# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION
**WASHINGTON, D.C. 20549**

# FORM 8-K

**CURRENT REPORT**

**Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934**

**Date of Report (Date of earliest event reported): December 12, 2024**

# Clearside Biomedical, Inc.

**(Exact name of Registrant as Specified in Its Charter)**

| **Delaware** | **001-37783** | **45-2437375** |
|---|---|---|
| **(State or Other Jurisdiction of Incorporation)** | **(Commission File Number)** | **(IRS Employer Identification No.)** |

| | |
|---|---|
| **900 North Point Parkway**<br>**Suite 200**<br>**Alpharetta, Georgia** | **30005** |
| **(Address of Principal Executive Offices)** | **(Zip Code)** |

**Registrant's Telephone Number, Including Area Code: (678) 270-3631**

**(Former Name or Former Address, if Changed Since Last Report)**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

**Securities registered pursuant to Section 12(b) of the Act:**

| **Title of each class** | **Trading Symbol(s)** | **Name of each exchange on which registered** |
|---|---|---|
| Common Stock, par value $0.001 per share | CLSD | The Nasdaq Stock Market LLC |

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

**Item 7.01 Regulation FD Disclosure.**

On December 12, 2024, Clearside Biomedical, Inc. (the "***Company***") updated its corporate presentation for use in meetings with investors, analysts and others. The presentation is available through the Company's website and a copy is attached as Exhibit 99.1 to this Current Report on Form 8-K.

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibit 99.1, is being furnished pursuant to Item 7.01 and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "***Exchange Act***") or otherwise subject to the liabilities of that section, and it shall not be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or under the Exchange Act, whether made before or after the date hereof, except as expressly set forth by specific reference in such filing to this item of this report.

**Item 8.01 Other Events.**

As disclosed above, on December 12, 2024 the Company updated its corporate presentation, which is attached as Exhibit 99.1 hereto. The information on slides 31 through 37 of Exhibit 99.1 is incorporated by reference herein.

**Item 9.01 Financial Statements and Exhibits.**

**(d) Exhibits**

| Exhibit Number | Exhibit Description |
|---|---|
| 99.1 | Corporate Presentation |
| 104 | Cover Page Interactive Data File (the cover page XBRL tags are embedded within the inline XBRL document). |

**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

**Clearside Biomedical, Inc.**

By: /s/ Charles A. Deignan
Charles A. Deignan
Chief Financial Officer

Date: December 12, 2024

Exhibit 99.1


CLEARSIDE
BIOMEDICAL
Investor Presentation
December 2024
™

# 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" or the negative of these terms and other similar words or 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, new risks and uncertainties may emerge from time to time, and 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; adverse differences between preliminary or interim data and final data; 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; Clearside's ability to expand its pipeline; developments and projections relating to Clearside's competitors and its industry; the impact of government laws and regulations; the timing, design and anticipated results of Clearside's preclinical studies and clinical trials and the risk that the results of Clearside's preclinical studies and clinical trials may not be predictive of future results in connection with future studies or clinical trials and may not support further development and marketing approval; findings from investigational review boards at clinical trial sites and publication review bodies; Clearside's estimates regarding future revenue, expenses, capital requirements and need for additional financing; 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, 2023, filed with the U.S. Securities and Exchange Commission (SEC) on March 12, 2024, Clearside's Quarterly Report on Form 10-Q filed with the SEC on November 12, 2024, and Clearside's subsequent filings 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.

# Delivering on the Potential of the Suprachoroidal Space

- **Validated Suprachoroidal Space (SCS) Delivery with Approved Product, Multiple Collaborations, and Comprehensive IP Portfolio**
- **Proven Leader in Suprachoroidal Delivery with Thousands of Injections Performed in the Clinic**
- **Differentiated SCS Clinical Program Targeting Multi-Billion Dollar Wet AMD Market**

# Promising Pipeline Using Clearside's 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 |



[1]XIPERE® (triamcinolone acetonide injectable suspension), for suprachoroidal use has received U.S. FDA Approval and is being commercialized by Bausch + Lomb.
[2]In licensed territories, Arctic Vision is responsible for clinical development of ARCATUS™ (triamcinolone acetonide injectable suspension), also known asARVN001, and known as XIPERE ® in the U.S.

# Multiple Validating Partnerships Expand Utilization of SCS Microinjector® Technology

**SCS Microinjector® Partner Clinical Development Programs**

| THERAPEUTIC | TYPE | INDICATION | IND-ENABLING | PHASE 1 | PHASE 2 | PHASE 3 | APPROVAL | PARTNER |
|---|---|---|---|---|---|---|---|---|
| Bel-Sar | Viral-like Drug Conjugate | Choroidal Melanoma | CoMpass | | | | | aura |
| ABBV-RGX-314 | AAV Gene Therapy | Diabetic Retinopathy (DR) Diabetic Macular Edema | ALTITUDE | | | | | REGENXBIO abbvie |
| ABBV-RGX-314 | AAV Gene Therapy | Wet AMD | AAVIATE | | | | | REGENXBIO abbvie |
| Avoralstat | Plasma Kallikrein Inhibitor | Diabetic Macular Edema | | | | | | biocryst |

aura

### Ocular Oncology

**2024:** Actively enrolling Phase 3

REGENXBIO

### Gene Therapy

**Q4 2024:**

- Wet AMD: Enrolling new cohort at dose level 4
- DME: Enrolling new cohort at dose level 4

**1H 2025:** Initiate global pivotal trial in DR

biocryst

### Plasma Kallikrein Inhibitor

- **2024:** Conduct formulation and nonclinical work
- **2025:** Begin clinical trials



[1]XIPERE® (triamcinolone acetonide injectable suspension), for suprachoroidal use has received U.S. FDA Approval and is being commercialized by Bausch + Lomb.
[2]In China, Arctic Vision is responsible for clinical development of ARCATUS™ (triamcinolone acetonide injectable suspension), formerly referred to as ARVN001, and known as XIPERE ® in the U.S.

# Core Competencies in Delivery & Formulation Drive Patented Technology

## KEY INTELLECTUAL PROPERTY COMPONENTS

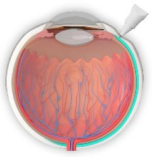
1. **Comprehensive IP portfolio** that includes protection of: SCS delivery technology, proprietary SCS Microinjector®, treatment of various conditions with SCS administration of therapeutic products
2. **28 U.S. and >80 European and International issued patents** with multiple pending patent applications
3. Granted patents provide exclusivity for our delivery technology and product candidates to mid-2030s with pending applications **potentially extending exclusivity beyond 2040**

### DEVICE PATENTS

- SCS Microinjector® features
- Methods of using SCS Microinjector® for drug delivery

### DRUG PATENTS

- Administration of a variety of drugs to the suprachoroidal space by microinjection



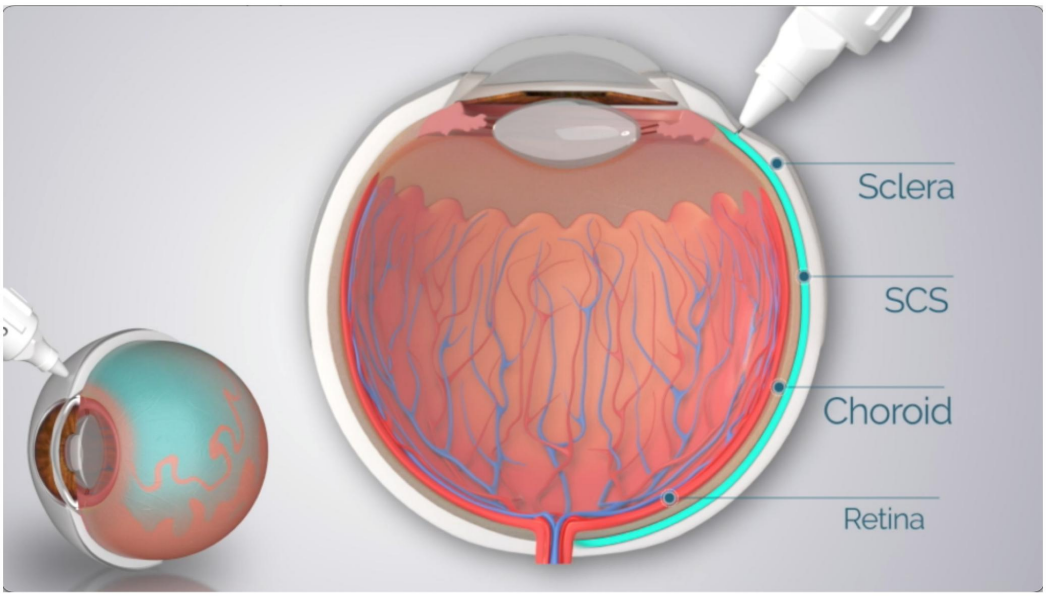
### DISEASE PATENTS

- Methods of treating ocular disorders by SCS administration

# Proven Commercial Capabilities in Suprachoroidal Delivery

# Suprachoroidal Delivery via SCS Microinjector®

# Delivering on the Potential of the Suprachoroidal Space (SCS®): A Novel Approach to Drug Delivery Into the Back of the Eye



# Benefits for Patients and Physicians Using SCS Microinjector® Delivery

## Enhanced Safety

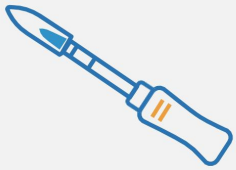
Much lower risk of endophthalmitis as direct contact to immune system vs intravitreal injection

## 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

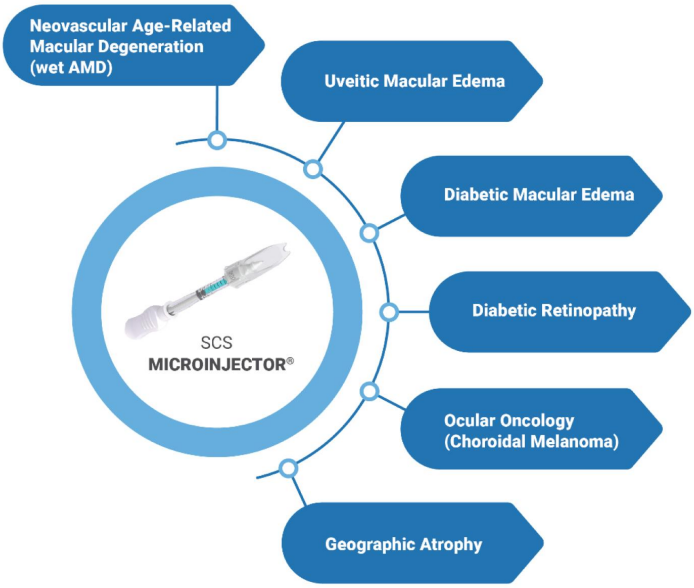


## Injection Similar to Intravitreal

Advanced technology requires only a few seconds longer for each injection

# SCS Microinjector®: Drug/Device Combination with Proven Versatility

- **Demonstrated ability for precise delivery into the suprachoroidal space**
- **First and Only FDA-approved SCS product**
- **Safety profile of SCS Microinjector comparable to intravitreal injections[1]**
- **Well-accepted by retinal physicians with thousands of injections performed**




Abbreviations: UME = uveitic macular edema; DME = diabetic macular edema; DR = diabetic retinopathy;
Sources: Clearside data on file | [1]Kurup, et. al, Macula Society 2021 *Safety of the Suprachoroidal Injection Procedure Utilizing SCS Microinjector® across Three Retinal Disorders.*

# Straightforward Suprachoroidal Injection Technique

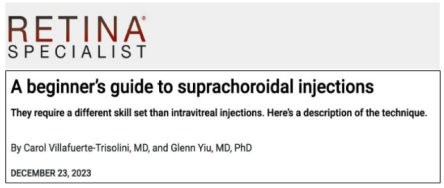

RETINA
THE JOURNAL OF RETINAL AND VITREOUS DISEASES

REVIEW

SUPRACHOROIDAL SPACE INJECTION TECHNIQUE

Expert Panel Guidance

Wykoff, Charles C. MD, PhD*; Avery, Robert L. MD†; Barakat, Mark R. MD‡,§; Boyer, David S. MD¶; Brown, David M. MD*; Brucker, Alexander J. MD**; Cunningham, Emmett T. Jr MD, PhD, MPH††,‡‡,§§,¶¶; Heier, Jeffrey S. MD***; Holekamp, Nancy M. MD†††,‡‡‡; Kaiser, Peter K. MD§§§; Khanani, Arshad M. MD, MA¶¶¶,****; Kim, Judy E. MD††††; Demirci, Hakan MD‡‡‡‡; Regillo, Carl D. MD§§§§; Yiu, Glenn C. MD, PhD¶¶¶¶; Ciulla, Thomas A. MD, MBA*****

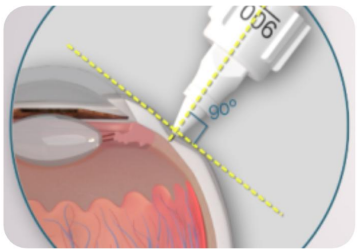

RETINA SPECIALIST

A beginner's guide to suprachoroidal injections

They require a different skill set than intravitreal injections. Here's a description of the technique.

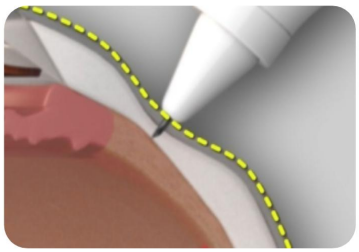
By Carol Villafuerte-Trisolini, MD, and Glenn Yiu, MD, PhD

DECEMBER 23, 2023




**Perpendicular**

Hold the microinjector **perpendicular** to the ocular surface



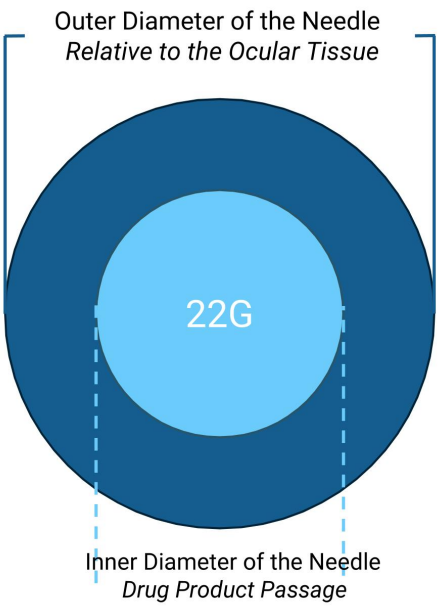
**Dimple**

Ensure firm contact with sclera by maintaining a **dimple** throughout injection

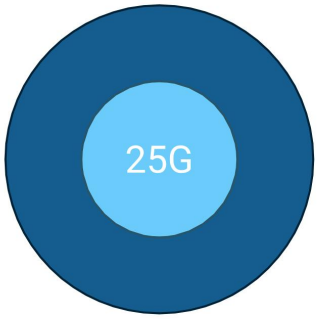
**Slow**

Inject **slowly** over 5 – 10 seconds

# Clearside Needle Size Equivalent to Most Commonly Used Intravitreal Injections and Smaller than Other TKIs in development

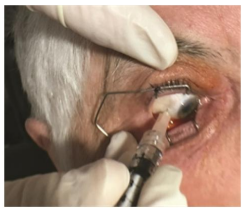



**30G needle results in less damage to the ocular tissue**
wound size to the ocular tissue is
>4x greater with 22G Needle
>2x greater with 25G Needle





Clearside
SCS Microinjector®





Gustavo Barreto Melo, et al. Progress in Retinal and Eye Research. "Critical analysis of techniques and materials used in devices, syringes, and needles used for intravitreal injections". https://doi.org/10.1016/j.preteyeres.2020.100862

# CLS-AX

(axitinib injectable suspension)

*New mechanism of action with potential for longer duration of effect for the treatment of wet AMD*

TM

# Axitinib is a Highly Potent, Highly Selective Pan-VEGF Inhibitor

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

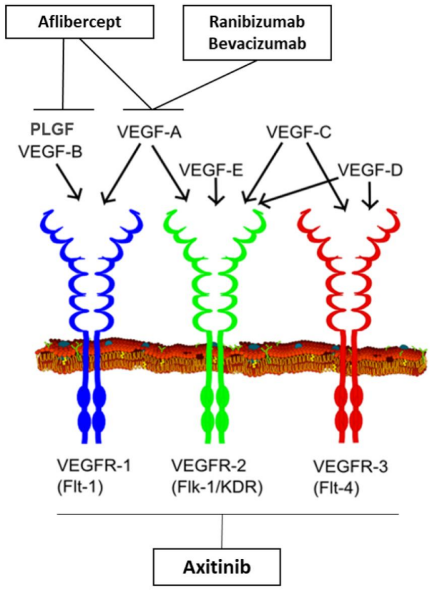
- Intrinsic pan-VEGF inhibition through receptor blockade
- More active than anti-VEGF-A in *in-vitro* angiogenesis model[1-2]
- Approved AMD treatments are focused VEGF-A inhibitors

**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**

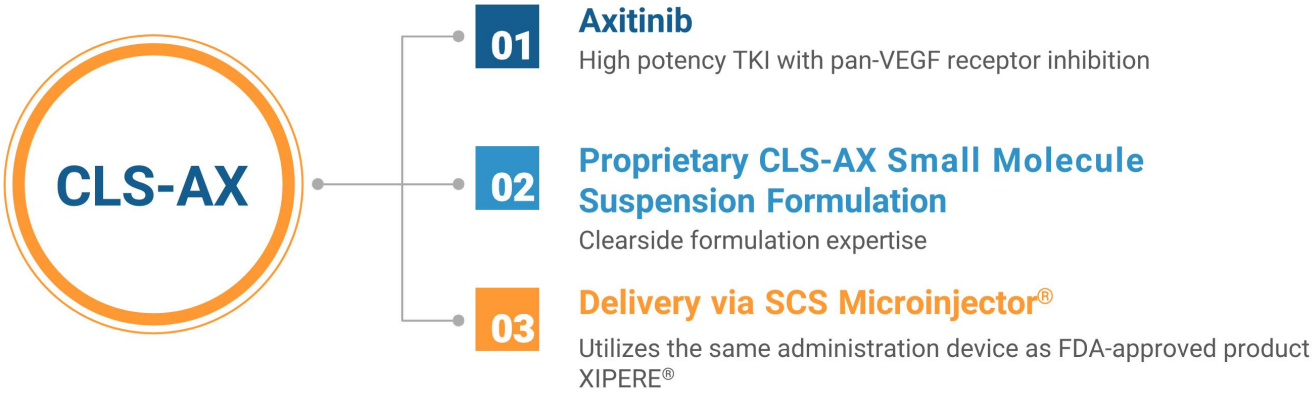
- Preclinical data showed regression of angiogenesis
- FDA-approved renal oncology treatment with established mechanism of action




**VEGF Receptor-2 primarily mediates angiogenesis**

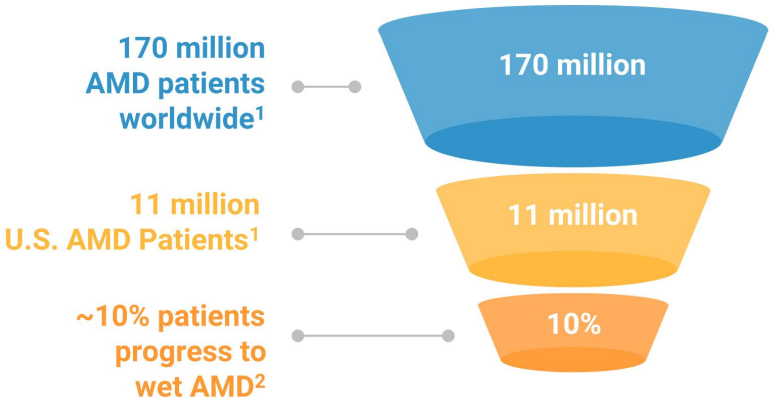
Sources: 1. Cabral T et al. Bevacizumab Injection in Patients with Neovascular Age-Related Macular Degeneration Increases Angiogenic Biomarkers. Ophthalmol Retina. 2018 January ; 2(1): 31–37. doi:10.1016/j.oret.2017.04.004. | 2. Lieu et al. The Association of Alternate VEGF Ligands with Resistance to Anti-VEGF Therapy in Metastatic Colorectal Cancer. PLoS ONE 8(10): e77117. | 3. Gross-Goupil 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/wim/2014.008. ISSN 2002-4436. Public Domain.

# Leveraging a Highly Potent Pan-VEGF Inhibitor with Suprachoroidal Delivery



# Age-Related Macular Degeneration (AMD) is a Multi-Billion Dollar Market

## A large and growing market opportunity




- AMD causes a progressive loss of central vision and is the most common cause of blindness in individuals over age 55[1]
- U.S. prevalence expected to increase to 22 million by the year 2050[1]
- Global prevalence expected to increase to 288 million by the year 2040[1]
- Current treatments require frequent injections and subset of patients experience disappointing visual outcomes[2]
- **Over $12 Billion Market and Growing[3]**

CLEARSIDE BIOMEDICAL

Sources: [1] Pennington, Katie L and DeAngelis, Margaret M, Eye and Vision, Epidemiology of age-related macular degeneration (AMD): associations with cardiovascular disease phenotypes and lipid factors, Dec 22, 2016.
[2] Prall, F Ryan and Ciulla, Thomas A, Medscape: Exudative (Wet) Age-Related Macular Degeneration (AMD), June 16, 2022.
[3] Annual financial reports from Regeneron Pharmaceuticals, Inc. and Genentech/Roche.

# Positioning CLS-AX for Real-World Success

## Maintain Vision & Reduce Office Visits

- Objective is to maintain visual acuity and reduce the number of injections; therefore, reducing the number of office visits
- Reduced treatment burden benefits patients, caregivers and payors with improved outcomes

## Ability to Re-dose

- Wet AMD is a chronic disease requiring ongoing treatment
- Goal is a label that allows re-dosing comparable to VABYSMO® and EYLEA HD® in the real-world setting

## Extend Duration Over Currently Approved Drugs

2x - 4x/year maintenance dosing anticipated for CLS-AX compared to approved drugs on label*:

- LUCENTIS®: 12x/year
- VABYSMO®: 3x - 12x/year
- EYLEA®: 6x - 12x/year
- EYLEA HD®: 3x - 6x/year



*Dosing regimens are per respective product labels | EYLEA® and EYLEA HD® are registered trademarks of Regeneron Pharmaceuticals| LUCENTIS® and VABYSMO® are registered trademarks of Genentech/Roche

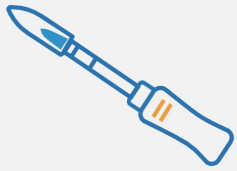
# Phase 2b Topline Data Summary and Phase 3 Plans

# CLS-AX Now Phase 3 Ready Based on Positive ODYSSEY Data in Wet AMD

ODYSSEY

**Enrolled Only Difficult-to-Treat Participants with Active Disease**

**Achieved Primary Outcome Maintaining Stable BCVA with Repeat Dosing**



**Compelling Intervention-Free Rates**

**Positive Safety Profile with Repeat Dosing**



Abbreviation: Wet AMD = neovascular age-related macular degeneration; BCVA = Best Corrected Visual Acuity

# ODYSSEY Phase 2b Clinical Trial

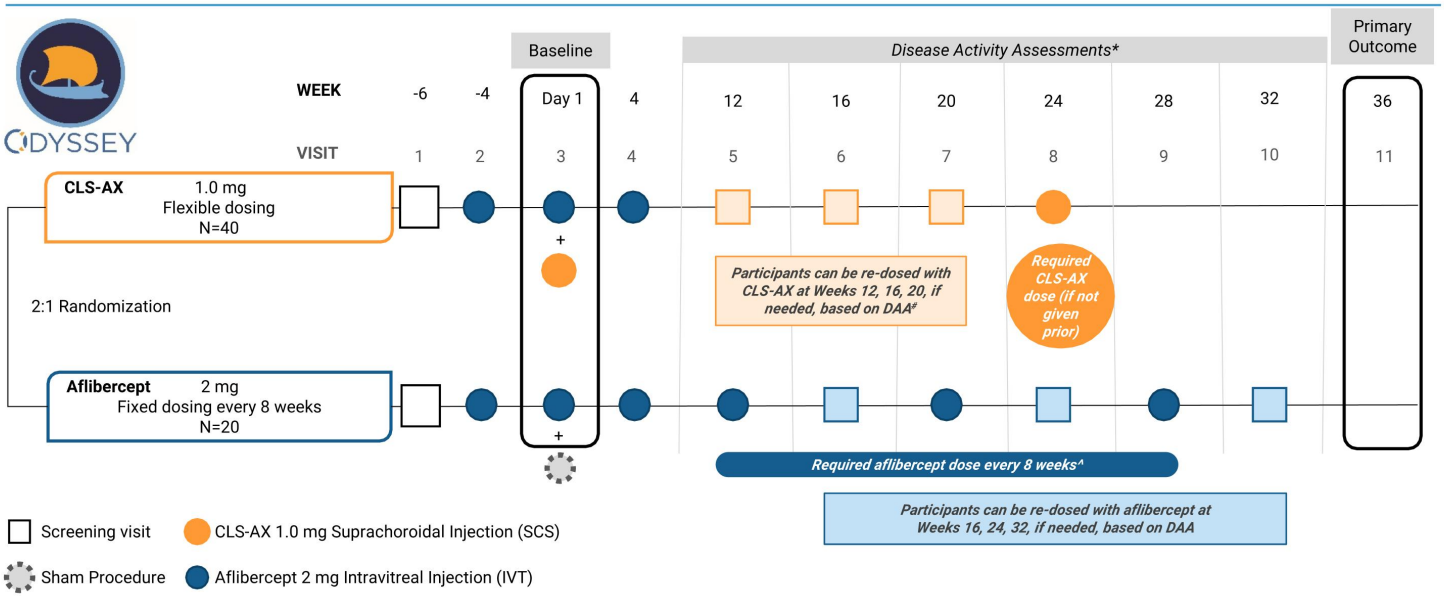
**Trial Objectives:**
Evaluate safety, efficacy & duration of CLS-AX in participants with wet AMD

- 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

# ODYSSEY Trial Design




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

CLEARSIDE BIOMEDICAL

* 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.

# Demographics and Baseline Characteristics

| Characteristics | CLS-AX | Aflibercept | Overall |
|---|---|---|---|
| No. of participants | 40 | 20 | 60 |
| Mean age (range), years | 76.9 (51-90) | 80.3 (54-96) | 78.0 (51-96) |
| Women, no. (%) | 25 (62.5) | 14 (70.0) | 39 (65.0) |
| Race, no. (%)<br>White<br>Asian | <br>37 (92.5)<br>3 (7.5) | <br>20 (100)<br>0 | <br>57 (95.0)<br>3 (5.0) |
| Median duration of wet AMD diagnosis (range), months | 9.65 (1.4-31.1) | 10.2 (1.4-20.8) | 9.9 (1.4-31.1) |
| Mean BCVA (range) at screening, ETDRS letters | 69.1 (37-80) | 69.1 (51-80) | 69.1 (37-80) |
| Mean CST (range) at screening, µm | 266.8 (175-378) | 294.3 (209-592) | 276.0 (175-592) |
| Mean Total Area of CNV (range) at screening, $mm^2$ | 6.8 (1.6-26.9) | 6.5 (0.5-20.8) | 6.7 (0.5-26.9) |
| Bilateral wet AMD, n | 17 | 6 | 23 |
| Mean annualized number of prior wet AMD treatments (injections/year) [a] (range) | 9.5 (3.2-17.2) | 9.2 (4.1-17.2) | 9.4 (3.2-17.2) |

Abbreviations: AMD = age-related macular degeneration; BCVA = best corrected visual acuity; CNV = choroidal neovascularization; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study.
[a]Annualized number of prior wet AMD treatments defined as the total number of prior wet AMD treatments divided by the duration of wet AMD diagnosis in years.

# CLS-AX Demonstrated Positive Clinical Activity in Wet AMD

## Overall

**Achieved Primary Outcome** in participants with confirmed active disease

## BCVA

**Stable BCVA throughout the trial**

Measured as mean change in BCVA from baseline to Week 36

## CST

**Stable CST throughout the trial**

Measured as mean change in CST from baseline to Week 36

## Durable Effect

**67% of participants did not require any additional treatment for up to 24 weeks (6 months)**

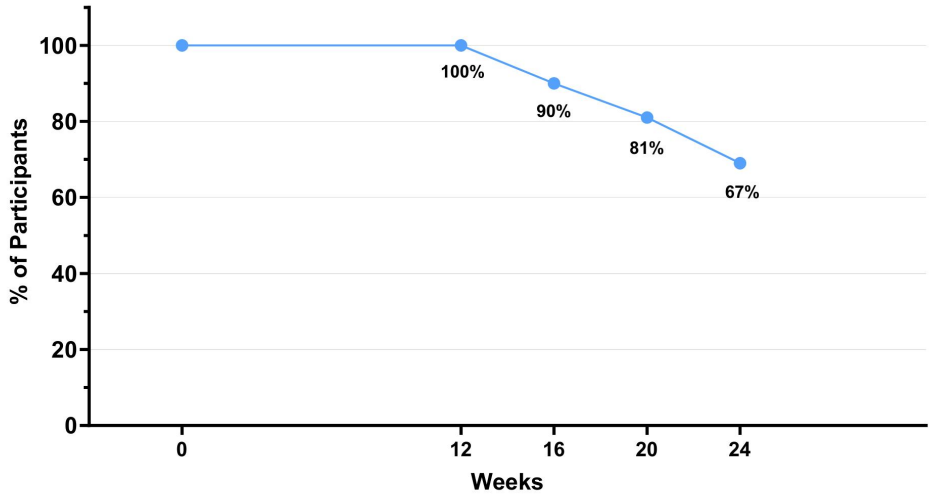
Injection frequency reduced by nearly 84% up to 24 weeks



Abbreviations: CST=Central Subfield Thickness
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.

# Two-Thirds of Participants Dosed with CLS-AX Reached Six Months Without Additional Treatment

## Intervention–Free Rates By Week Up to Each Visit




Week 12: 40/40 (100%)
Week 16: 35/39 (89.7%)
Week 20: 30/37 (81.1%)
Week 24: 26/39 (66.7%)

Calculation accounts for missed treatments; time of initial administration of study drug shown as month 0 on figure. Intervention-free rate calculation: if participant received intervention at a study visit, those were reflected in the count at the following study visit.

# 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**

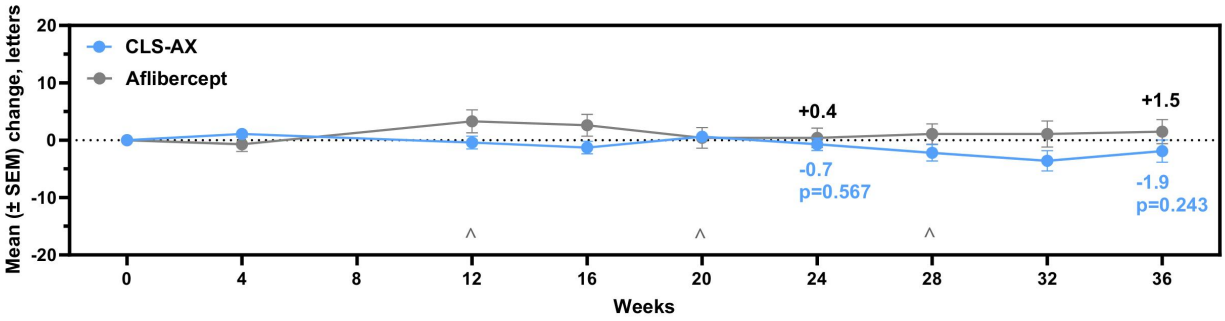
**Reduced injection frequency by**

**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.

# Stable Best Corrected Visual Acuity (BCVA) Over 36 Weeks

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



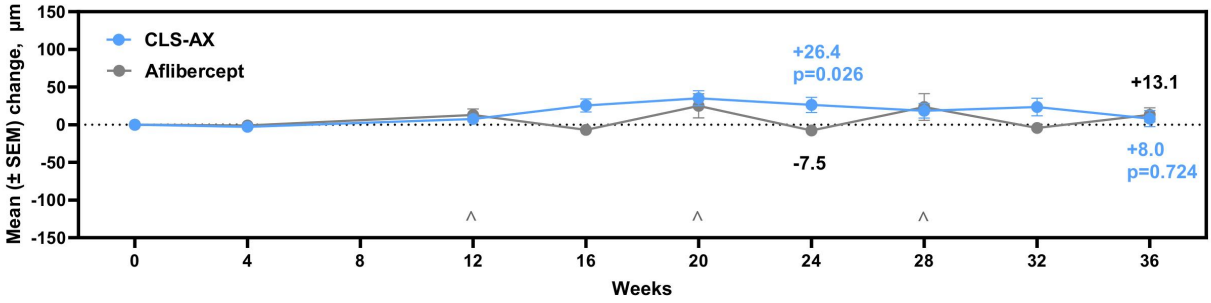

*CLS-AX results do not include supplemental therapy with aflibercept*



^Study drug administration for aflibercept participants given at Weeks 12, 20 and 28.
Abbreviations: BCVA = best corrected visual acuity; SEM = standard error of the mean.
P-value based on a 2-sample t-test between treatment groups .

# Stable Central Subfield Retinal Thickness (CSRT) Over 36 Weeks as Verified by Independent Reading Center

## 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 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

# CLS-AX Phase 3 Program Current Plans

# CLS-AX Flexible Dosing of a Biologic with the Duration of a TKI

## Phase 3 Program Summary

Two pivotal, non-inferiority trials

Two arms with ~225 participants per arm: CLS-AX 1mg vs aflibercept 2mg

Similar to Phase 3 trial design of EYLEA HD and VABYSMO in maintenance phase

Phase 3 flexible dosing data will be differentiated from other TKI programs

End-of-Phase 2 Meeting expected in Q1 2025

Expect to initiate both trials in 2H 2025

# CLS-AX Phase 3 Non-Inferiority Study Design in Wet AMD Designed to Optimize Success

Target patient population:

- **Treatment naïve**
- **No more than 1 previous injection of anti-VEGF**

→ **Potentially increase commercial value**

→ **Easier recruitment anticipated**

Two strategies to reduce variability to enhance success in non-inferiority trial:

- At Screening
  - Participants must have 20/80 to 20/32 AND CST <500 at diagnosis
  - **Minimizes enrollment of highly variable participants**

→ **Intended to increase probability of success**

- Prior to Randomization

**At Visit 4 (Wk -4) following three aflibercept loading doses, eliminate:**

- Participants with ≥ 10 letter change from Visit 3 (Wk -12) OR
- CST (AI assessment) increases by ≥ 100 microns

→ **Intended to increase probability of more consistent results**

# Flexible Dosing to Support Commercial Success

*Personalized Treatment Interval (PTI) assessment enables physicians to use "real world" approach with flexible dosing schedule based on participant needs*

## Re-Dosing Criteria with CLS-AX

- **Improve consistency in assessing need for re-dosing** by using OCT biomarkers (IRF and SRF) determined in office using AI tool

## Rescue Criteria with Aflibercept

- ≥ 10 letter loss AND
- ≥ 100 microns in 2 consecutive visits

Rationale based on learnings from ODYSSEY

- TKIs may take longer to act, thus some participants need to be re-dosed earlier
- There is variability in physician's approach to providing rescue treatment



IRF = intraretinal fluid; SRF = subretinal fluid; AI = artificial intelligence

**Phase 3 plans are in development and subject to change*

# Year 1 Study Designed to Maximize Commercial and Competitive Potential in Wet AMD

| | | | | | | R/BL | | | | | | | | | PE | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | -20 | -16 | -12 | -8 | -4 | D1 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 |
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| Activity | | | | | EC | | | | PTI | PTI | PTI | | | | | PTI | PTI | PTI | PTI |
| CLS-AX FLEX | A | A | A | | A | C | S | | | | | C | S | S | S | S | S | C | S |
| | | | | | | | | | | | C | S | S | S | S | C | S | S | S |
| | | | | | | | | | | C | S | S | S | C | S | S | S | C | S |
| | | | | | | | | | C | S | S | C | S | S | C | S | S | C | S |
| Aflibercept Q8W | A | A | A | | A | S | A | | A | S | A | S | A | S | C | S | S | S | C |

Reduce variability

A, Aflibercept 2mg; C, CLS-AX 1 mg; S, Sham injection;
R/BL, Randomization/Baseline; PE, Primary Endpoint;
EC, Exclusion Criteria;
PTI, Personalized Treatment Interval assessment by AI tool: IRF and/or SRF changes from Visit 6 (Baseline, Day 1).

**EC: At Week -4, participants with high variation will be discontinued from the study.**
At Weeks 12-20, participants meeting PTI criteria will be dosed at that visit and will continue on q12w, q16w or q20w until the primary endpoint.
Participants not meeting PTI criteria at these visits will be dosed at Week 24 and will continue on q24w until the primary endpoint.

# Study Design Intended to Provide Additional Safety and Efficacy Data After Primary Endpoint

**After 36-Week Primary Endpoint:**

- Aflibercept arm moves to CLS-AX every 16 weeks (q16w)
  - To maintain masking
  - To collect more safety data
  - To collect efficacy data for q16w CLS-AX in year 2

- CLS-AX arm stays on the original assignment after PTI assessment
  - Allows readjustment of dosing in CLS-AX arm (close to **real world** situation)
    - Similar to EYLEA HD and VABYSMO study designs



IRF = intraretinal fluid; SRF = subretinal fluid; AI = Artificial Intelligent

**Phase 3 plans are in development and subject to change*

# Year 2 Evaluation After Primary Endpoint

| Week | | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 76 | 80 | 84 | 88 | 92 | 96 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
| Activity | | PTI | PTI | PTI | PTI | PTI | PTI | PTI | PTI | PTI | PTI | PTI | PTI | PTI | PTI | EOS |
| **CLS-AX FLEX** | **Q24W** | S | S | C[a] | S | S | S | S | S | C[a] | S | S | S | S | S | |
| | **Q20W** | C[a] | S | S | S | S | C[a] | S | S | S | S | C | S | S | S | |
| | **Q16W** | S | S | C[a] | S | S | S | C[a] | S | S | S | C[a] | S | S | S | |
| | **Q12W** | S | S | C | S | S | C | S | S | C | S | S | C | S | S | |
| **Aflibercept Q8W** | | S | S | S | C | S | S | S | C | S | S | S | C | S | S | |

C, CLS-AX 1 mg; S, Sham injection; EOS, End of Study.
For masking purposes, PTI assessments will be performed in all participants at all visits starting at Week 40.

[a] For participants randomized to CLS-AX on a dosing interval of q24w, q20w, or q16w after Week 36, if PTI criteria are met at an active injection visit, then the next dosing interval will be reduced by 4 weeks, to a minimum of q12w.

# Pipeline Expansion Opportunity in Geographic Atrophy

# Potential Advantages of Suprachoroidal Delivery in Geographic Atrophy

Potential Target Product Profile (TPP) Aligns with SCS Suspension or SCS Gene Therapy

**Able to reach the choroid first**
- Fluid spreads circumferentially and posteriorly when injected within the suprachoroidal space, bathing the choroid, RPE, retina and adjacent areas with drug

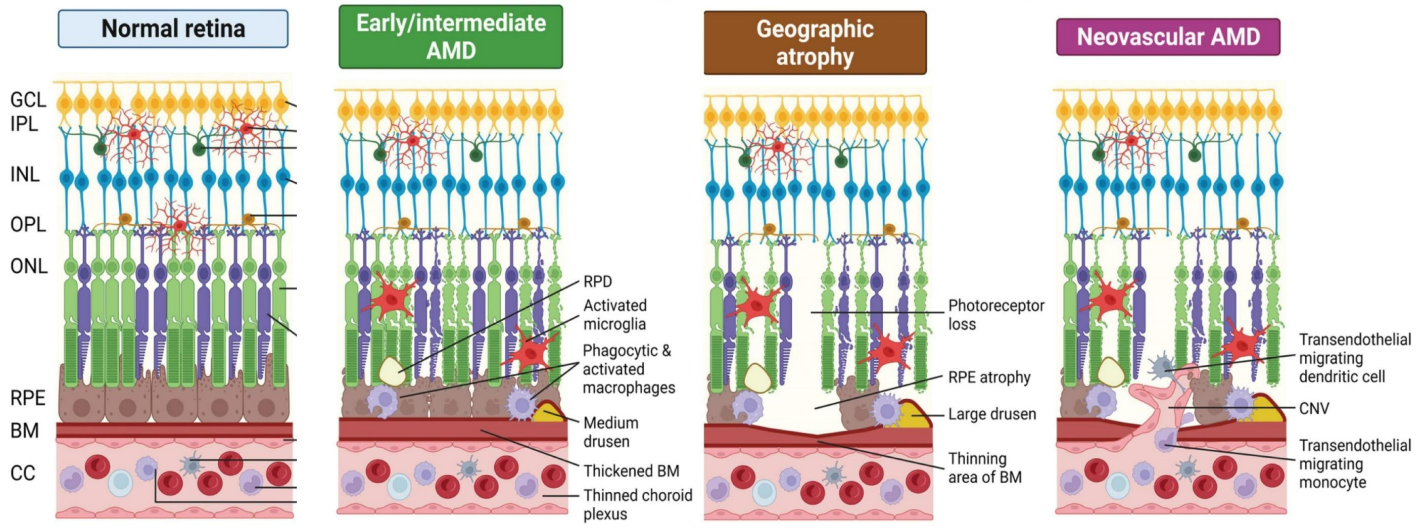
**Small molecules may have better efficacy than current therapies**
- Potential to treat complement activation in both RPE and choroid

**Suprachoroidal suspension/gene therapy may have longer duration (3 to 6 months)**
- Intravitreal gene therapy may not achieve efficacy
- Subretinal has additional risks

**Less invasive, in-office procedure**
- Systemic therapy may be effective, but potential infection risks in this elderly population
- Local ocular therapy may have fewer adverse events

**Targeted delivery compartmentalized to the posterior segment**
- Potentially fewer adverse events

# Pathology of Age-Related Macular Degeneration (AMD)



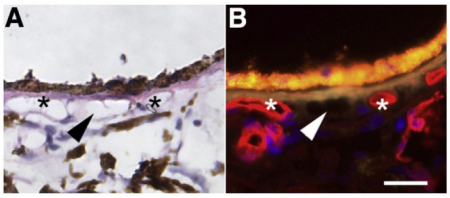



Wong JHC et al., Front Neurosci 16: 1009599

# Geographic Atrophy is a Choroidal Disease

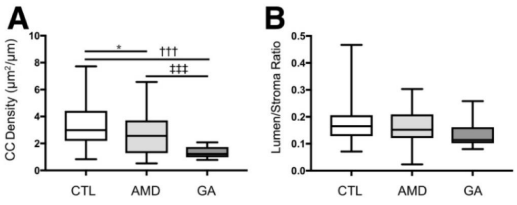
## Choroidal Hypoxia Theory and Choriocapillaris are Damaged First

**1**



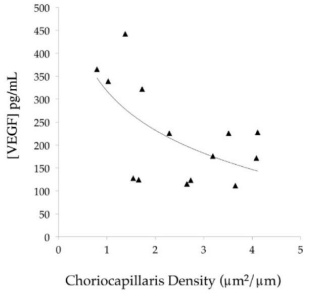

Choriocapillaris endothelial cells damage with ghost vessels before any significant RPE changes

**2**




- Choriocapillaris (CC) vascular density is significantly lower in GA donor
- No meaningful differences in vascular lumen area / stroma area

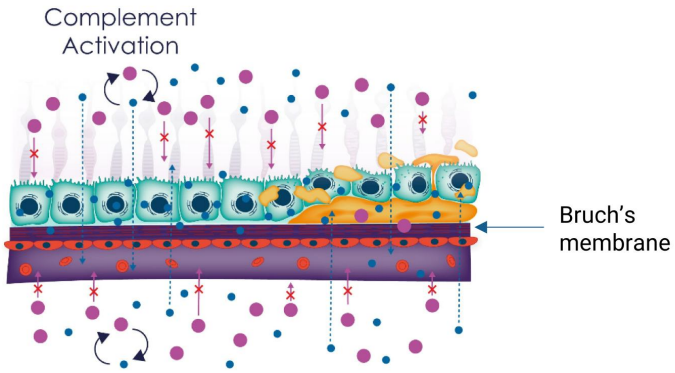
**3**

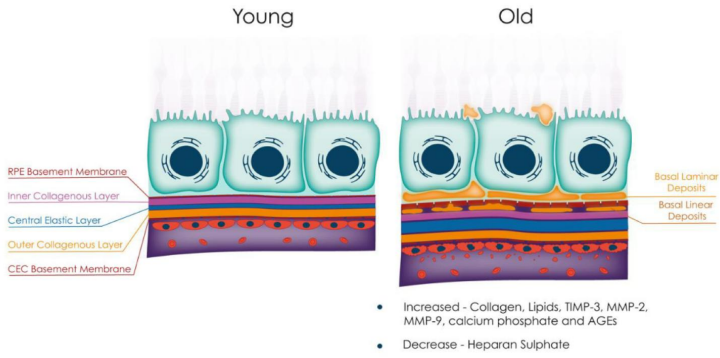



VEGF level increased with low vascular density support the choroidal hypoxia theory

RPE = Retinal Pigment Epithelium
Images modified from Sohn EH et al., Am J Path 2019: 189: 1473-80

# Small Molecule Can Access the Diseased Area of the RPE and Choroid




**Larger molecules cannot get through Bruch's membrane**

**So, if given intravitreally, it can only treat the RPE side**

**Aging intensifies disease actions and even peptides might not be able to get through**



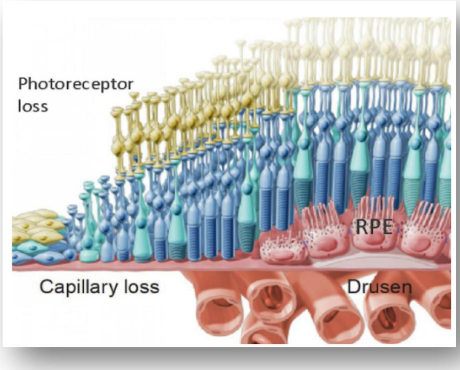
Images modified from Hammadi et al JCM 2023, 12 (8), 2870

# A Differentiated and Promising Approach Focusing on Choroidal Health and Capillary Homeostasis

- Neuroprotection
  - Promising preclinical evidence
  - Limited clinical success
- Lipid pathway
  - Complex lipid metabolism pathways
  - Clinical effectiveness likely to require removal of lipid from Bruch's
- Extracellular matrix modulation
  - (HTRA1, TIMP3 & MMPs)
  - Molecular mechanism is not controversial
  - Anti-HTRA1 failed in clinical trial
- Visual cycle modulation
  - Lacks robust clinical efficacy
  - Multiple failed trials

**Complement inhibition**

- Clinically validated
- Approved therapies have limited efficacy




**Reduce choriocapillaris degeneration & improve choroidal perfusion**

- Choriocapillaris degeneration precedes RPE and PR loss
- Implicated in the pathophysiology of AMD
- Warrants further clinical investigation

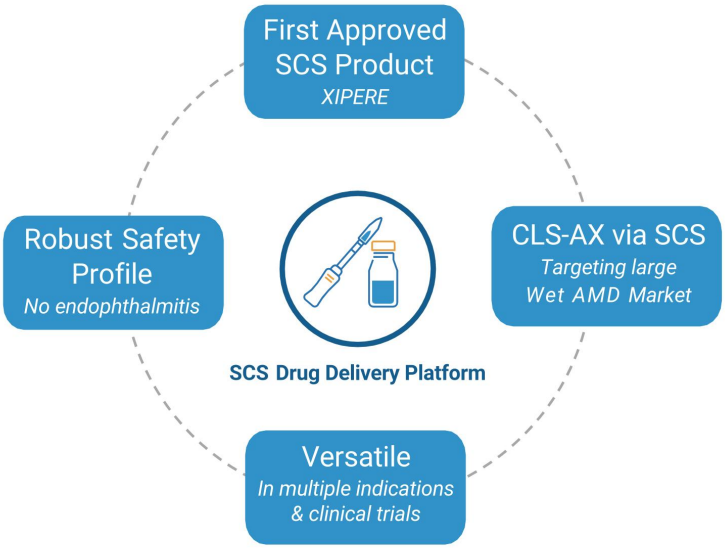
**Control proinflammatory microenvironment**

- Well-studied inflammatory pathways (macrophages, microglia, mast cells)
- Controls multiple disease-triggering insults

Image Source: NEI
Abbreviations: HTRA1: High-Temperature Requirement Factor A1; TIMP3:tissue inhibitor of metalloproteinases 3;
MMPs: Matrix Metalloproteinases

# Summary

# Innovative and Experienced Leader in Suprachoroidal Drug Delivery




## Upcoming Potential Catalysts

**CLS-AX (axitinib injectable suspension)**

- ✓ **ODYSSEY Phase 2b Topline Results**
- **Q4 2024:** Phase 3 Planning
- **Q1 2025:** End-of-Phase 2 meeting with FDA

**Medical/Scientific meeting presentations**

- ✓ **Q1 2024:** Macula Society; Next Generation Ophthalmic Drug Delivery Summit
- ✓ **Q2 2024:** Retina World Congress; Clinical Trials at the Summit
- ✓ **Q4 2024:** AAO; Asia-Pacific Vitreo-Retina Society; Floretina

**Publications**

- ✓ **Q2 2024:** Expert panel practice guidelines on SCS® delivery in *Retina*
- ✓ **H2 2024:** OASIS Data in *Ophthalmology Science*


CLEARSIDE
BIOMEDICAL
Nasdaq: CLSD
TM

# Appendix

# ODYSSEY Trial Focused on Participants with Active Disease

**Key Inclusion Criteria**

- Diagnosed with neovascular AMD (wet AMD) within 36 months of screening
- History of 2 to 4 anti-VEGF treatments in 6 months before screening and response to prior anti-VEGF treatment for wet AMD
- **Reading center confirmation of persistent active disease**; BCVA of 20 to 80 letters[#]

**Dosing Regimen**

- **Participants in both arms received 3 aflibercept (2 mg) loading doses (2nd dose = Baseline visit)**
- **CLS-AX arm received one dose of CLS-AX (1.0 mg) at Baseline visit**
- Unless DAA required more frequent dosing, **CLS-AX arm dosed at least every 24 weeks** & aflibercept arm dosed every 8 weeks

**Disease Activity Assessments (DAA)**

- **Monthly DAA: Weeks 12 through 32 in both arms** to determine if there is need for supplemental treatment
- Supplemental treatment criteria: Decrease in BCVA, increase in CST, or new or worsening vision-threatening hemorrhage due to wet AMD

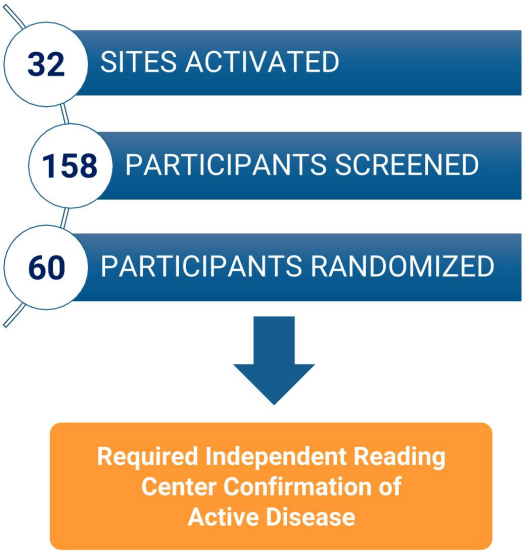
**Criteria for Supplemental Treatment**

- BCVA reduction of >10 letters from Baseline measurement
- Increase in CST of >100 microns on SD-OCT from Baseline measurement
- BCVA reduction of > 5 letters from Baseline measurement AND increase in CST of >75 microns on SD-OCT from Baseline measurement
- Presence of new or worsening vision-threatening hemorrhage

CLEARSIDE BIOMEDICAL

Aflibercept is dosed via intravitreal injection (IVT); CLS-AX is dosed via suprachoroidal injection.
[#] Using the Early Treatment Diabetic Retinopathy Study (ETDRS) measurement.
Abbreviations: SD-OCT (Spectral Domain Optical Coherence Tomography).

# ODYSSEY Trial Enrolled Rapidly



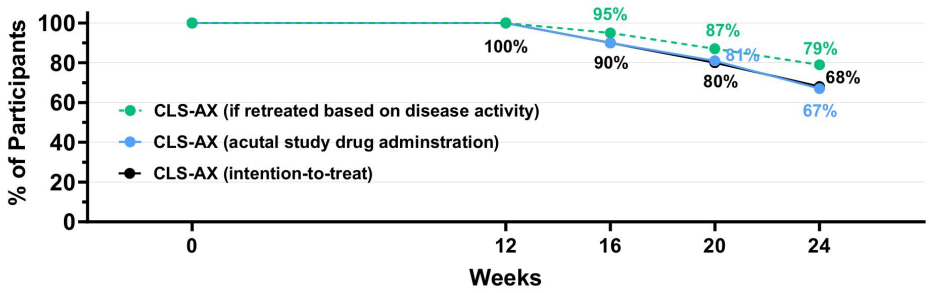

| Study Activity | Date |
|---|---|
| First Participant Randomized | July 12, 2023 |
| Last Participant Randomized | December 13, 2023 |

| Disposition | CLS-AX | Aflibercept | Overall |
|---|---|---|---|
| Enrolled, n | | | 158 |
| Randomized, n | 40 | 20 | 60 |
| Completed, n (%)<br>24 weeks<br>36 weeks* | <br>39 (97.5)<br>36 (90.0) | <br>19 (95.0)<br>17 (85.0) | <br>58 (96.7)<br>53 (88.3) |

*Discontinuation rate was similar between arms

# Two-Thirds of Participants Dosed with CLS-AX Reached 6 Months Without Supplemental Therapy

## Intervention–Free Rates By Week Up to Each Visit




Based on disease activity[1]
Week 12: 40/40 (100%)
Week 16: 37/39 (94.9%)
Week 20: 32/37 (86.5%)
Week 24: 30/38 (78.9%)

Actual study drug administration[1]
Week 12: 40/40 (100%)
Week 16: 35/39 (89.7%)
Week 20: 30/37 (81.1%)
Week 24: 26/39 (66.7%)

Intention-to-Treat
Week 12: 40/40 (100%)
Week 16: 36/40 (90.0%)
Week 20: 32/40 (80.0%)
Week 24: 27/40 (67.5%)

[1]Calculation accounts for missed visits or assessments; Time of initial administration of study drug shown as month 0 on figure. Intervention-free rate calculation: if participant received intervention at a study visit, those were reflected in the count at the following study visit.

# ODYSSEY Confirmed the Ability to Administer Multiple Doses of CLS-AX with a Well-Tolerated Safety Profile

## Of the 40 participants in the trial on study drug:

## 32 received two doses of CLS-AX and 6 received three doses of CLS-AX

| Multi-Dosing Data | | |
|---|---|---|
| CLS-AX Doses Received Including Baseline | | |
| # Doses | # Participants | % of total enrolled (n=40) |
| 1 | 2 | 5% |
| 2 | 32 | 80% |
| 3 | 6 | 15% |