Advancing Targeted, Compartmentalized & Long-Acting Depot Delivery: Suprachoroidal Delivery of Particulate Formulations

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Disclosures

- Dr. Kansara has an employment relationship and holds equity in Clearside Biomedical

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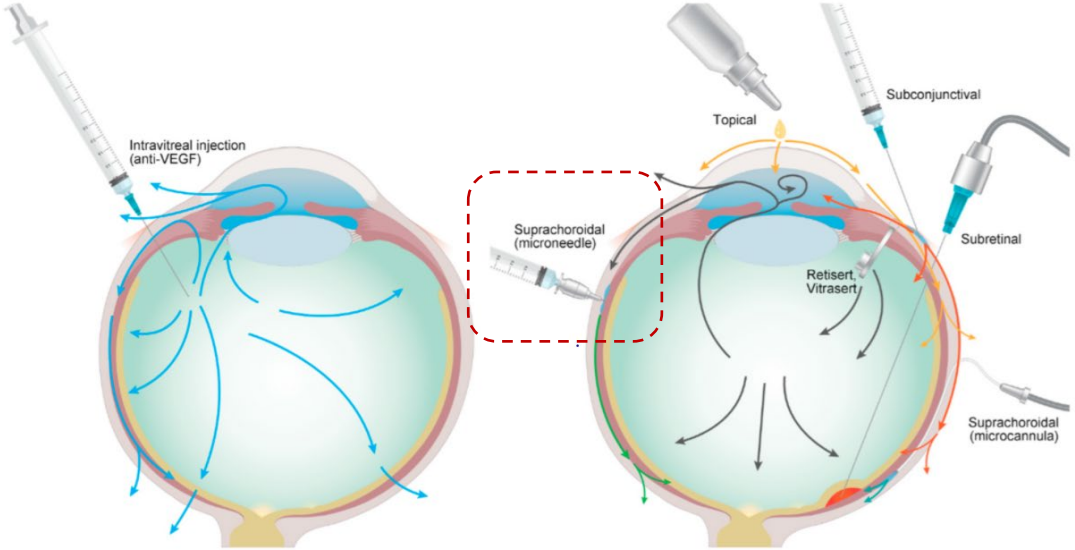
Suprachoroidal Delivery of Small Molecule Suspensions

- Suprachoroidal Delivery
  - What is the suprachoroidal space (SCS)?
  - SCS Microinjector®-based SCS Delivery
- SCS Delivery of Small Molecule Suspensions
  - Compartmentalized
  - Targeted
  - Long-acting
- Case Study: CLS-AX for wAMD
  - Preclinical data: PK and Pharmacology
  - Clinical data
- Take home messages

Routes of Administration for Chorioretinal Drug Delivery



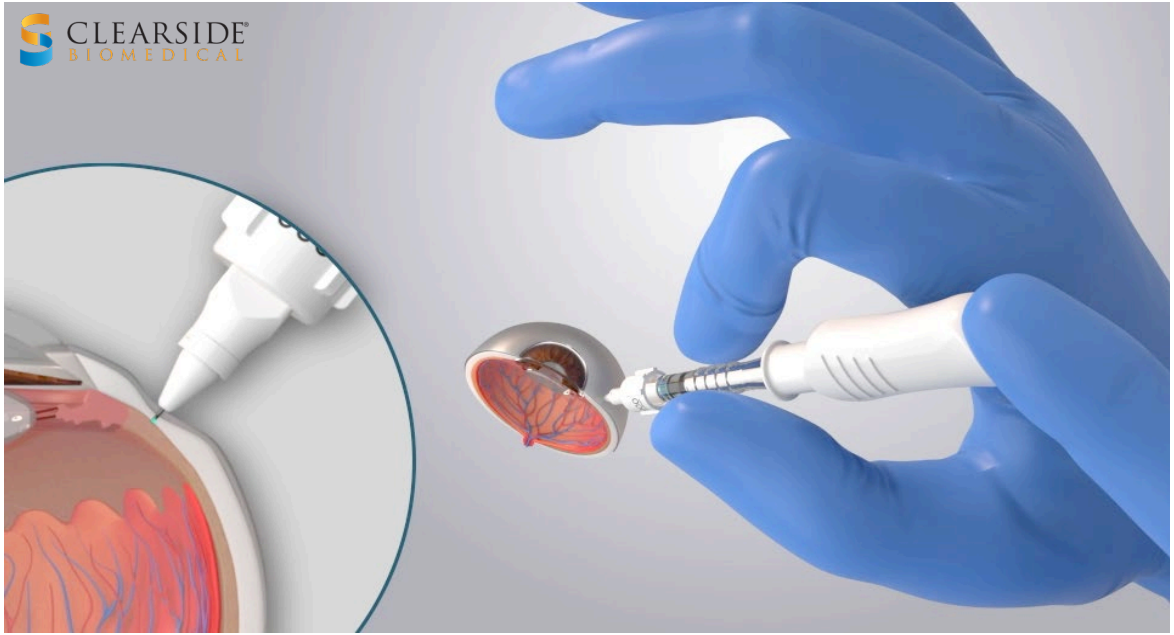
Kim, H.M.; Woo, S.J. Ocular Drug Delivery to the Retina: Current Innovations and Future Perspectives. Pharmaceutics 2021, 13, 108.

Potential Ocular Tolerability and Safety Risks
Suprachoroidal Vs. Intravitreal Administration

	Suprachoroidal suspension	Intravitreal Suspension	Intravitreal "soft" implant (hydrogel)	Intravitreal solid implant
Needle gauge → endophthalmitis	30 G	25G	25-27G	22-25G
Risk of depot migration into the anterior chamber	none	high	moderate	low - moderate
Drug exposure to the non-target tissues (lens, aqueous humor, cornea)	none - low	moderate - high	moderate - high	moderate - high
Risk of vitreous floater	none	moderate - high	moderate	low

Röck D, Bartz-Schmidt KU, Röck T. Risk factors for and management of anterior chamber intravitreal dexamethasone implant migration. BMC Ophthalmol. 2019 May 28;19(1):120.
CLINICAL TRIAL DOWNLOAD: Discussing New Safety Data on GB-102 Early results for a potential 6-month wet AMD treatment. *RETINAL PHYSICIAN*MAY 1, 2019.
www.asrs.org. fact-sheet-30-intravitreal-injections.

Suprachoroidal Delivery using SCS Microinjector®



Clearside Biomedical's SCS Microinjector®

Source: Clearside Biomedical

SCS Microinjector® is The First and Only FDA-Approved Way of Delivering Therapeutics to the Suprachoroidal Space[1]

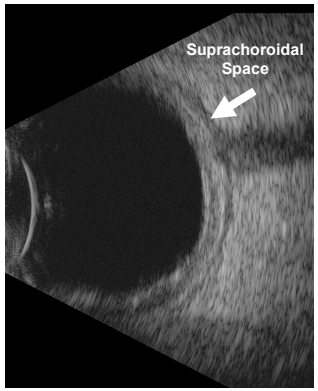
SCS Microinjector® has been well accepted by physicians in clinical trials to date[2]

[1]XIPERE has been approved by the FDA for suprachoroidal use with the SCS Microinjector®
[2]Retina 44(6):p 939-949, June 2024. Wycoff, Charles et al. SUPRACHOROIDAL SPACE INJECTION TECHNIQUE Expert Panel Guidance.

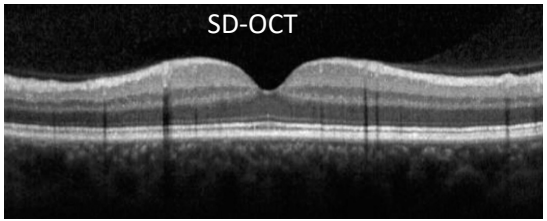
Clinical Visualization and Monitoring of Suprachoroidal Space

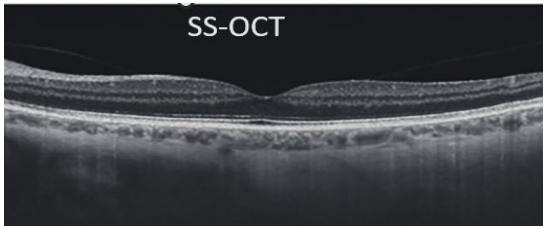
EDI SD-OCT Could Be The Most Accurate Modality to Visualize The SCS

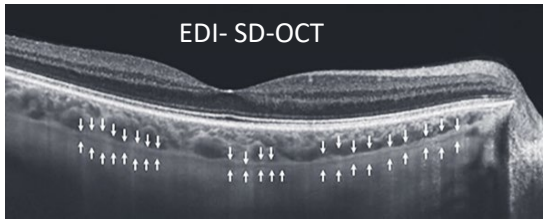
Ultrasound B-Scan:
"Pre-OCT" era



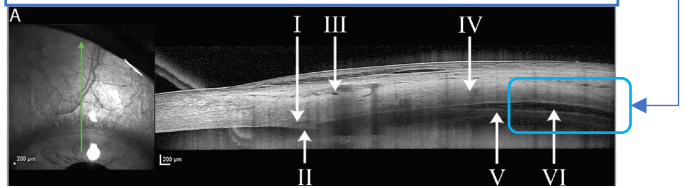
OCT / SD-OCT / EDI-SD-OCT and Thermal Imaging



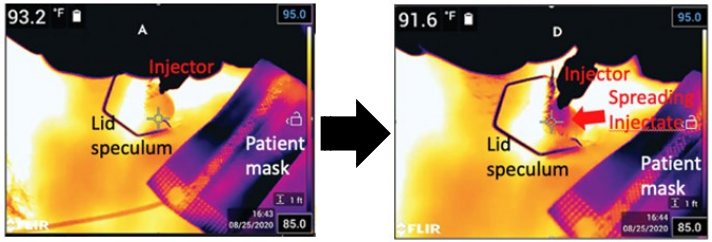




Anterior Segment OCT
Post-injection SCS Expansion, **Anterior**, *Clinical Trial Subject, SCS Microinjector®*



Thermal Imaging

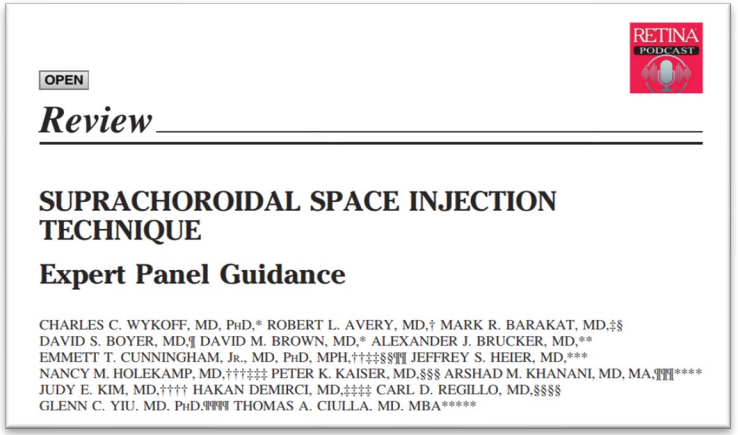


SC injections with Clearside Biomedical's SCS Microinjector®

Yiu et al., JAMA Ophthalmol, 2014 | Asian J Ophthalmol. 2019;16:323-328. Optimized imaging of the suprachoroidal space with swept-source OCT. | Int Ophthalmol Clin. 2019 Winter; 59(1): 195-207. Medical and Surgical Applications for the Suprachoroidal Space. | Retinal Physician. 2021. The Latest in the Suprachoroidal Drug Delivery Space. | Lampen et al. Ophthalmic Surg Lasers Imaging Retina. 2018;49(9):692-697.

Commercial and Clinical Acceptance of SCS Injection Procedure Using SCS Microinjector®

- SCS Injection Procedure using SCS Microinjector® across has been **well-accepted by retinal physicians** with **thousands of injections** performed to date, including in the commercial use of XIPERE®
- Overall, across 8 clinical trials involving NIU, DME, and RVO, the **safety profile** of SCS injections, either as monotherapy or in conjunction with IVT injection, is **comparable to that reported in registration trials involving IVT injections alone**.
- Physicians' real-world perspective: **92% of participants were satisfied with SCS-TA treatment outcomes**. Early adopters of SCS-TA indicate that the suprachoroidal injection technique was **easy to learn and resulted in favorable patient outcomes** consistent with clinical trial data.


OPEN

Review

SUPRACHOROIDAL SPACE INJECTION TECHNIQUE

Expert Panel Guidance

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Henry *et al. BMC Research Notes* (2024) 17:317
https://doi.org/10.1186/s13104-024-06969-4

BMC Research Notes

RESEARCH NOTE Open Access

Early adoption of triamcinolone acetonide suprachoroidal injection for uveitic macular edema: a physician survey

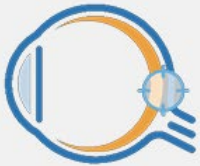
Christopher R. Henry[1], Scott D. Walter[2], Peter Y. Chang[3], David J. Warrow[4], Parisa Emami Naeini[5], Kevin J. Blinder[6], Teresa Brevetti[7], Mohamed Yassine[7], Mark S. Dacey[8], David S. Chu[9], Veena R. Raiji[10], Lana M. Rifkin[11], Milan Shah[12] and Michael A. Singer[13*]

Macula Society 2021. Kurup, et. al, *Safety of the Suprachoroidal Injection Procedure Utilizing SCS Microinjector® across Three Retinal Disorders.*
TVST Oct 2020 Vol 9, 27. Wan et. al, Clinical Characterization of Suprachoroidal Injection Procedure Utilizing Microinjector Across Three Retinal Disorders.
Henry CR, et al. Early adoption of triamcinolone acetonide suprachoroidal injection for uveitic macular edema: a physician survey. BMC Res Notes. 2024 Oct 23;17(1):317.

Benefits to Patients and Physicians for using SCS Microinjector®

Enhanced Safety

Much lower risk of endophthalmitis as direct contact to immune system vs intravitreal injection



Injectate Flows to Back of the Eye

Reduced risk of floaters, snow globe effect, or other visual disturbances

No Implants or Devices in the Vitreous

Can be easily re-dosed for potentially longer durability

Injection Similar to Intravitreal

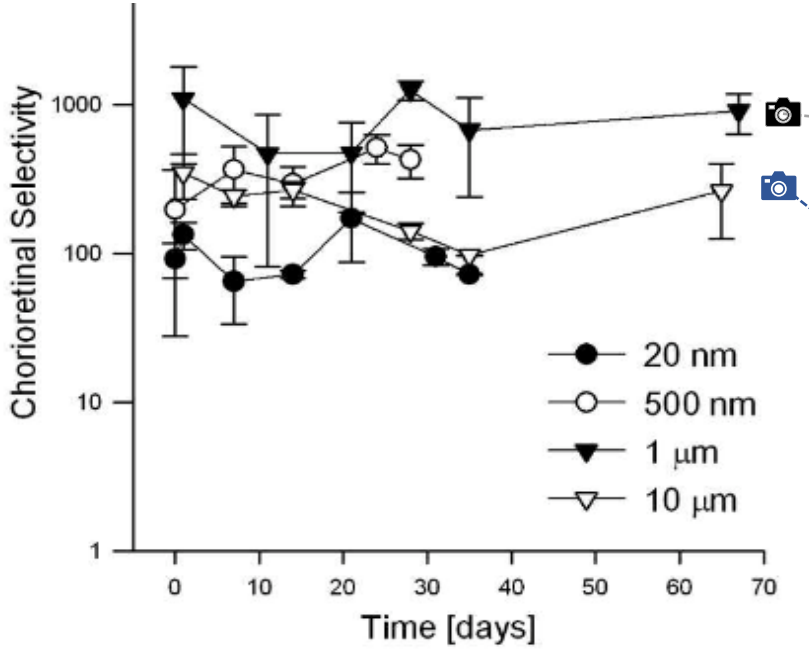
Advanced technology requires only a few seconds longer for each injection

Source: Clearside Biomedical

Suprachoroidal Delivery Accommodates a Range of Particulate Formulations and Offers Sustained Retention in the SCS

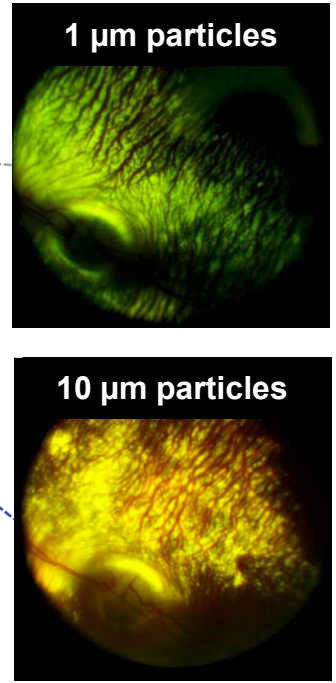
Chorioretinal Selectivity of SCS Administration

SCS Administration of various particle sizes in rabbit model



Fundus Images under Fluorescence

in vivo, 60 days post injection

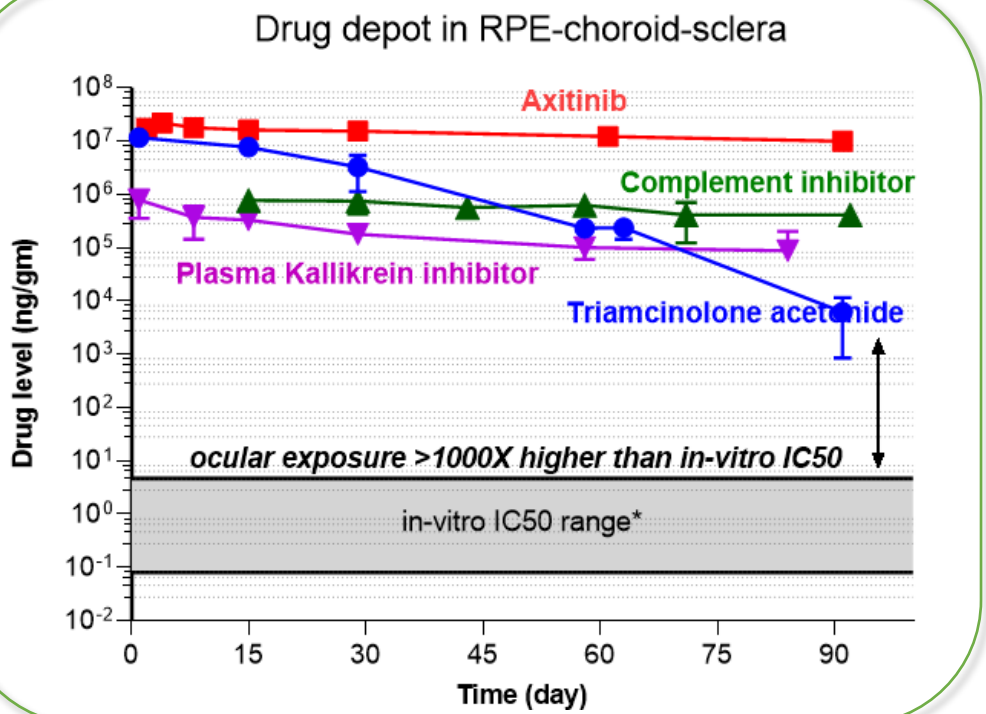


Patel SR, Berezovsky DE, McCarey BE, Zarnitsyn V, Edelhauser HF, Prausnitz MR. Targeted administration into the suprachoroidal space using a microneedle for drug delivery to the posterior segment of the eye. Invest Ophthalmol Vis Sci. 2012;53(8):4433-4441. Published 2012 Jul 1. doi:10.1167/iovs.12-9872

Suprachoroidal Delivery of Small Molecule Suspensions Offers Potential of Long-Acting Duration

Rabbit Ocular Pharmacokinetic

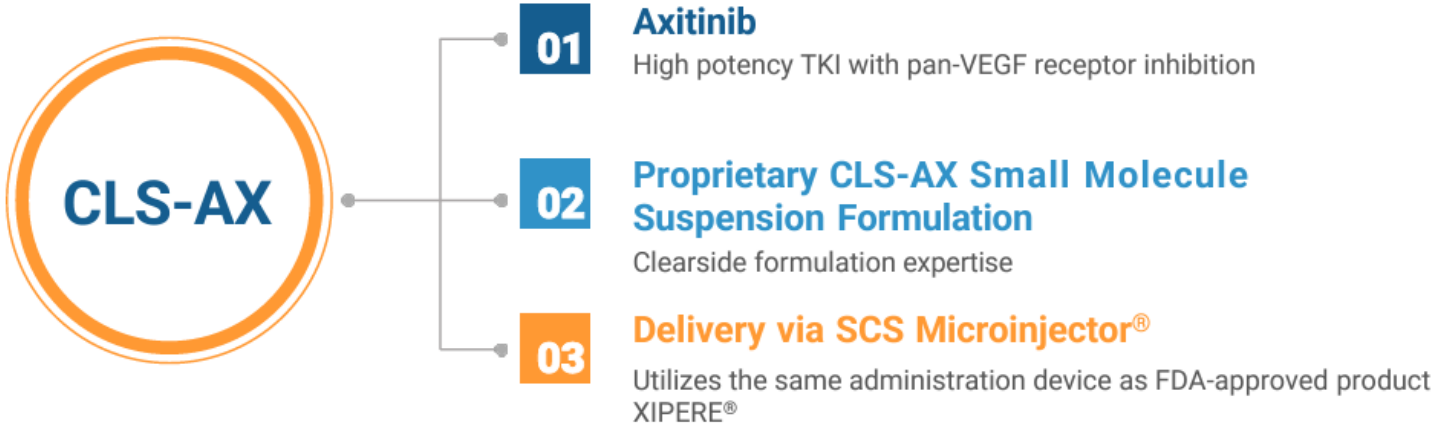
- Dutch-Belted Pigmented Rabbits
- Single unilateral suprachoroidal (SC) injection
- N=4 eyes/ timepoint



Source: Data on file (Clearside)

*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

Leveraging Synergistic Combination of A Potent Small Molecule Suspension and Suprachoroidal Injection



Targeted to Macula, Compartmentalized to Chorioretina, Long-acting Suspension Depot

Pan-VEGF Inhibition via A Highly Potent and Selective Tyrosine Kinase Inhibitor, Axitinib For the Treatment of wet Age-Related Macular Degeneration

Inhibits ALL VEGF Receptors (VEGFR-1, VEGFR-2, VEGFR-3)

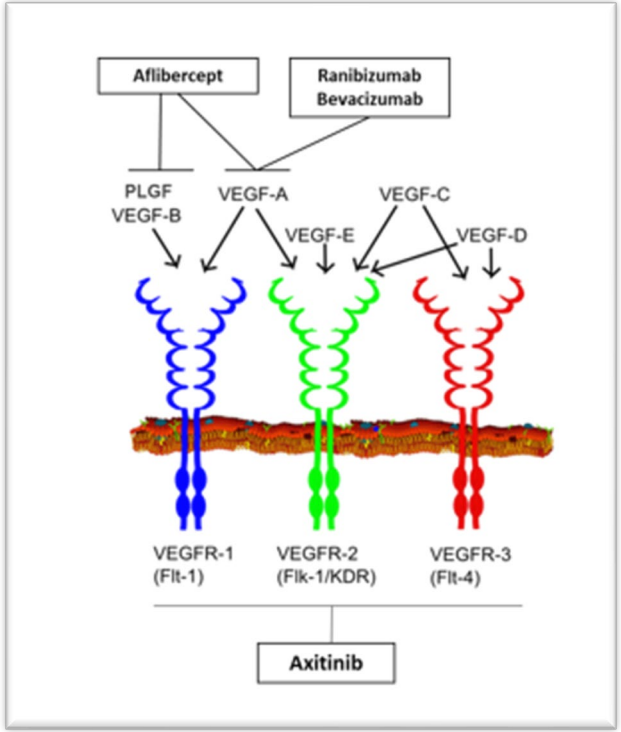
- Intrinsic pan-VEGF inhibition through receptor blockade
- More active than anti-VEGF-A in *in-vitro* angiogenesis model[1-2]
- Approved AMD treatments are focused VEGF-A inhibitors

Tyrosine kinase inhibitor (TKI) with the highest potency

- >10x more potent than other TKIs in in-vitro studies[3]
- Better ocular cell biocompatibility than other TKIs[4]
- More active than other TKIs for experimental corneal neovascularization in preclinical models

Small molecule formulated into suspension for SCS delivery

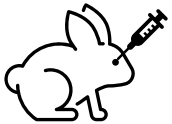
- Preclinical data showed regression of angiogenesis
- FDA-approved renal oncology treatment with established mechanism of action



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. GrossGoupil et al. Axitinib: A Review of its Safety and Efficacy in the Treatment of Adults with Advanced Renal Cell Carcinoma. Clinical Medicine Insights: Oncology 2013:7. | 4. Thiele 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.

Suprachoroidal Axitinib Suspension Provides Superior Bioavailability in the Posterior Segment Compared to Intravitreal Administration At an Equivalent Dose

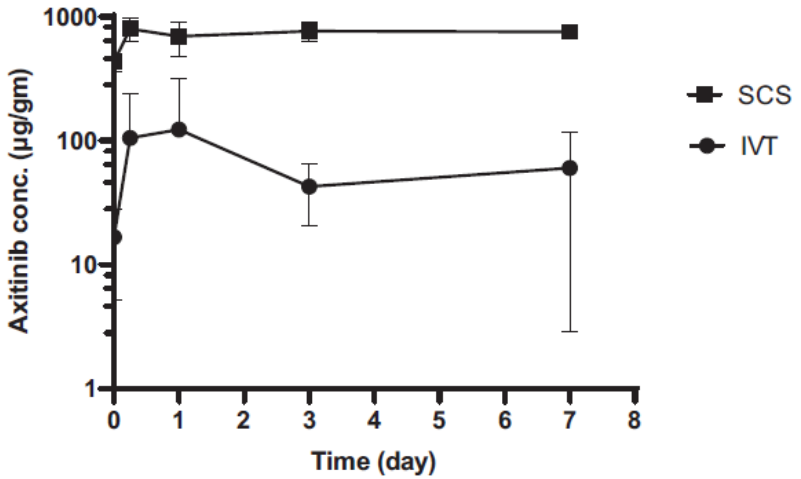
Rabbit Ocular Pharmacokinetics



- New Zealand White Rabbits
- Single bilateral suprachoroidal (SC) injection (1 mg/eye)
- Single bilateral Intravitreal injection (1 mg/eye)
- PK: Posterior eye cup (RPE-choroid-retina-sclera), Vitreous, Plasma
- N=4 eyes/ timepoint
- 7-day ocular PK

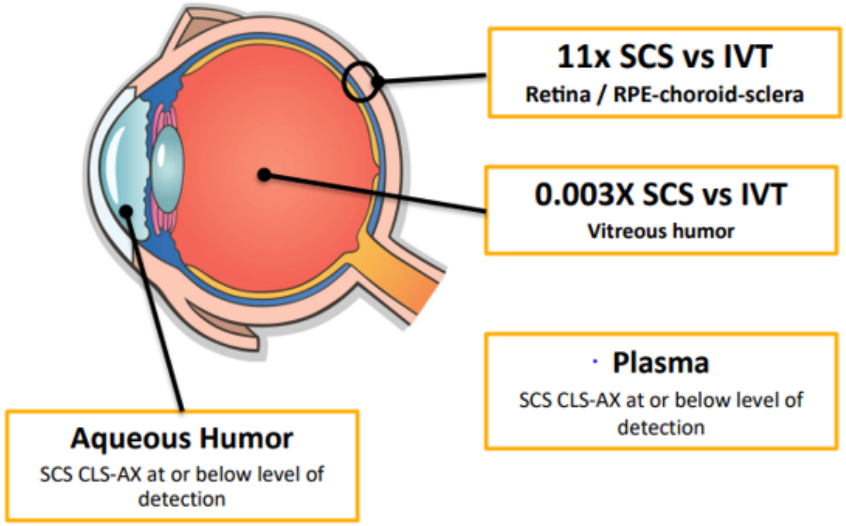
SC injection Vs. IVT injection

PK profiles of axitinib in the Posterior Eye Cup



Kansara VS, Muya LW, Ciulla TA. Evaluation of long-lasting potential of suprachoroidal axitinib suspension via ocular and systemic disposition in rabbits. Transl Vis Sci Technol. 2021;10(7):19.

Suprachoroidal Axitinib Suspension Provides Compartmentalized Delivery to Chorioretina Compared to Intravitreal Administration



Rabbit Model

Values: area under the curve ratios, SCS / IVT

SCS : 1 mg/eye, 100 µL. | IVT: 1 mg/eye, 25 µL

Single bilateral injection, 1-wk rabbit PK studies

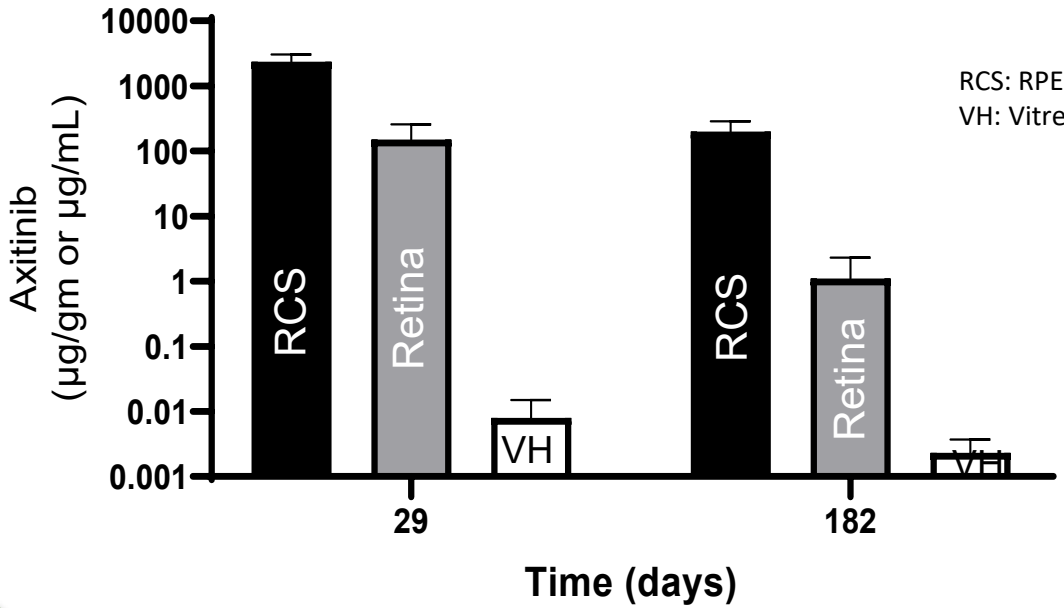
Source: Data on file | Clearside Bio.

Suprachoroidal Axitinib Suspension (CLS-AX) Shows Durability and Compartmentalization In Rabbit Model

Rabbit Ocular Toxicokinetic

- Dutch-Belted Pigmented Rabbits
- Single unilateral suprachoroidal (SC) injection (1 mg/eye)
- N=4 eyes/ timepoint

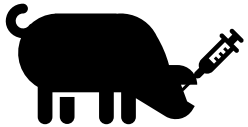
Axitinib levels in ocular tissues post a single bilateral SC injection of CLS-AX



Kansara VS, Muya LW, Ciulla TA. Evaluation of long-lasting potential of suprachoroidal axitinib suspension via ocular and systemic disposition in rabbits. Transl Vis Sci Technol. 2021;10(7):19.

Suprachoroidal Axitinib Suspension Reduces Fluorescein Leakage and New Vessel Growth In Porcine Model

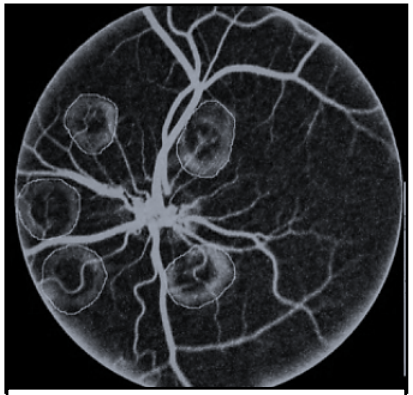
Porcine Laser CNV model



- Laser CNV: 6 lesions per eye
- N=8 Weanling Pigs
- Treatment:
  - OD: Suprachoroidal axitinib (4mg/ 0.1 mL)
  - OS: 0.1 mL Saline
- Single dose followed by imaging at week 1 and week 2

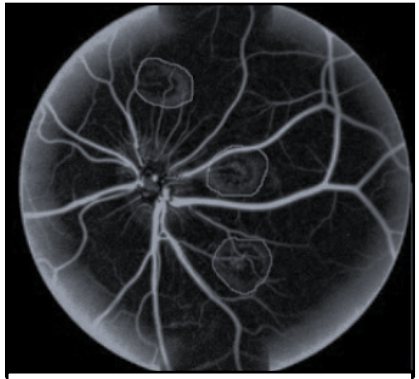
Suprachoroidal axtinib significantly reduced fluorescein leakage| 10.5% @ week 1 (p=0.009) & 16.0% @ week 2 (p=0.0015)

BSS treated eye



Increased vascular leakage
(marked region represents lesion area)

CLS-AX treated eye



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

Source: Data on file | Clearside Bio.

ODYSSEY Phase 2b Clinical Trial

Trial Objectives:
Evaluate safety, efficacy & duration of CLS-AX in participants with wet AMD

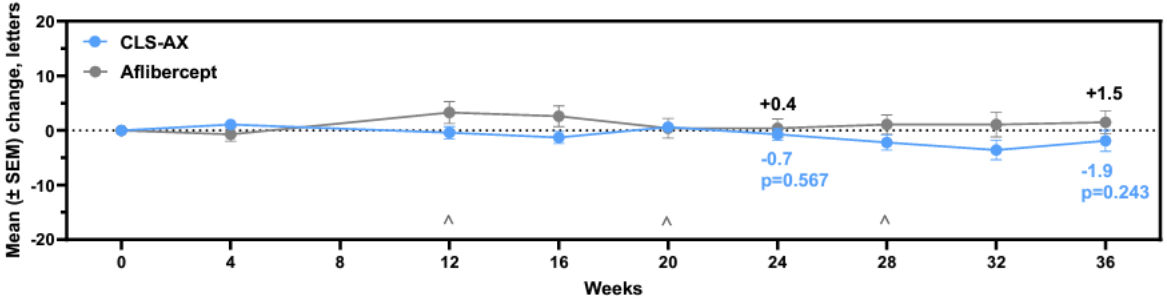
- Primary Outcomes: Mean change in BCVA from Baseline to **Week 36**; Safety & tolerability
- Secondary Outcomes: Other changes in visual function and retinal imaging, including CST; Need for supplemental treatment; Treatment burden as measured by total injections

Participant Profile:
60 total with 2:1 randomization (40 in CLS-AX arm & 20 in aflibercept arm)

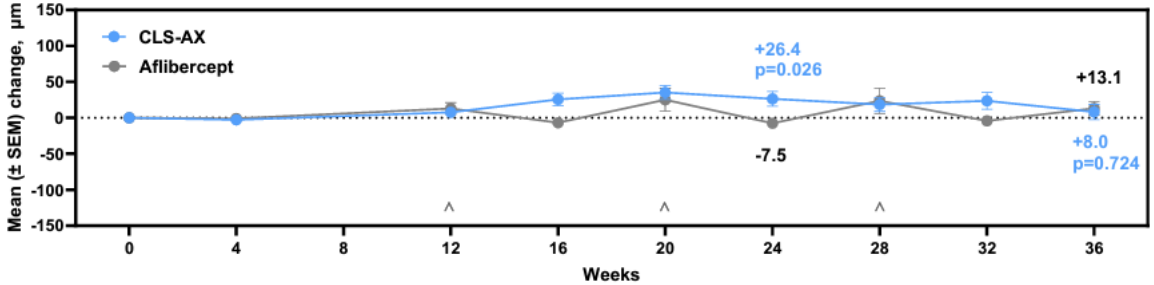
- Treatment experienced participants with reading center confirmation of **persistent active disease**
- Protocol requires **re-dosing with CLS-AX** in study arm
  - Participants receive at least 2 doses of CLS-AX
  - Provides important data to plan Phase 3 in chronic disease

CLS-AX Demonstrates Positive Clinical Activity and Durability in wet AMD Patients

BCVA Within 2 Letters From Baseline at Both Week 24 and Week 36 in CLS-AX Arm



CLS-AX Demonstrates Stable Anatomical Control and Reduces Fluctuation



CLS-AX results do not include supplemental therapy with aflibercept

^Study drug administration for aflibercept participants given at Weeks 12, 20 and 28. Abbreviations: CSRT = central subfield retinal thickness – as reported by the reading center; SEM = standard error of the mean. P-value based on a 2-sample t-test between treatment groups.

CLS-AX Consistently Reduced the Frequency of Injections

Comparison of Wet AMD Treatments Pre- and Post- Randomization

24 Weeks Before and After

Average number of treatments
24 Weeks prior to Screening Visit:
2.95 injections

Average number of treatments
up to 24 Weeks after Baseline Visit:
0.475 injections

Reduced injection frequency by

84%

- Injection post Baseline includes re-dosing with CLS-AX and/or supplementary treatment with aflibercept.
- Injection frequency reduction calculated by the average number of treatments 24 Weeks prior to Screening Visit as compared to average number of treatments up to 24 Weeks after Baseline Visit.

CLS-AX Demonstrated A Positive Safety Profile

Safety Profile

Well-tolerated safety profile through 36 weeks including after mandatory re-dosing of CLS-AX at Week 24

No Serious Adverse Events (SAEs)

No ocular SAEs or treatment-related SAEs:

- No drug or procedure related ocular SAEs
- No reported drug or procedure related systemic SAEs
- No endophthalmitis
- No retinal vasculitis

Positive Adverse Event (AE) Profile

Ocular AEs were considered **clinically mild** in both arms

- Only one reported incident related to mild eye pain out of 84 total CLS-AX injections (1.2%)

Discontinuation Rates

Similar discontinuation rates between treatment and comparator groups

CLS-AX Now Phase 3 Ready Based on Positive ODYSSEY Data

- Achieved Primary Objective: Stable BCVA to Week 36
  Difficult-to-treat Wet AMD participants with confirmed activity
- Compelling injection free rates up to 6 months
  Injection frequency reduced by nearly 84%
- Positive safety profile
  No ocular SAEs or treatment-related SAEs
  CLS-AX was well-tolerated after re-dosing
- Only Phase 2 trial in wet AMD with repeat TKI dosing data to better inform and potentially de-risk Phase 3 design

Take Home Messages

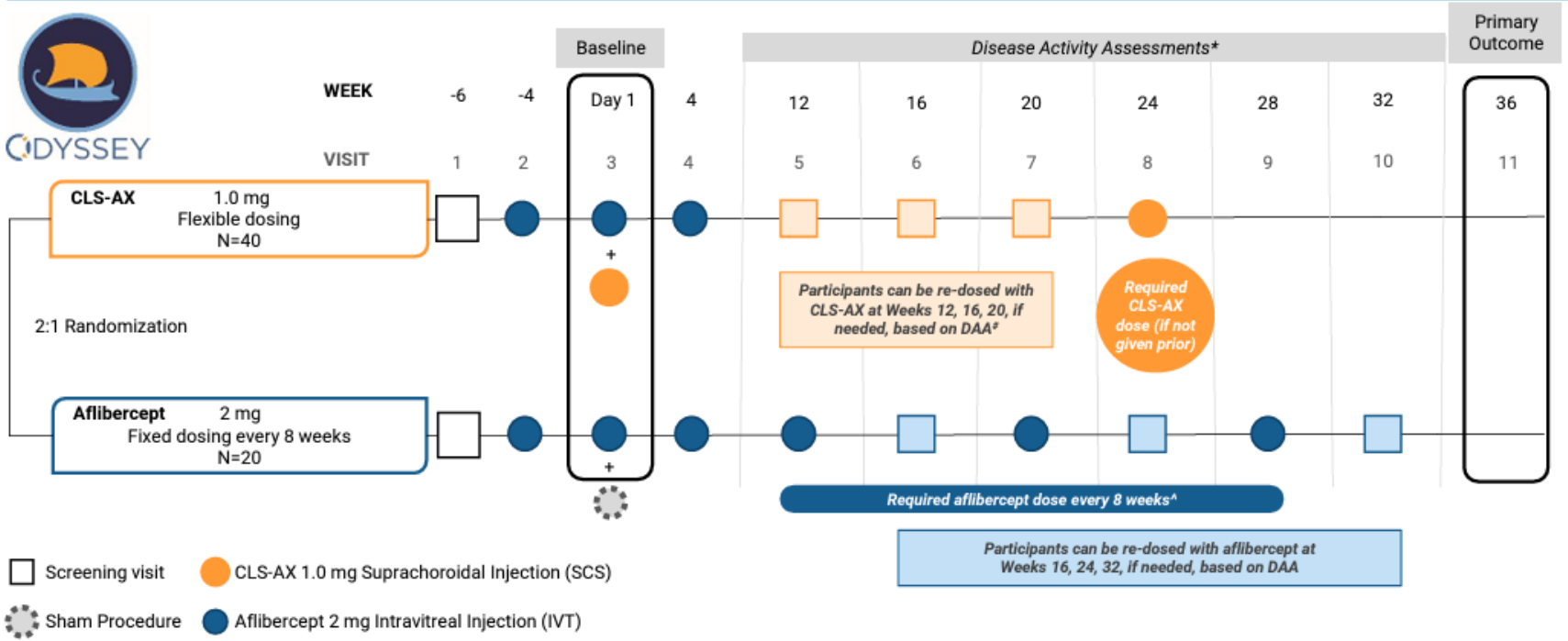
1. The suprachoroidal injection procedure using SCS Microinjector® is safe and well-accepted by clinicians. It can be easily performed in an office-based noninvasive setting.

2. Suprachoroidal delivery of small molecule suspensions offers the potential for compartmentalized, targeted (macula), and sustained drug delivery to the chorioretina.

3. SCS Microinjector-based suprachoroidal delivery of axitinib suspension has demonstrated clinical safety, efficacy, and long-acting potential for wet AMD patients in Phase 2 clinical trials.

Q&A

ODYSSEY Trial Design



#Participants can be re-dosed with CLS-AX up to every 12 weeks: All arms are sham controlled

Disease Activity Assessments (DAA): Conducted at Week 12 through 32 to determine need for supplemental treatment. # In CLS-AX arm, following 3 loading doses of aflibercept and initial dose of CLS-AX at Baseline, participants will receive CLS-AX at least every 24 weeks unless more frequently required based on DAA; if disease is active and participant is <12 weeks since last CLS-AX injection, participant receives dose of aflibercept; if disease is active and participant is >12 weeks since last CLS-AX injection, participant receives dose of CLS-AX. ^ In aflibercept arm, following 3 loading doses of aflibercept, participants will receive aflibercept on fixed dosing regimen every 8 weeks unless more frequently required based on DAA; if disease is active, participant receives dose of aflibercept.

Clearside's Small Molecule Suspension-based Suprachoroidal Injection Platform

Clearside Research and Clinical Development Programs

THERAPEUTIC	MECHANISM	INDICATION	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	APPROVAL	PARTNER
CLS-AX (axitinib)	Tyrosine Kinase Inhibitor	Wet AMD						
Undisclosed	Improve choroidal perfusion	Geographic Atrophy (GA)						
Undisclosed	Modulate pro-inflammatory cells	Geographic Atrophy (GA)						

Commercial Asset: XIPERE® (triamcinolone acetonide injectable suspension) for suprachoroidal use

THERAPEUTIC	LOCATION	INDICATION	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	APPROVAL	PARTNER
XIPERE®	United States	Uveitic Macular Edema[1]						B+L BAUSCH+LOMB
XIPERE® / ARCATUS™	Australia and Singapore	Uveitic Macular Edema[2]				NDAs Accepted		arctic VISION
XIPERE® / ARCATUS™	China	Uveitic Macular Edema[2]						arctic VISION Santen
XIPERE® / ARCATUS™	Asia Pacific ex-Japan	Diabetic Macular Edema[2]						arctic VISION