CLEARSIDE BIOMEDICAL

# Top Line Results from ODYSSEY

## CLS-AX Program Update

Thomas A. Ciulla, MD, MBA

February 12, 2025

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

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

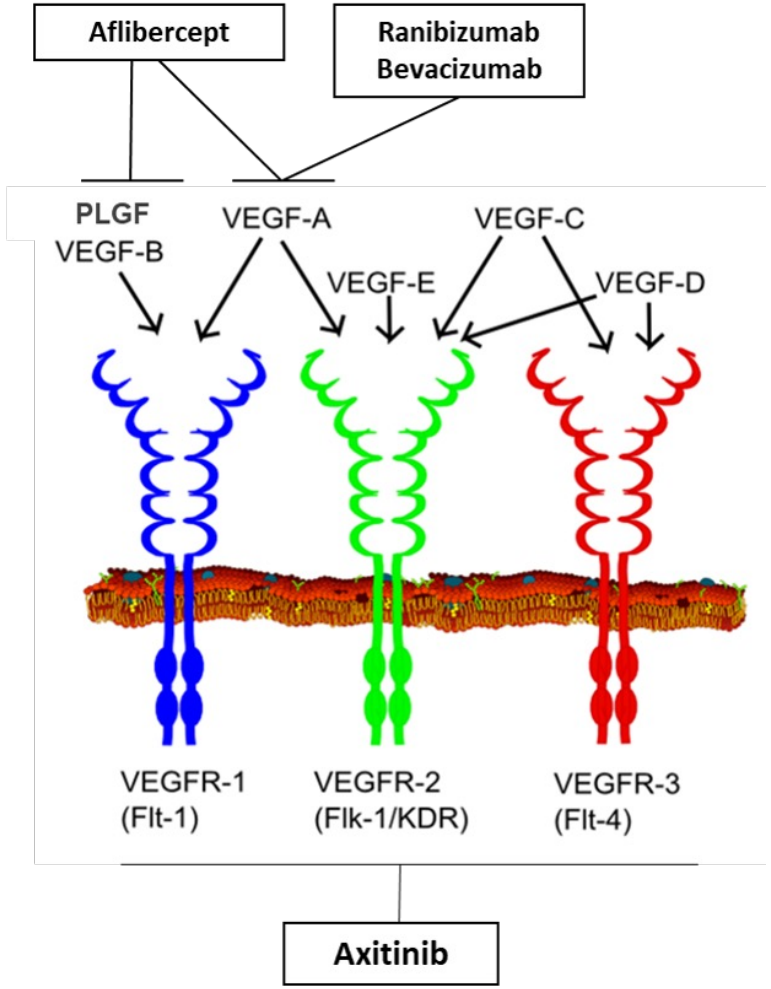
- Intrinsic pan-VEGF inhibition through receptor blockade
- More active than anti-VEGF-A in *in-vitro* angiogenesis model[1-2]
- Approved AMD treatments are focused VEGF-A inhibitors

**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/wjm/2014.008. ISSN 2002-4436. Public Domain.

# Straightforward Suprachoroidal Injection Technique

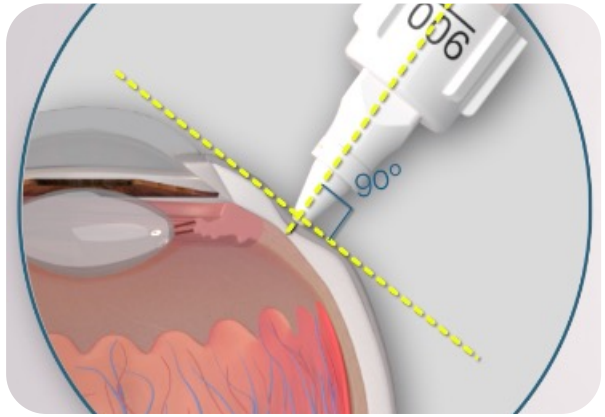
RETINA
THE JOURNAL OF RETINAL AND VITREOUS DISEASES

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*****




## Perpendicular

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

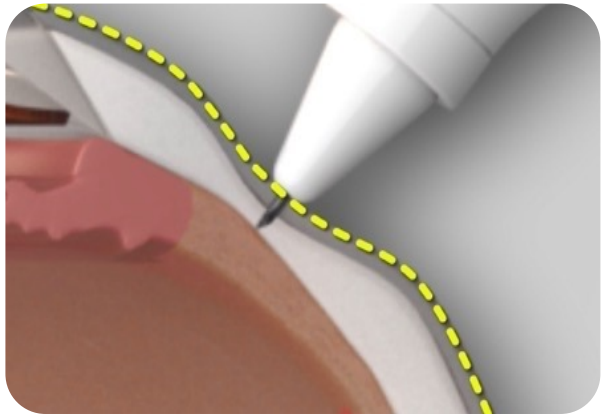
RETINA SPECIALIST

**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



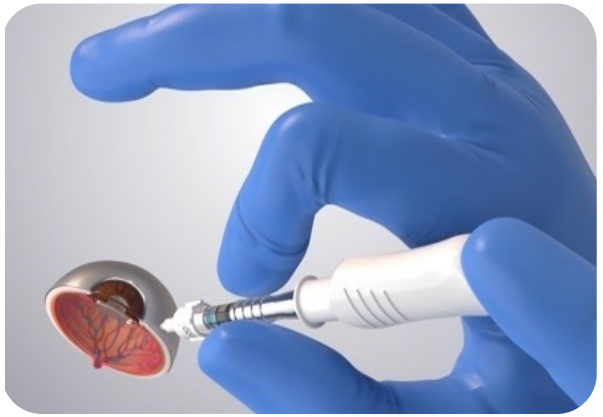
## Dimple

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

BMC Part of Springer Nature

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

Christopher R. Henry, Scott D. Walter, Peter Y. Chang, David J. Warrow, Parisa Emami Naeini, Kevin J. Blinder, Teresa Brevetti, Mohamed Yassine, Mark S. Dacey, David S. Chu, Veena R. Raiji, Lana M. Rifkin, Milan Shah & Michael A. Singer



## Slow

Inject **slowly** over 5 – 10 seconds

# 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 required **re-dosing with CLS-AX** in study arm
  - Participants received at least 2 doses of CLS-AX
  - **Provided important data to plan Phase 3** in chronic disease

# 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) |

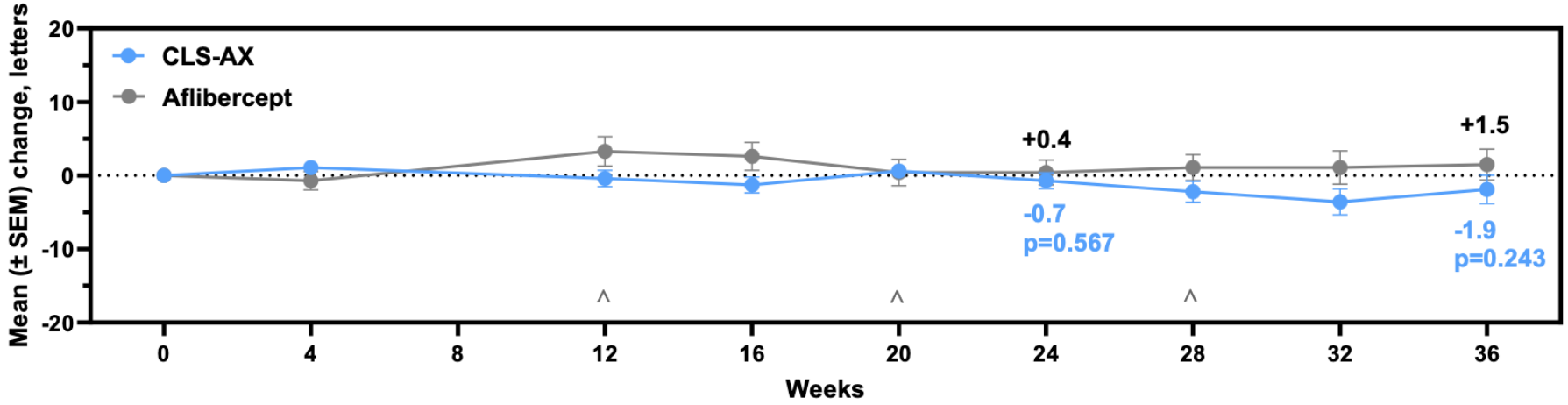
Abbreviations: AMD = age-related macular degeneration; BCVA = best corrected visual acuity; CNV = choroidal neovascularization; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study.
[a]Annualized number of prior wet AMD treatments defined as the total number of prior wet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

# Stable Best Corrected Visual Acuity (BCVA) and Central Subfield Retinal Thickness (CST) Over 36 Weeks

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

## BCVA

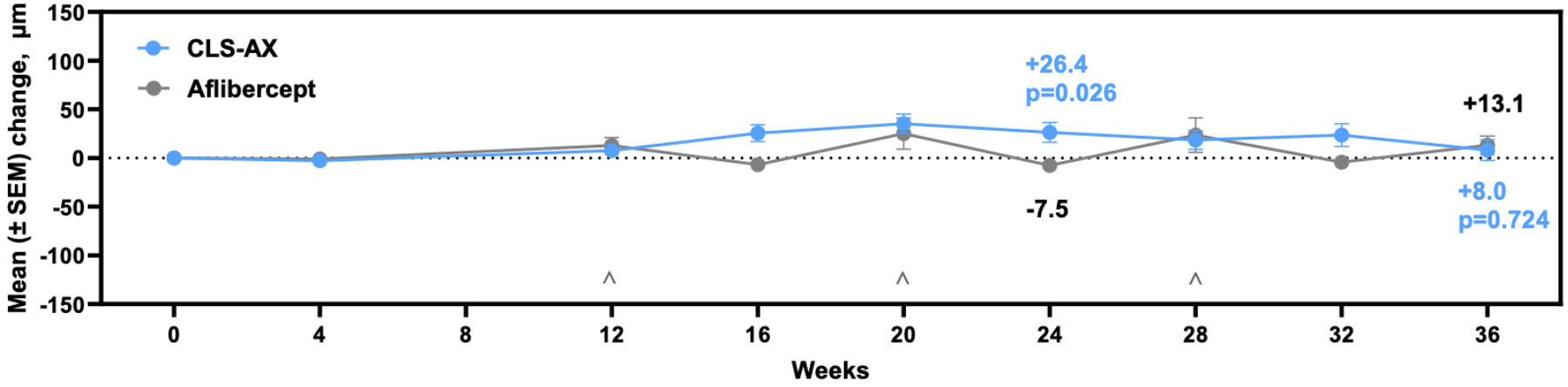
**Within 2 letters from Baseline at Week 24 and Week 36 in CLS-AX arm**




## CST

**Stable anatomical control**

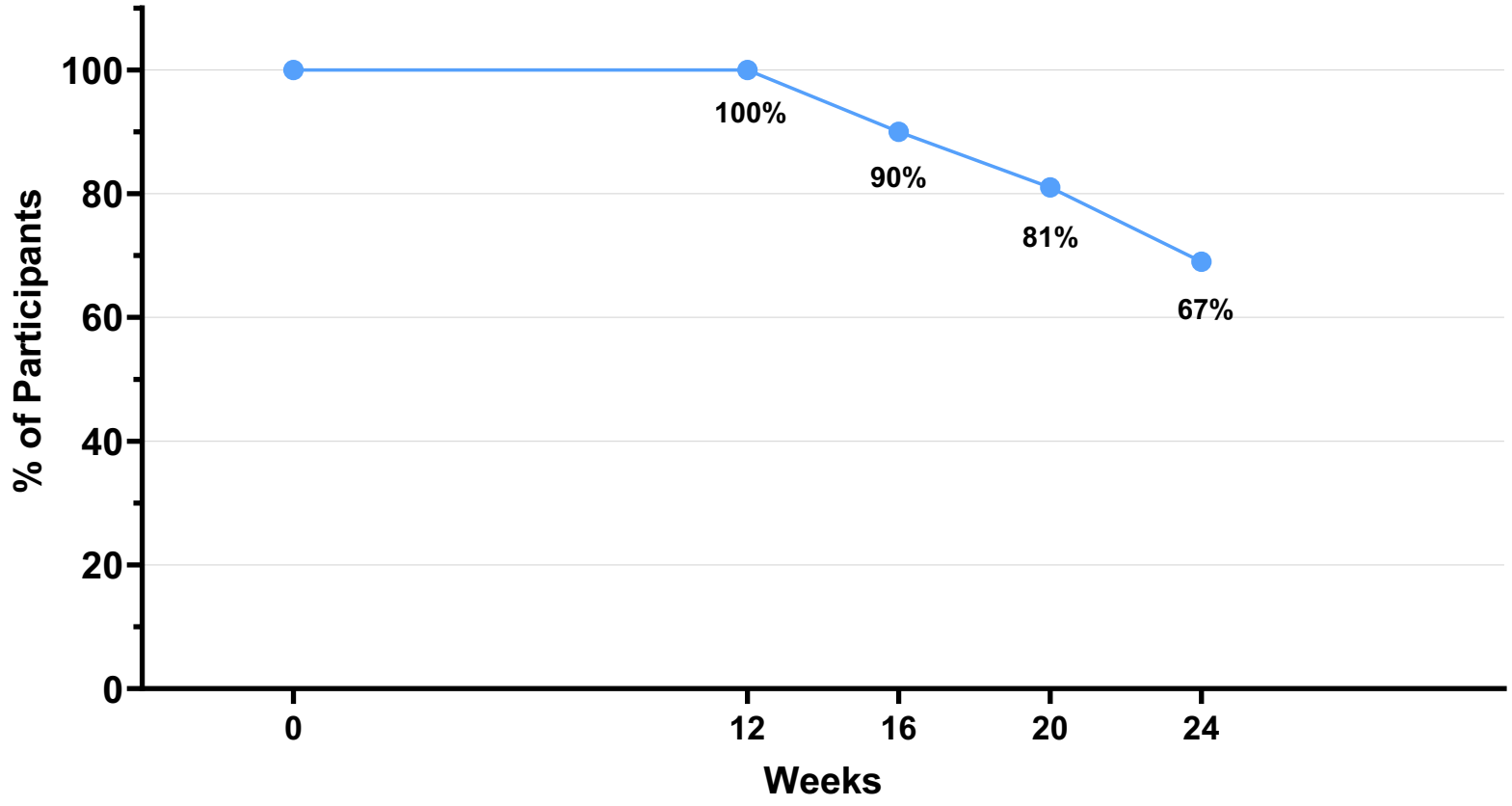
**Reduces fluctuation**




^Study drug administration for aflibercept participants given at Weeks 12, 20 and 28.
Abbreviations: BCVA = best corrected visual acuity; CST = central subfield 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 .

# 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.

***Preliminary Topline Results Subject to Change***

# CLS-AX Demonstrated Positive Safety Profile

## No Ocular SAEs and No Treatment-Related SAEs

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



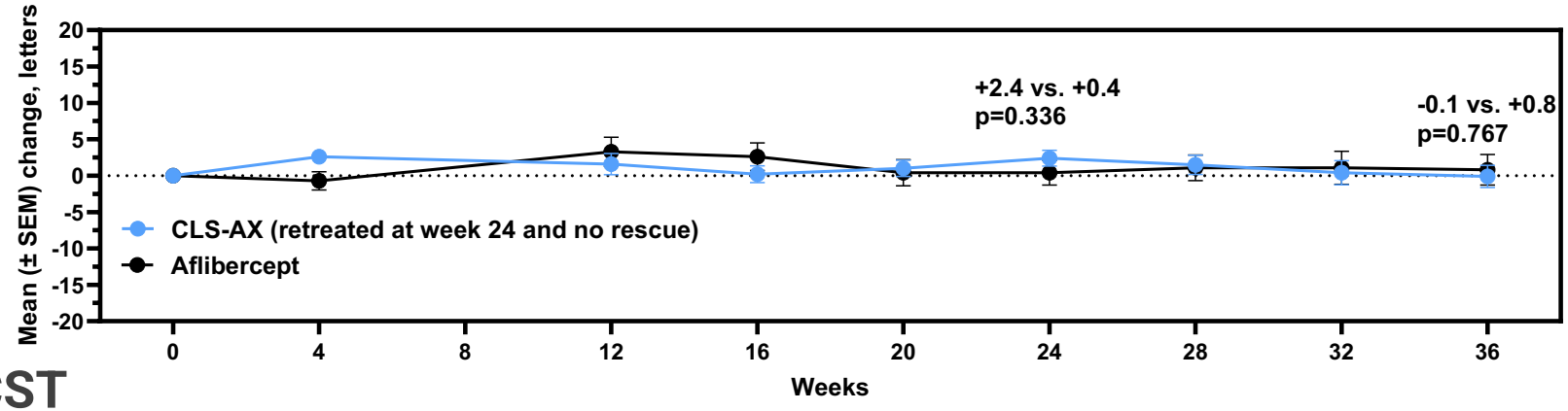
Abbreviations: AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

# Sub-Group Analysis: Patients Re-Dosed with CLS-AX at Week 24 Only

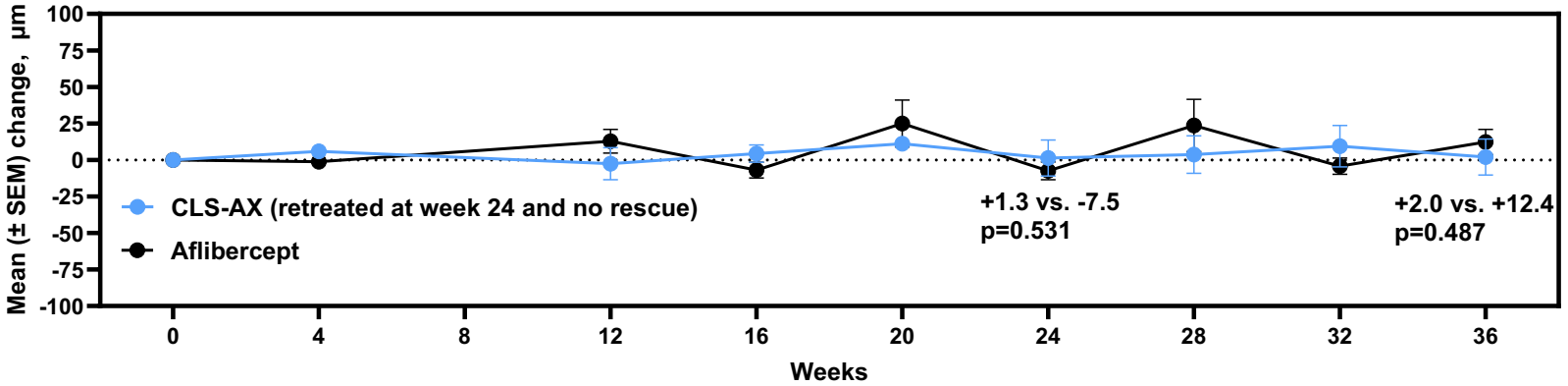
## *Did not require aflibercept rescue or CLS-AX re-dosing prior to Week 24*

*Supports Enrolling Treatment Naïve Patients in the CLS-AX Phase 3 Program*

**BCVA**




**CST**




Sub-Group Analysis Including CLS-AX Participants Solely Re-dosed with CLS-AX at Week 24 vs. Aflibercept Comparator Participants

## Key Insights for Phase 3 Planning

In ODYSSEY, with more challenging-to-treat patients:

- **67% CLS-AX patients did not require rescue or re-dosing from baseline to the 6-month mandatory CLS-AX re-dosing**

In the planned Phase 3 program, by targeting treatment naïve or the more general wet AMD population, there may be an even greater percentage reaching 6-months without rescue or re-dosing.

Abbreviations: BCVA, best corrected visual acuity; CST, central subfield retinal thickness; SEM, standard error of the mean. Analysis includes CLS-AX patients retreated at Week 24 who never received rescue therapy, all other CLS-AX patients, and all aflibercept patients. P-values are based on a 2-sample t-test.

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

## Phase 3 Program Summary

Two pivotal, non-inferiority trials with treatment naïve participants

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

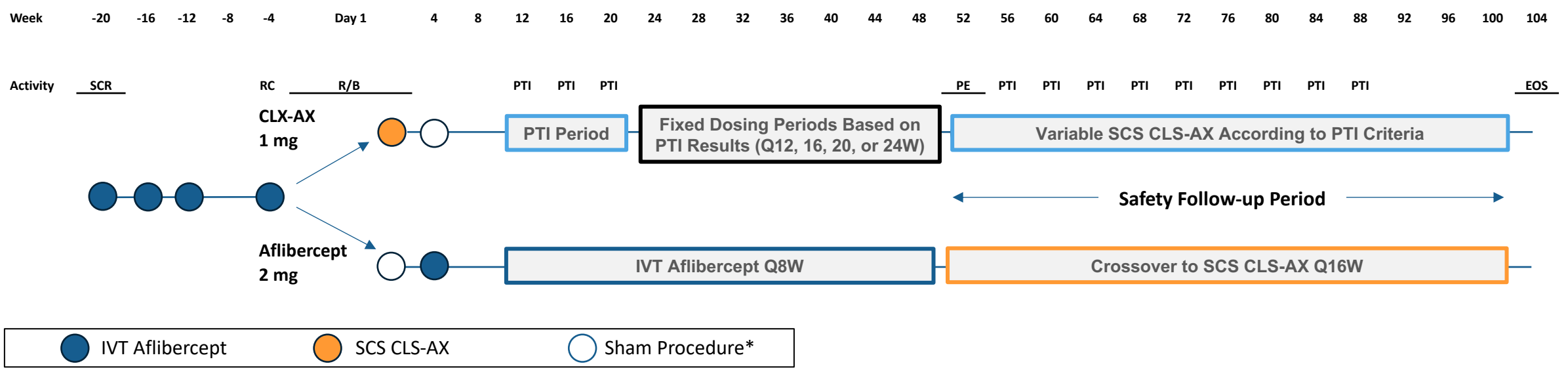
Similar to Phase 3 trial design of EYLEA HD and VABYSMO in maintenance phase

CLS-AX flexible dosing should be important differentiation vs other TKI programs

Employ more “real world” clinical practice re-dosing criteria for CLS-AX

Expect to initiate both trials in 2H 2025

# Non-inferiority Study Design in nAMD




Participants will be randomized 1:1 to CLS-AX 1 mg, aflibercept 2 mg, or CLS-AX 0.03 mg on Day 1. At Weeks 12, 16, and 20, participants will undergo an assessment of disease activity based on PTI criteria. Participants with anatomic signs of disease activity at these timepoints will receive q12w, q16w, or q20w dosing respectively, rather than q24w. For participants randomized to CLS-AX on a dosing interval of q24w, q20w, or q16w on or after Visit 17 (Week 52), 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.

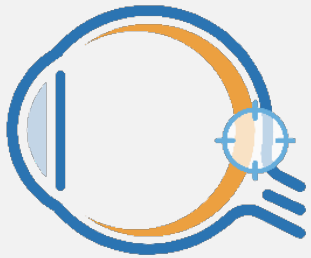
SCR, Screening Visit; RC, Randomization Criteria; R/B, Randomization/Baseline; PE, Primary Endpoint;
PTI, Personalized Treatment Interval Assessment; IVT, intravitreal injection; SCS, suprachoroidal injection.
*Participants will receive either a sham procedure, IVT injection, or SCS injection at each visit to maintain masking

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

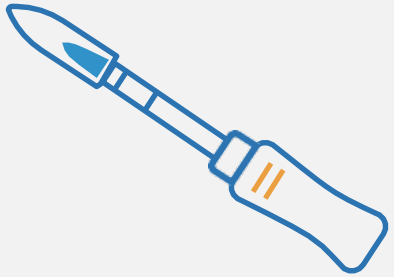
# CLS-AX Now Phase 3 Ready Based on Positive ODYSSEY Data in Wet AMD

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

*Preliminary Topline Results Subject to Change*