  
technology

5

Apparatus using  
loss-of-resistance  
technology

4

Apparatus having /  
methods using an  
adjustable  
puncture member

1

Ocular  
injection  
apparatus  
packaging

1

Administration of any  
anti-inflammatory  
drug to the  
suprachoroidal space  
by microinjection

4

Administration of  
any drug to the  
suprachoroidal  
space by  
microinjection

1

Administration  
of any drug to  
the eye by  
inserting a  
microinjector  
into the sclera

3



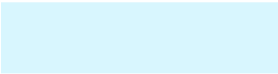
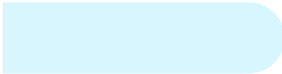


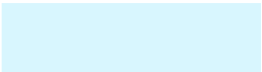
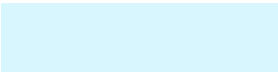
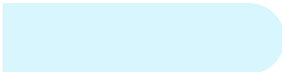
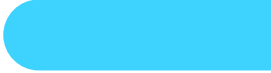

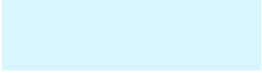
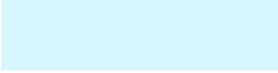
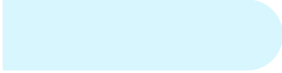

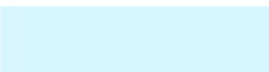
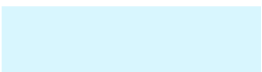
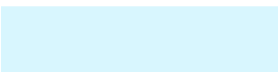
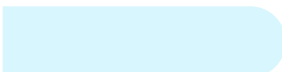
Methods of  
treating posterior  
ocular disorders  
including macular  
edema or uveitis

DEVICE PATENTS

DRUG PATENTS




DISEASE  
PATENTS

# Suprachoroidal Internal Development Pipeline


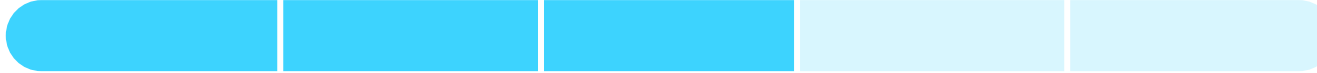
STUDY DRUG	INDICATION	RESEARCH	PRECLINICAL	PHASE 1/2	PHASE 3	NDA
CLS-AX (axitinib injectable suspension)	Wet AMD			Planned YE 20		
Gene Therapy: Intracellular protein	Inherited Retinal Disease					
Gene Therapy: Extracellular protein	“Therapeutic Biofactory”					
Integrin Inhibitor (Injectable suspension)	Diabetic Macular Edema (DME)					

# Partnered Suprachoroidal Pipeline

## Development and Commercial Programs using SCS Microinjector®

PARTNER	INDICATION	IND-Enabling	PHASE 2	PHASE 3	NDA
REGENXBIO	Wet AMD (AAVIATE)				
REGENXBIO	Diabetic Retinopathy		Planned 2H 20		
AURA BIOSCIENCES	Ocular Oncology / Choroidal Melanoma		Planned 3Q 20		

## XIPERE™ Commercial Licenses

PARTNER	TERRITORY	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	NDA
BAUSCH HEALTH	U.S. & Canada; options outside North America					
ARCTIC VISION	Greater China & South Korea					

# **CLS-AX**

## **(axitinib injectable suspension)**

# CLS-AX (axitinib injectable suspension): A Potential Solution for Treatment Burden

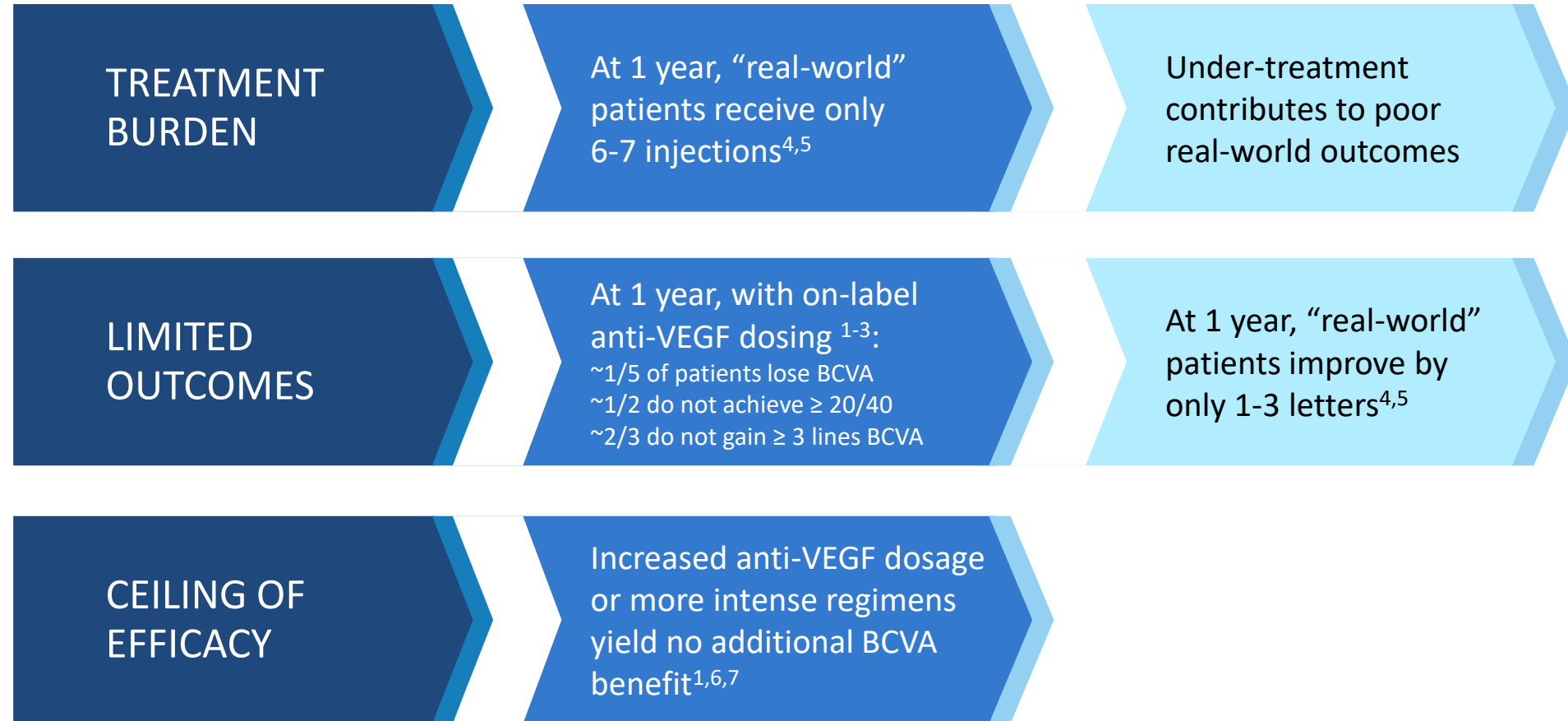
## Primary Need

Durable maintenance of vision  
and reduced treatment burden  
in wet AMD patients

## The Opportunity

- Reduce patient burden from monthly injections to every six months or longer
- Pan-VEGF inhibition potentially more efficacious than current approaches
- 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 toxic exposure to TKIs

# CLS-AX via SCS May Address Unmet Needs in wet AMD

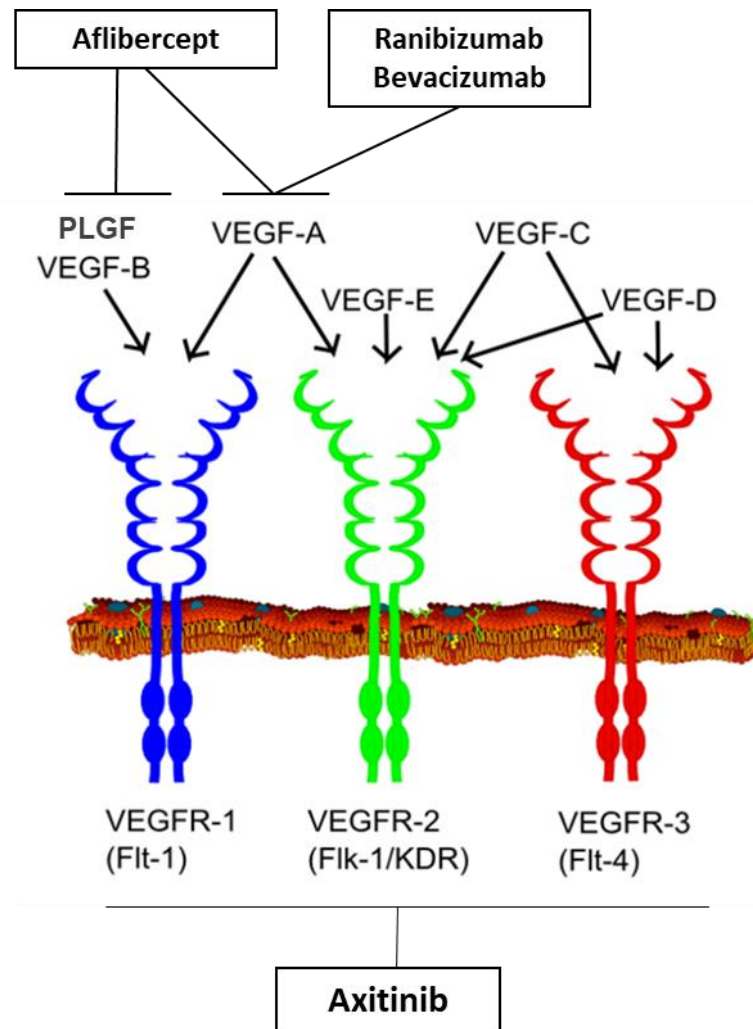


Sources: 1. Heier JS et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119:2537-2548. | 2. Brown DM et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR 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 Binding VEGF-A

- Anti-VEGF-A increases expression of VEGF-C<sup>1</sup> VEGF-D<sup>2</sup>
- Broad VEGF receptor blockade may improve outcomes
- A Phase 2 study yielded better AMD outcomes with anti-VEGF-A,C,D vs anti-VEGF-A

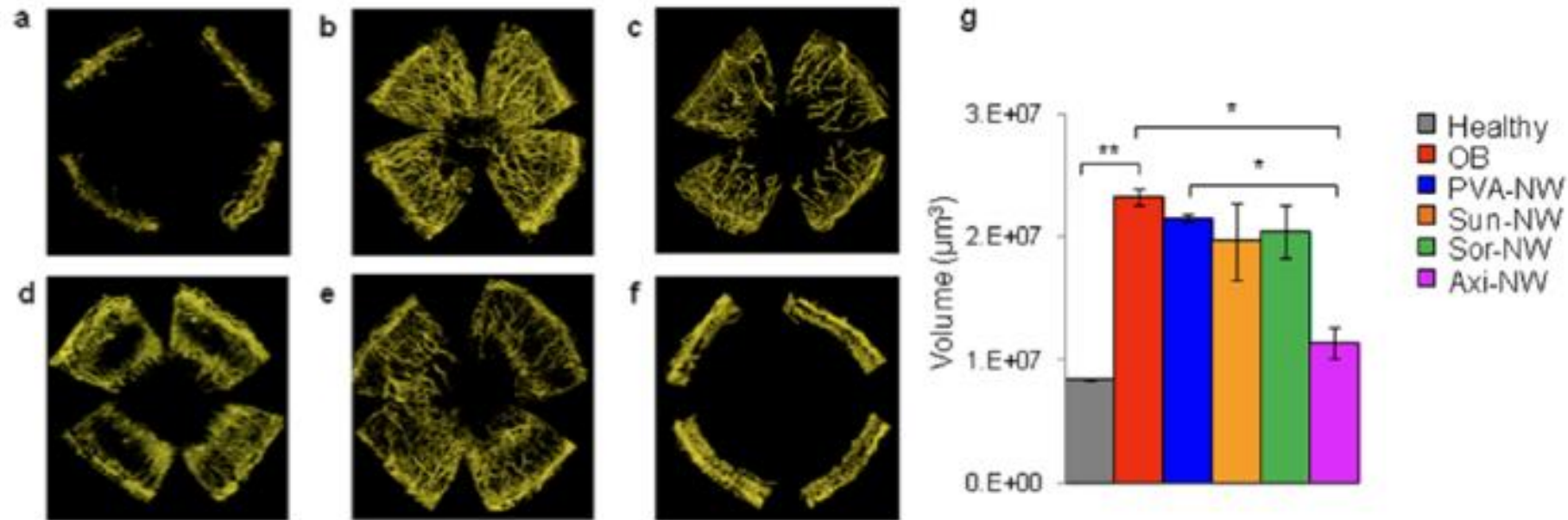


## Suprachoroidal Axitinib May Improve Outcomes with Its Broad VEGF Receptor Blockade

- Inhibits **VEGFR-1**, **VEGFR-2**, **VEGFR-3** receptors
- Inhibited corneal, retinal, and choroidal angiogenesis in animal models<sup>3-7</sup>
- More effective than other TKIs for experimental corneal neovascularization in animal models
- Better ocular cell biocompatibility than other TKIs<sup>8</sup>

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.

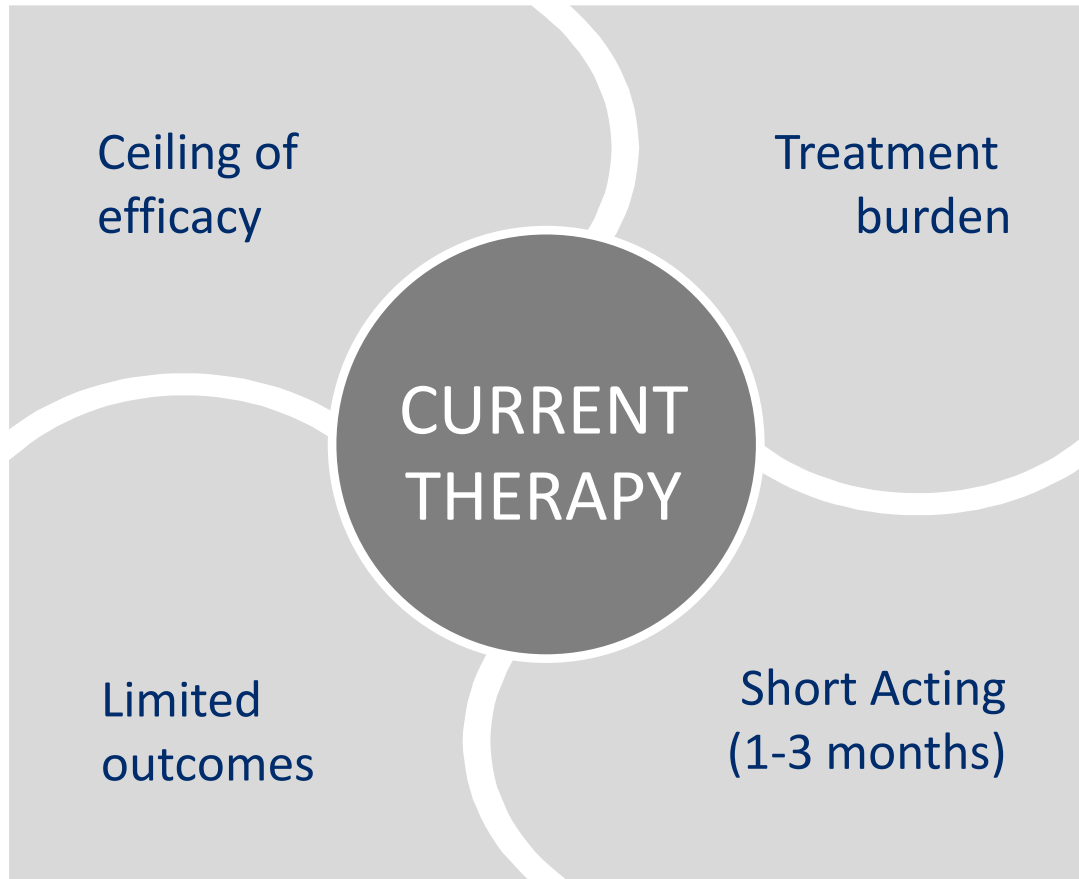
# Topical Axitinib More Effectively Inhibited Experimental Murine Corneal Neovascularization than Sunitinib and Sorafenib (same dose)



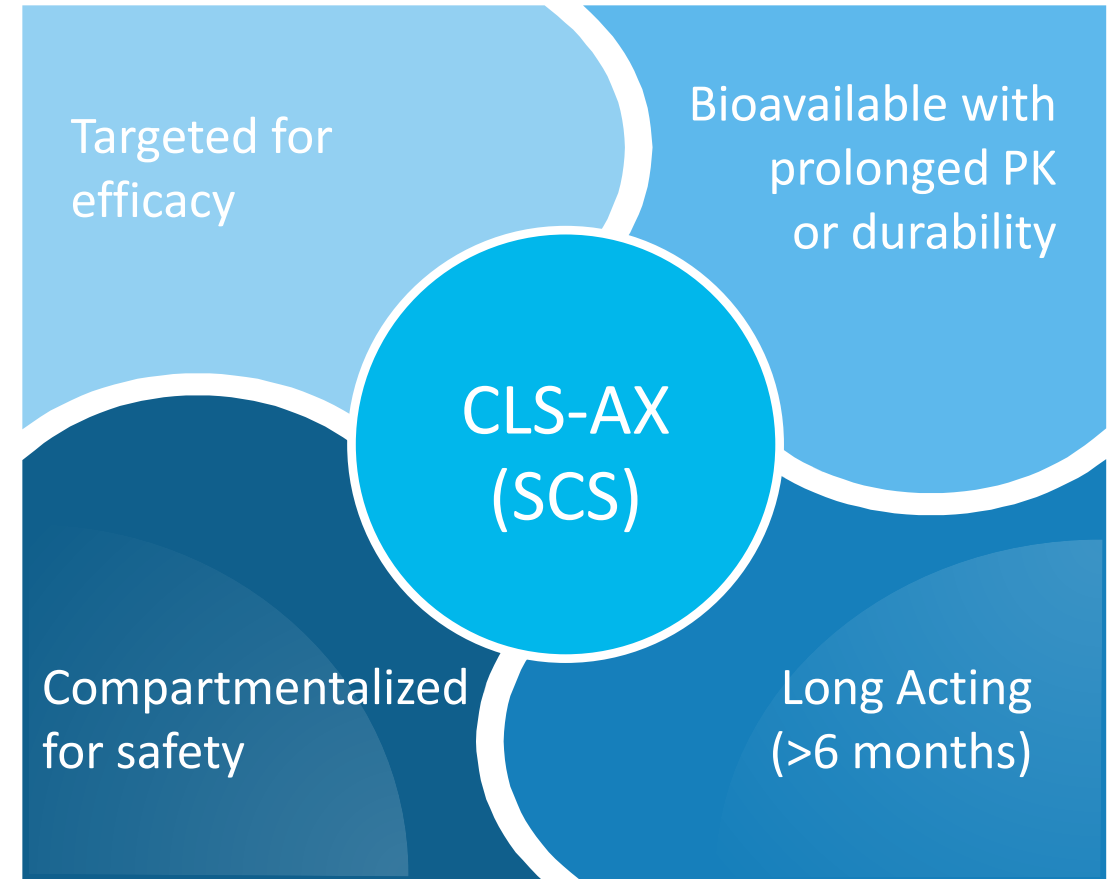
Screening of tyrosine kinase inhibitor drugs loaded nanowafer for their relative therapeutic efficacy in inhibiting corneal neovascularization after 10 days of treatment. Representative 3D reconstructed corneal images of fluorescence confocal microscopy: (a) healthy cornea (control); (b) untreated ocular 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.

# Potential to Disrupt the AMD Treatment Landscape

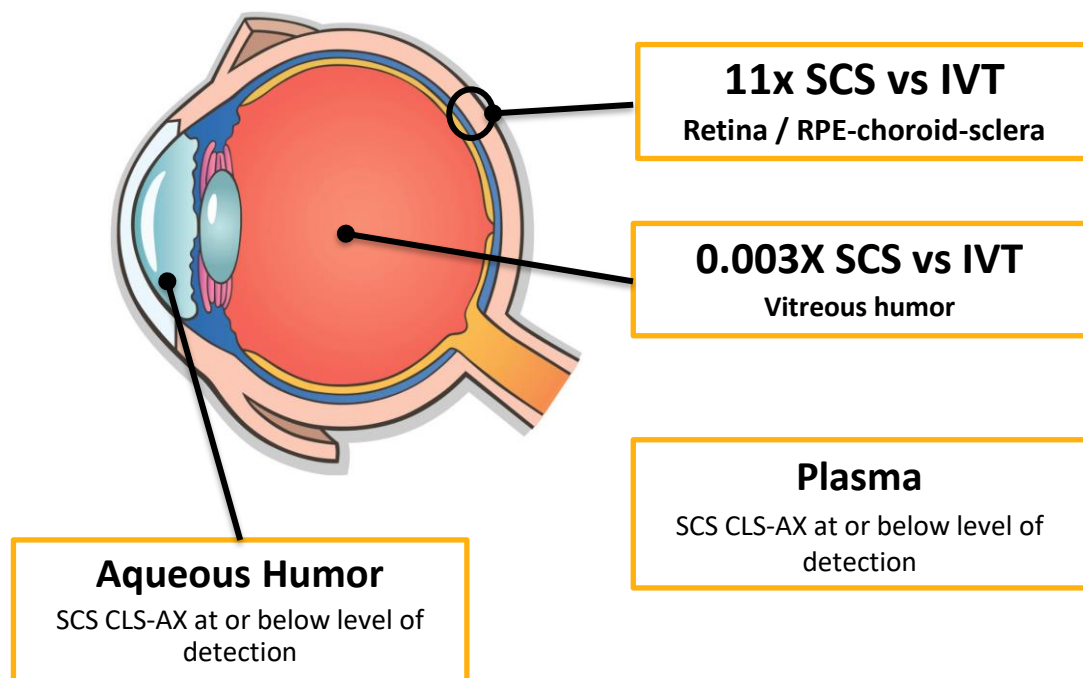
## Focused VEGF Blockade



## Broad VEGF Blockade



# Suprachoroidal Injection of CLS-AX Provides Targeted Delivery Relative to Intravitreal Injection at Same Dose



## Rabbit Model

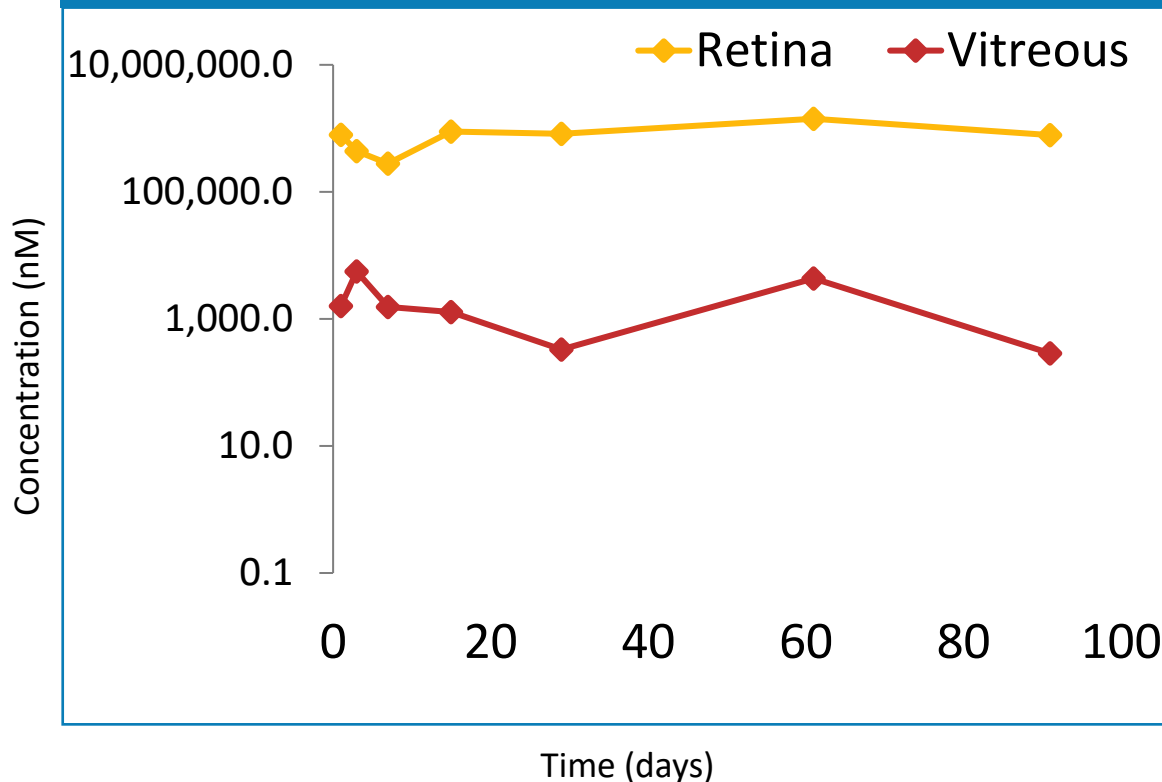
Values: area under the curve ratios, SCS / IVT

SCS : 1 mg/eye, 100  $\mu$ L. | IVT: 1 mg/eye, 25  $\mu$ L

Single bilateral injection, 1-wk rabbit PK studies

# CLS-AX: Durable, High Drug Levels Maintained in the Retina after Suprachoroidal Administration

- ❖ High Retina Levels: Sufficient to block VEGF pathway
- ❖ Low Plasma Levels: <1 ng/mL



# CLS-AX Phase 1/2a Clinical Trial in Wet AMD

## 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

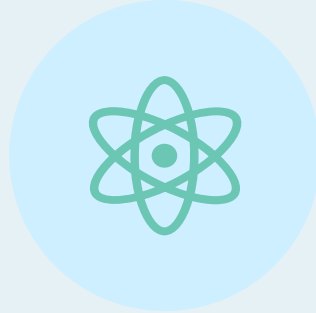


## Key Inclusion Criteria

- 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  $\geq 20$  letters (20/400) and  $\leq 75$  letters (20/32) with  $< 5$  letters change between screening and baseline to ensure patient stability after anti-VEGF

# CLS-AX Phase 1/2a Study Objectives

## Primary Endpoint



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

## Secondary Endpoints



Evaluate and compare 3 cohorts on **visual function and ocular anatomy, and need for additional treatment** with IVT injected aflibercept



Evaluate pharmacokinetics (**PK**)

# Early Stage Pipeline Opportunities

# Broad Applicability of SCS Injection Platform: Ocular Gene Therapy

## Primary Need

Targeted delivery of ocular gene therapies in safe, effective, repeatable, and non-surgical manner

## The Opportunity

- Avoid risks of vitrectomy (surgery)
- Avoid risks of retinotomy, subretinal injection, and macular detachment
- Deliver larger genes using non-viral vectors
- Convert gene therapy into an office-based procedure
- Potential for broader retinal coverage
- Enhance patient access

# Preclinical Studies Demonstrate Suprachoroidal Injections of DNA nanoparticles (DNPs) May Offer the Potential for a Safe and Efficient Delivery Method

## Potential Advantages

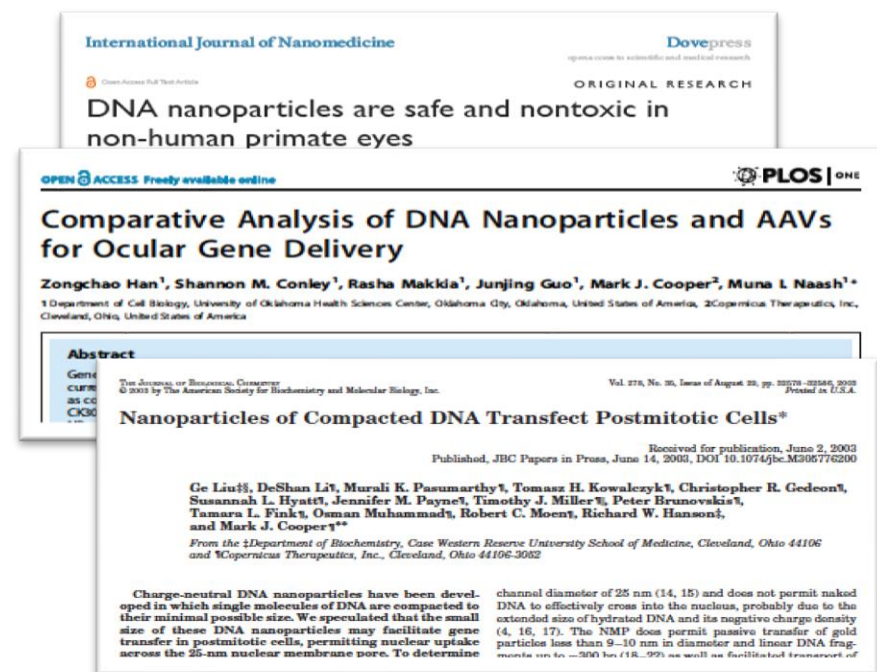
**Efficacy:** demonstrated in numerous ocular animal models

- Transfer large genes (up to ~20 kb)

**Safety:** Non-immunogenic, without viral capsid proteins or pre-existing immunity.

- Potential for repeat dosing facilitated by suprachoroidal injection
- Higher doses possible to enhance transfection

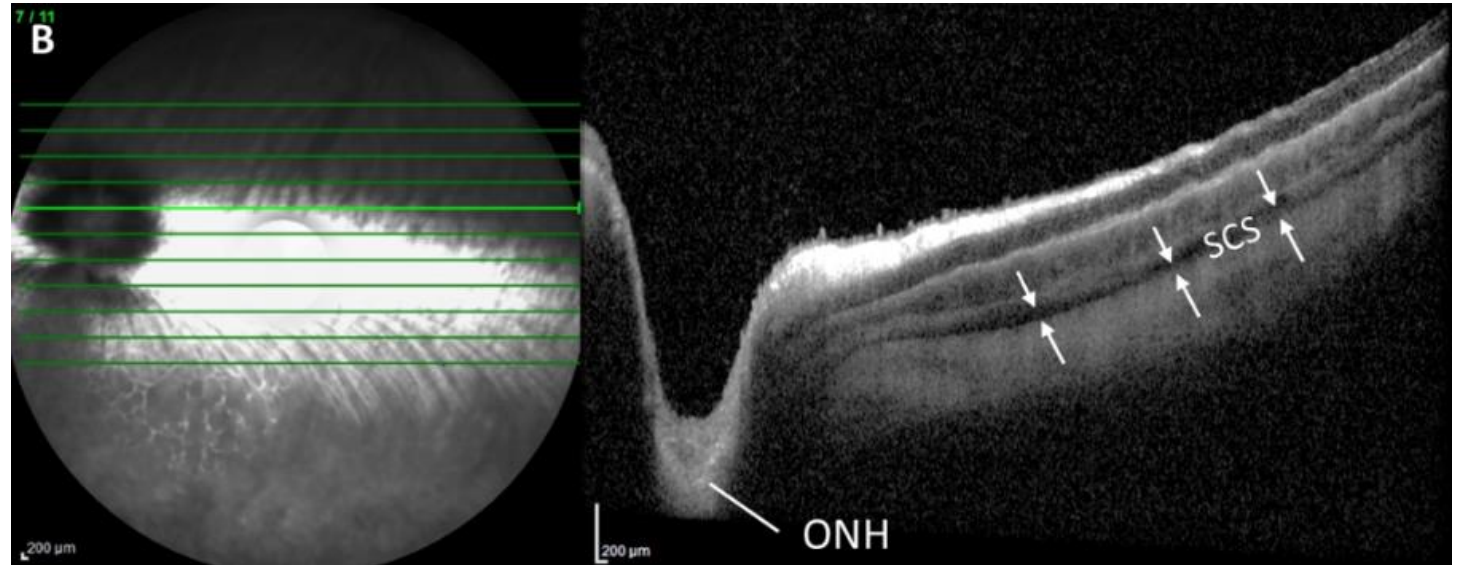
Well established literature on DNA nanoparticle gene therapy



# The Suprachoroidal Space Reversibly Opens Posteriorly and Circumferentially Following DNA Nanoparticle Administration in Rabbits

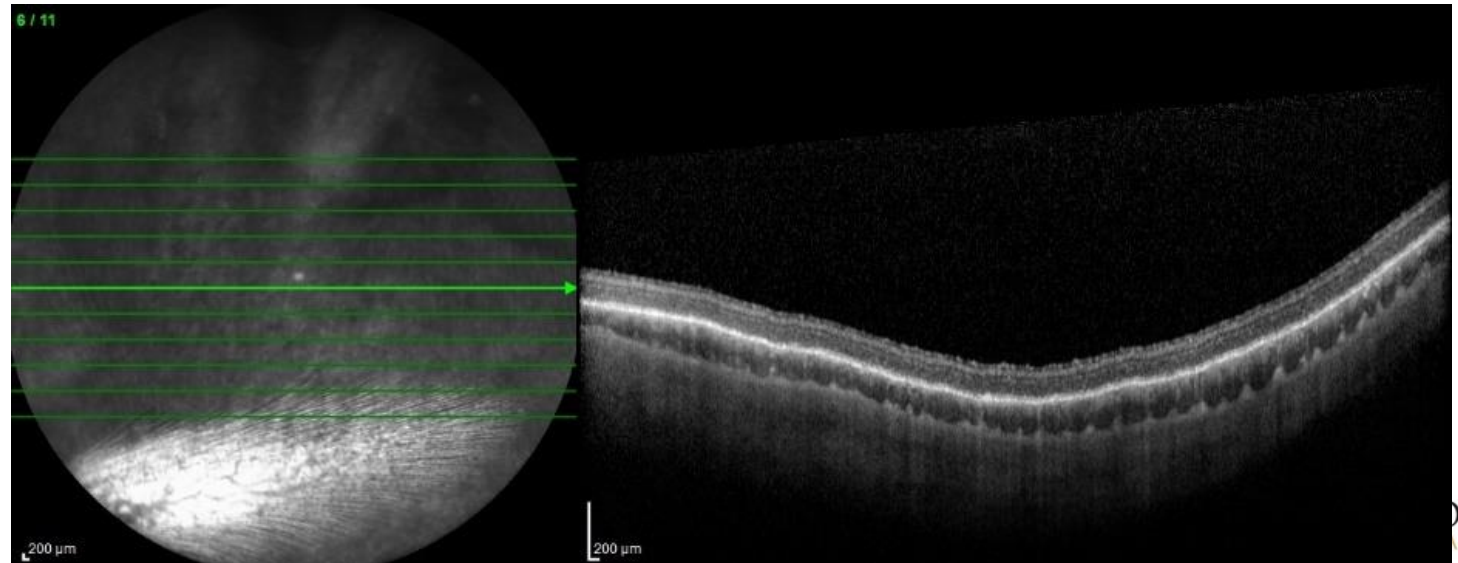
[Day 1]

The suprachoroidal space (SCS) opens posteriorly to the optic nerve head (ONH) after DNA nanoparticle administration.



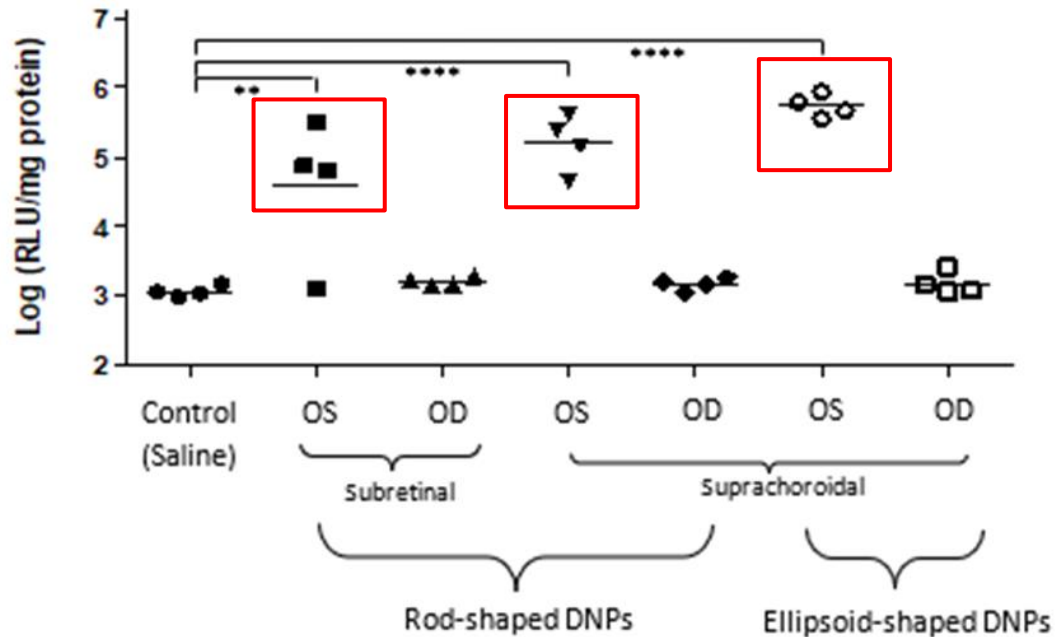
[Day 30]

There is well-tolerated reversible closure of the SCS after DNA nanoparticle administration.

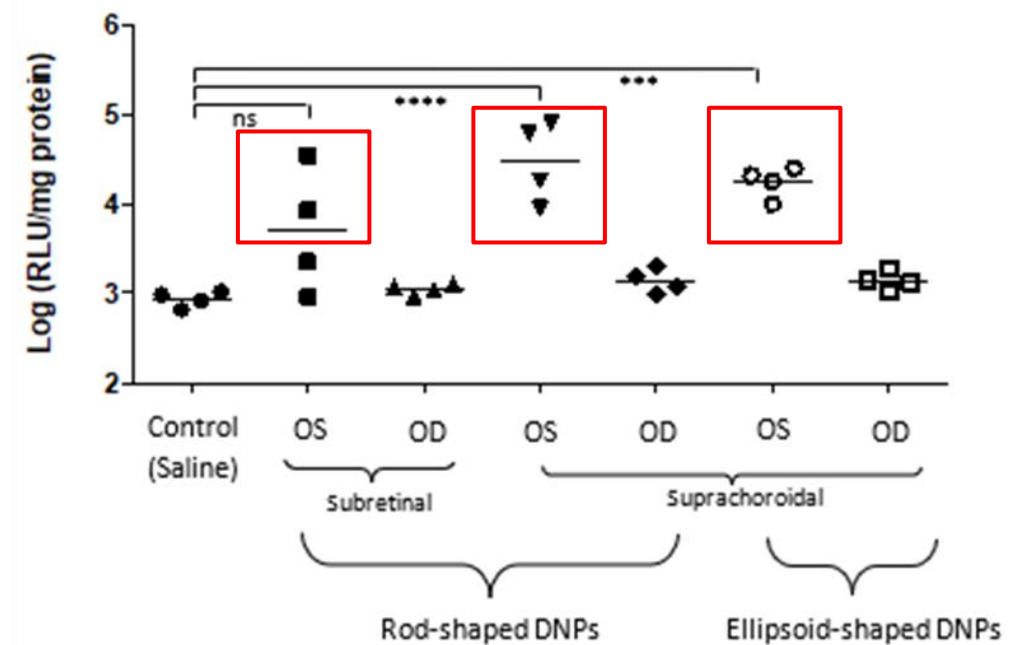


# Preclinical Suprachoroidal and Subretinal Injections of DNA Nanoparticles Produced Comparable Luciferase Activity

CHOROID-RPE-Sclera  
Non-Viral Luciferase, Rabbit



RETINA  
Non-Viral Luciferase, Rabbit

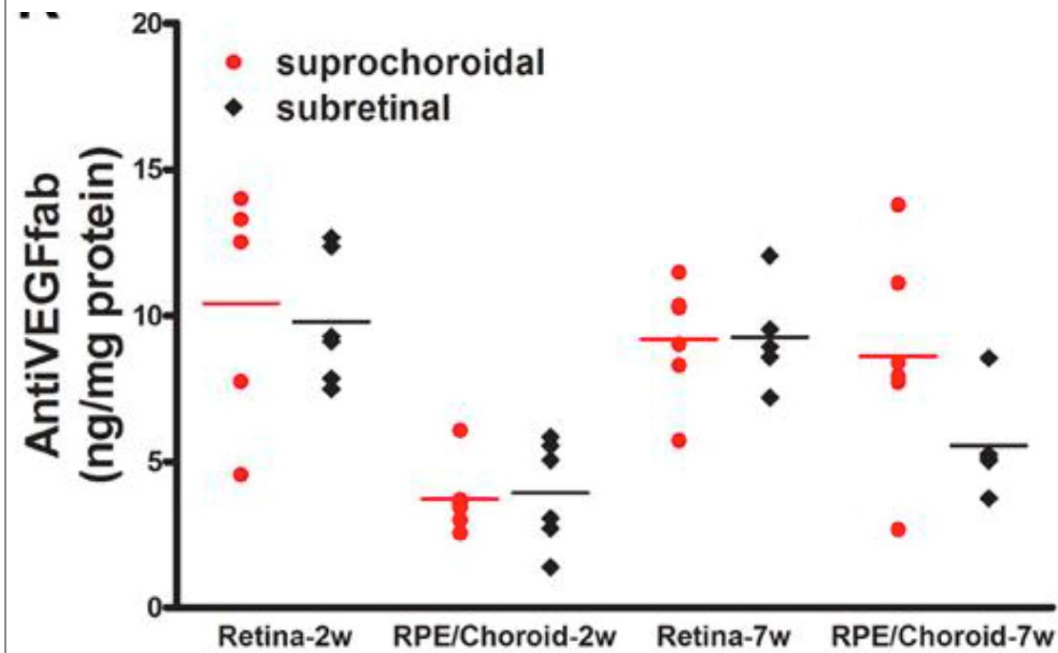


DNA Nanoparticles Transfect Choroid and Retina

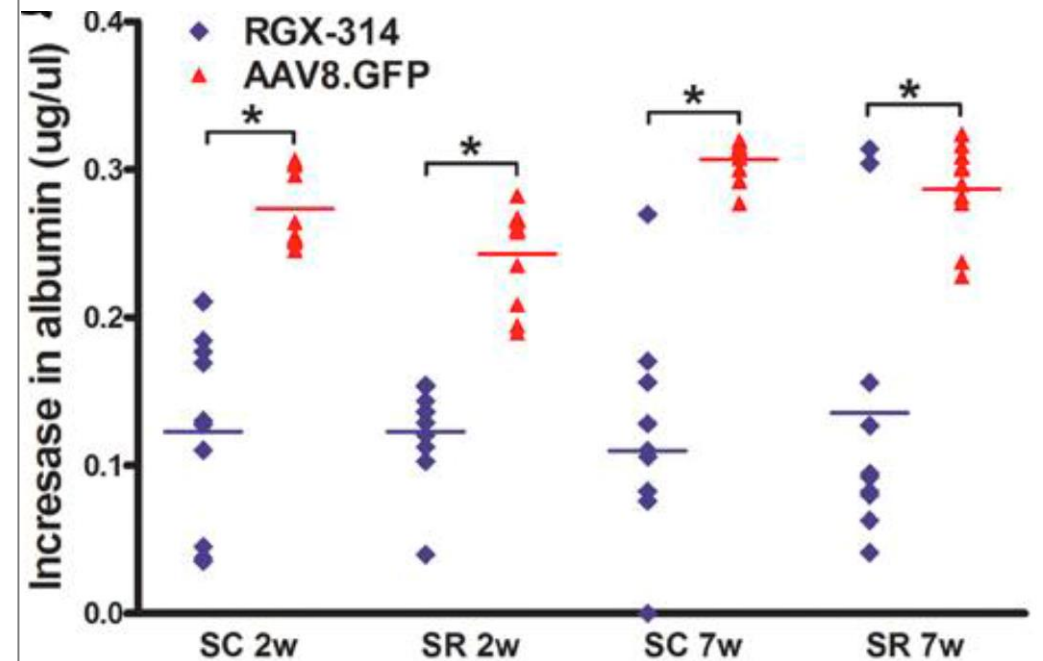
# Published Preclinical Data on Viral Vectors in SCS

Suprachoroidal delivery of NAV AAV8-based gene therapy produced similar protein expression and suppression of vascular leakage

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



# Broad Applicability of SCS Injection Platform: Integrin Inhibitor

## Primary Need

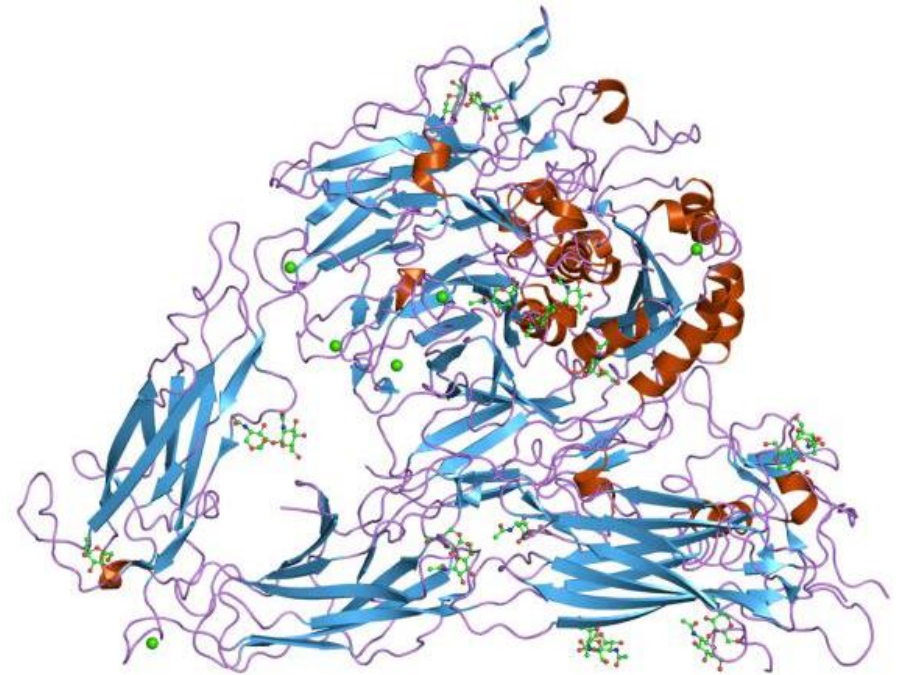
Targeted delivery addressing  
disease-modifying pathways  
beyond anti-VEGF therapy

## The Opportunity

- Novel target
- Early industry validation in DME and AMD
- Advantages of targeted suprachoroidal administration with potential for:
  - Extended durability
  - Improved safety profile, through compartmentalization in SCS
  - Enhanced efficacy, through drug levels at affected tissues
- Limited potential competition

# Integrin Inhibitors

- Multi-functional cell-adhesion molecules, heterodimeric receptors with  $\alpha$  and  $\beta$  subunits
  - Connect extracellular matrix (ECM) to actin cytoskeleton in the cell cortex
  - Regulate cellular adhesion, migration, proliferation, invasion, survival, and apoptosis
  - Also play a role in inflammation, angiogenesis and fibrosis
- Integrins  $\alpha_v\beta_3$  and  $\alpha_v\beta_5$  implicated in DR and AMD
  - Given unique MOA, could serve as:
    - Primary therapy
    - Adjunctive therapy to anti-VEGF
    - Secondary therapy in refractory cases
- Clearside anti-integrin therapy
  - Formulated as a suprachoroidal suspension with extended duration potential
  - Initiating preclinical studies



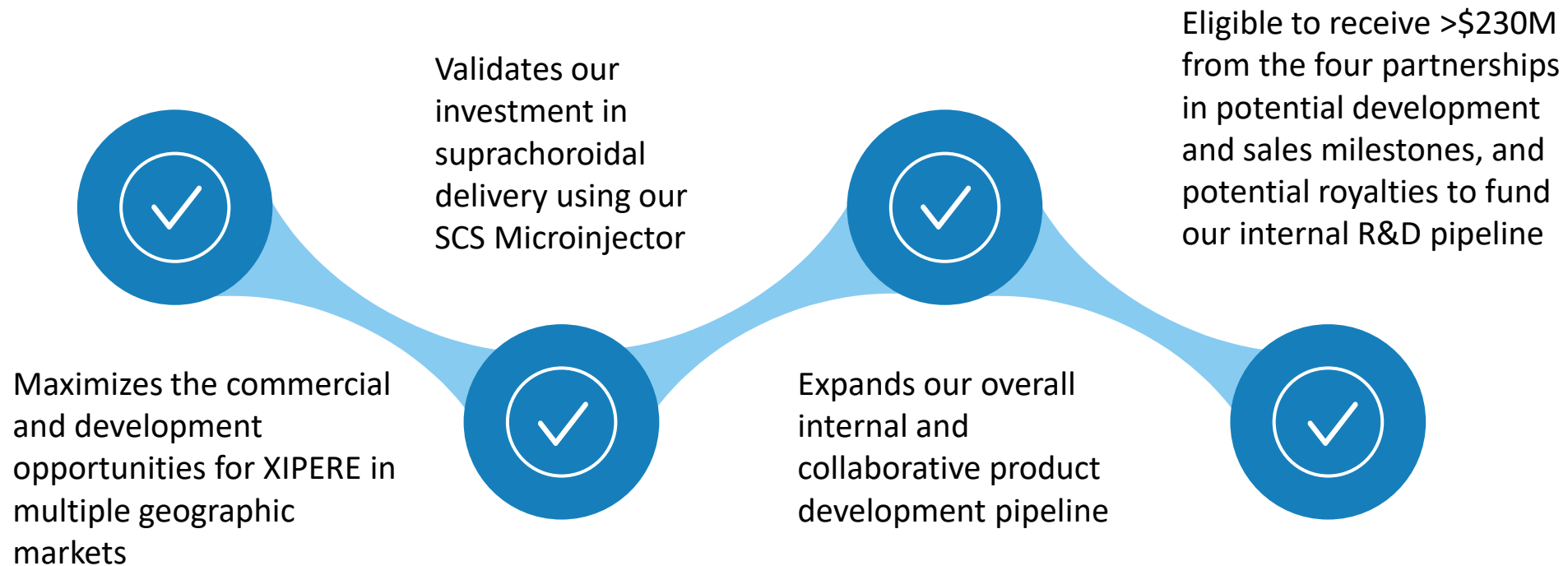
# Corporate Collaborations

# Four Partnering Deals to Drive Growth

**BAUSCH** Health



**aura**



# Enabling In-office Delivery of Gene Therapy for Retinal Disease

## The Opportunity: Gene Therapy

- Exclusive worldwide rights to our SCS Microinjector for delivery of adeno-associated virus (AAV)-based therapeutics to the suprachoroidal space to treat wet AMD, diabetic retinopathy and other conditions for which anti-VEGF treatment is the standard of care
- Delivery of gene therapy through the SCS may provide a targeted, in-office, non-surgical treatment approach option
- Encouraging preclinical results delivering RGX-314 into the SCS

## The Terms:

- \$2M upfront / exercise of option
- Up to \$34M in development milestones across multiple indications
- Up to \$102M in sales milestones
- Mid single digit royalties on net sales of products using SCS Microinjector



# REGENXBIO Initiating Two Phase 2 Trials Using SCS Microinjector®

- RGX-314 for Treatment of Wet Age-Related Macular Degeneration (wet AMD)
  - REGENXBIO Phase 2 AAVIATE trial of suprachoroidal delivery of RGX-314 using SCS Microinjector™ for treatment of wet AMD **is active**. Enrollment expected to begin in **Q3 2020**.
  - AAVIATE is a multi-center, open-label, randomized, active-controlled, dose-escalation study that will evaluate the efficacy, safety and tolerability of suprachoroidal delivery of RGX-314. N=40 patients with severe wet AMD who are responsive to anti-VEGF treatment.
  - Interim data is expected from Cohort 1 by the **end of 2020**.
- RGX-314 for Treatment of Diabetic Retinopathy (DR)
  - REGENXBIO plans to initiate Phase 2 trial of suprachoroidal delivery of RGX-314 using SCS Microinjector for treatment of DR in **second half of 2020** with interim data expected **in 2021**.



# Optimizing Ocular Oncology Drug Delivery with SCS Microinjector™

## The Opportunity: Ocular Oncology

- Worldwide licensing agreement for the use of our SCS Microinjector to deliver their proprietary drug candidates into the SCS for the potential treatment of certain ocular cancers, including choroidal melanoma
- Non-surgical alternative to intravitreal delivery of Aura's oncology drug candidates via our SCS Microinjector
- Choroidal melanoma is the most common, primary intraocular tumor in adults
- Expect Aura to initiate clinical testing using our SCS Microinjector in the **third quarter of 2020**

aura

## The Terms:

- Potential future financial upside for Clearside from pre-specified development and sales milestones
- Royalties on net sales of products using SCS Microinjector

# Novel Approach to Targeting Uveitic Macular Edema Using SCS Microinjector<sup>®</sup>

**XIPERE<sup>™</sup>**  
(triamcinolone acetonide suprachoroidal  
injectable suspension) 40 mg/mL

- Macular edema is the leading cause of vision loss in patients with non-infectious uveitis
- Pivotal Phase 3 PEACHTREE trial met its primary endpoint
- MAGNOLIA Phase 3 extension study demonstrated durability
- If approved, XIPERE would be the first therapy for this indication
- Expect to resubmit NDA with three months additional stability data in 1H, 2021

# Maximizing Commercial Potential of XIPERE™

## The Opportunity: XIPERE Commercialization & Development

- Exclusive license for XIPERE commercialization and development in the U.S. and Canada
- Exclusive options for (i) Europe and the United Kingdom, (ii) Australia and New Zealand, (iii) South America & Mexico
- Right to develop and commercialize XIPERE for additional ophthalmic indications including diabetic macular edema and retinal vein occlusion
- Right to develop and commercialize a specified set of corticosteroids and non-steroidal anti-inflammatory drugs in ophthalmology using our proprietary SCS Microinjector

## The Terms:

- Received \$5M upfront payment
- Up to \$15M in FDA approval and pre-launch milestones
- Up to \$57.3M in milestone payments
- Tiered royalties at increasing percentages from the high-teens to 20% on annual net sales

# Maximizing Commercial Potential of XIPERE™

## The Opportunity: XIPERE Commercialization & Development in Greater China and South Korea

- Exclusive license to develop and commercialize XIPERE for indications associated with uveitis in Greater China (mainland China, Hong Kong, Macau and Taiwan) and South Korea
- Right to develop and commercialize XIPERE for additional ophthalmic indications in Greater China and South Korea, with consent from Clearside

## The Terms:

- Received \$4M upfront payment
- Up to \$31.5M in approval, development and sales milestones
- Tiered royalties of 10% to 12% based on annual net sales starting at product launch and going until the later of ten years after launch or loss of patent protection or marketing exclusivity in the territory



# Research and Development Investment Highlights

Versatile therapeutic platform with proprietary access to the suprachoroidal space

## Patented technology & delivery approach

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Scientific presentations and publications

✓ **1Q 20**

- *Ophthalmology*
- Angiogenesis
- Macula Society

✓ **2Q 20: ARVO**

**3Q 20: ASRS & Retina Society**

**4Q 20: AAO**

## Building an internal R&D pipeline

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✓ **Mid 2020: IND**  
Submission for CLS-AX

**YE 20: Initiate Phase 1/2a**  
Trial for CLS-AX

**2H 20: Initiate Integrin**  
Inhibitor Preclinical Studies

Exploratory preclinical SC  
non-viral vector delivery  
studies ongoing

## Partnering to expand use of SCS platform

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**REGENXBIO: RGX-314\***

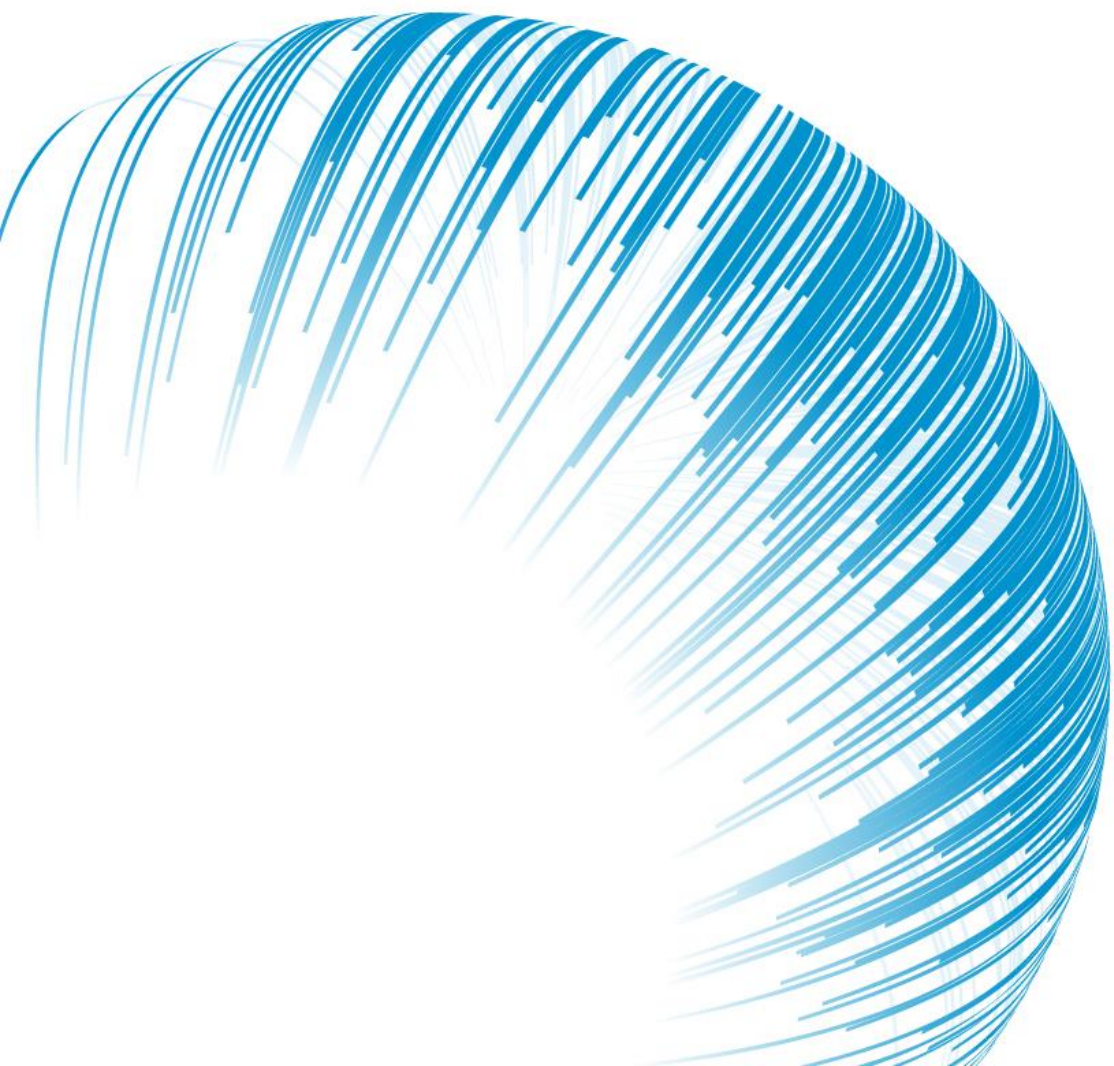
✓ **3Q 20: Initiate Phase 2**  
AAVIATE Trial in wet AMD

**YE 20: AAVIATE Cohort 1 Data**

**2H 20: Initiate Phase 2 in DR**

**AURA: AU-011^**

**3Q 20: Initiate Phase 2 Clinical**  
Testing in Choroidal Melanoma



Nasdaq: CLSD