Phase 2b CLS-AX ODYSSEY Trial Results

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On behalf of the ODYSSEY investigators

Angiogenesis 2025

Financial Disclosures

RAG

- **Clearside (G [SRC], C)**

- 4DMT (G)
- Abbvie (G, C)
- Adverum (C)
- Affamed (G)
- Alexion (G)
- Alimera (C)
- Annexon (G, C)
- Apellis (G, C, S)
- Avirmax (G)
- Boehringer Ingelheim (G, C)
- Cognition (G)
- Emmetrope Ophthlamics (E)
- EyePoint (G, C)
- Genentech (G, C, S)
- Janssen (G, C)
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- NovoNordisk (G)
- Ocular Therapeutix (G, C)
- Orasis (C)
- StealthBio (G, C)
- Regeneron (G, C)
- UnityBio (G)
- Zeiss (G, C)

G, Grant support; C, consultant/advisor; S, speaker; E, equity

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

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

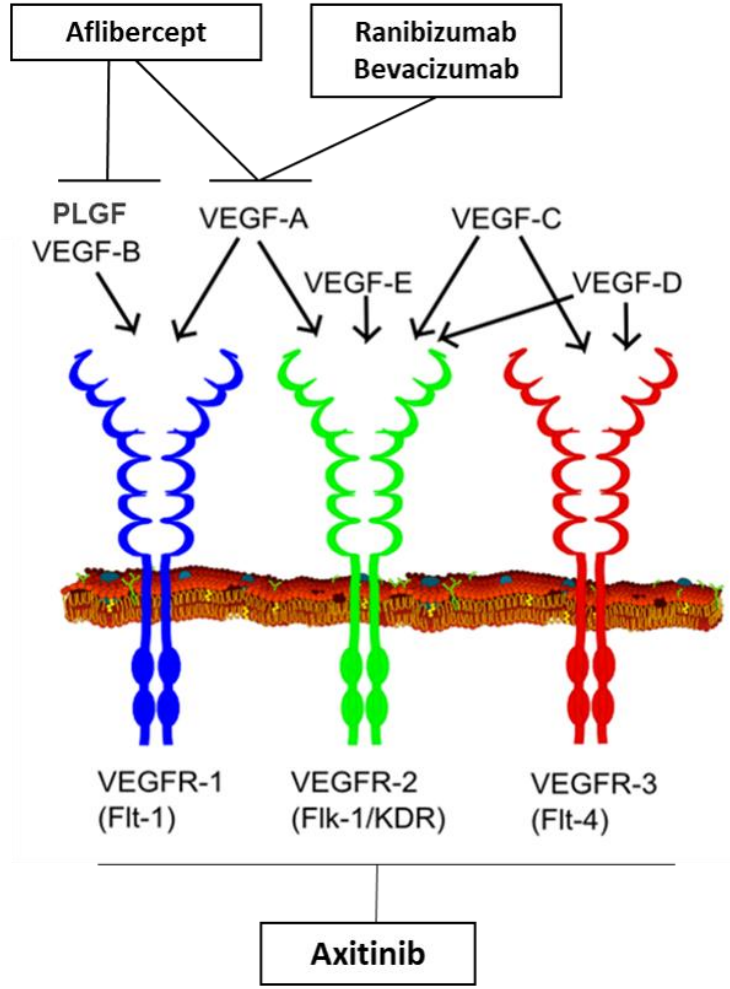
- Intrinsic pan-VEGF inhibition through receptor blockade
- More active than anti-VEGF-A in *in-vitro* angiogenesis model[1-2]
- Approved AMD treatments are focused VEGF-A inhibitors

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

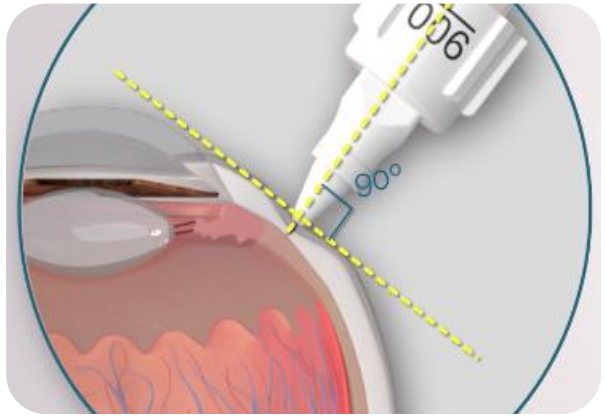
RETINA
THE JOURNAL OF RETINAL AND VITREOUS DISEASES

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

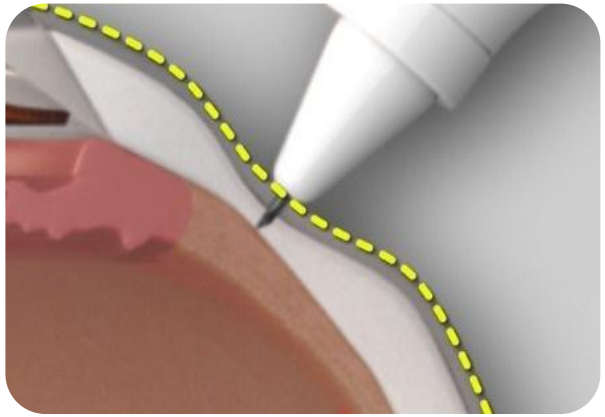
RETINA SPECIALIST

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

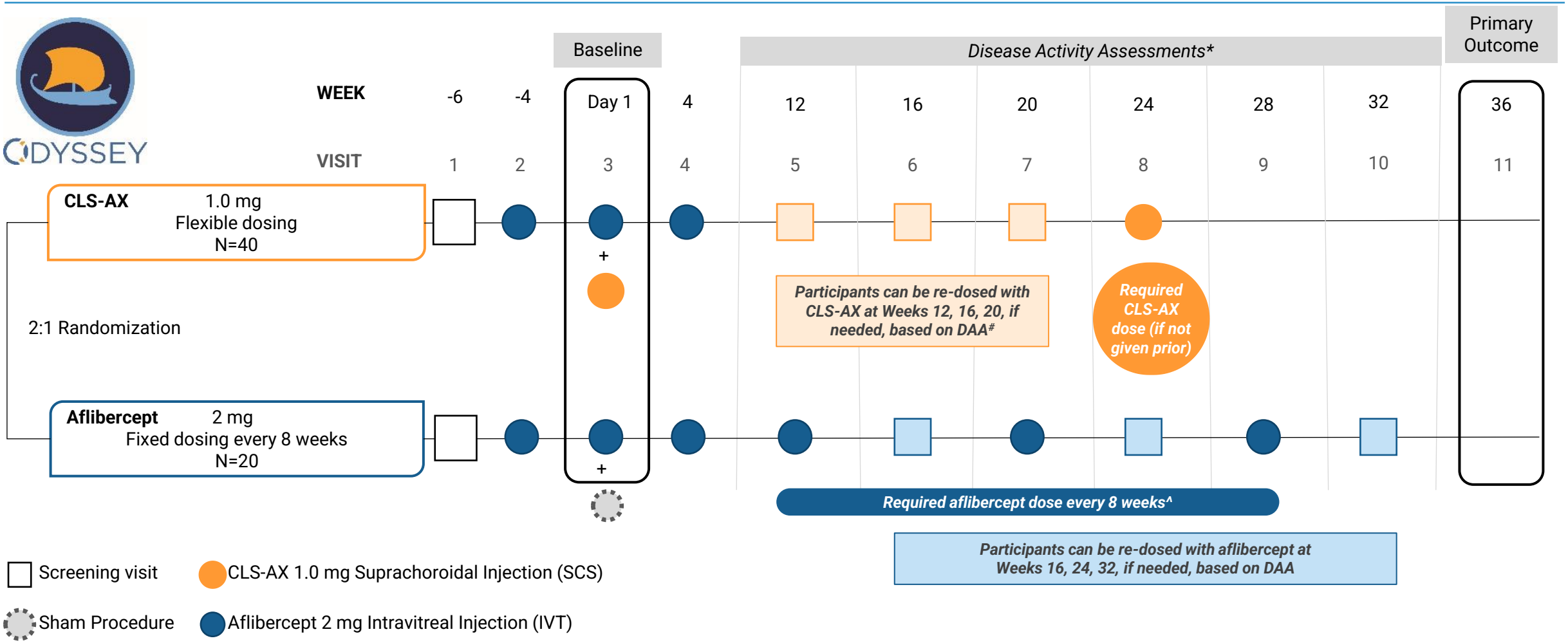
Trial Objectives:
Evaluate safety, efficacy & duration of CLS-AX in participants with wet AMD

- 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

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.

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. (%) White Asian	 37 (92.5) 3 (7.5)	 20 (100) 0	 57 (95.0) 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)

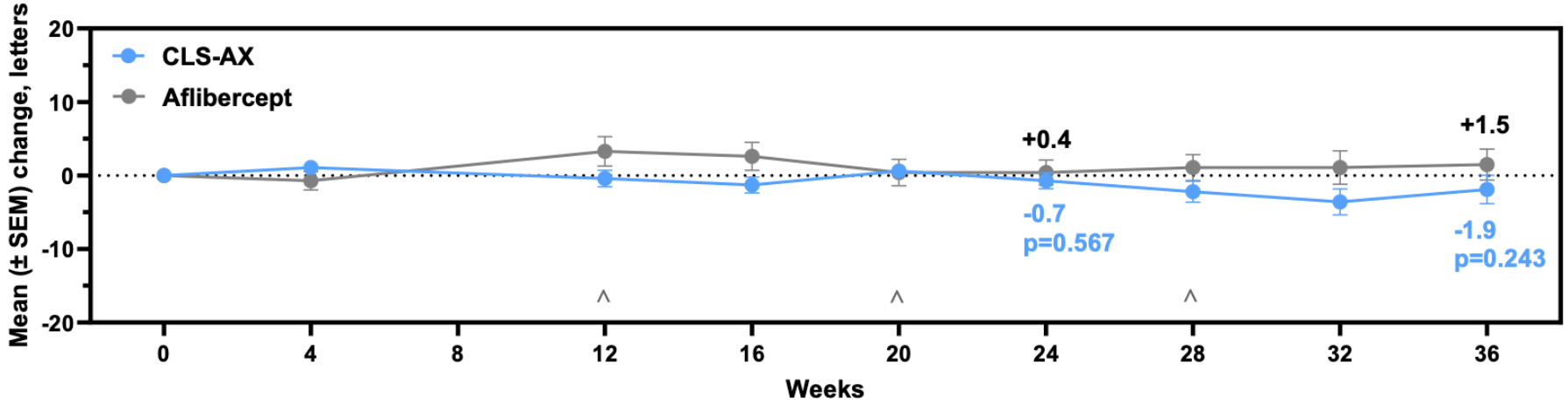
Abbreviations: AMD = age-related macular degeneration; BCVA = best corrected visual acuity; CNV = choroidal neovascularization; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study.
[a]Annualized number of prior wet AMD treatments defined as the total number of prior wet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

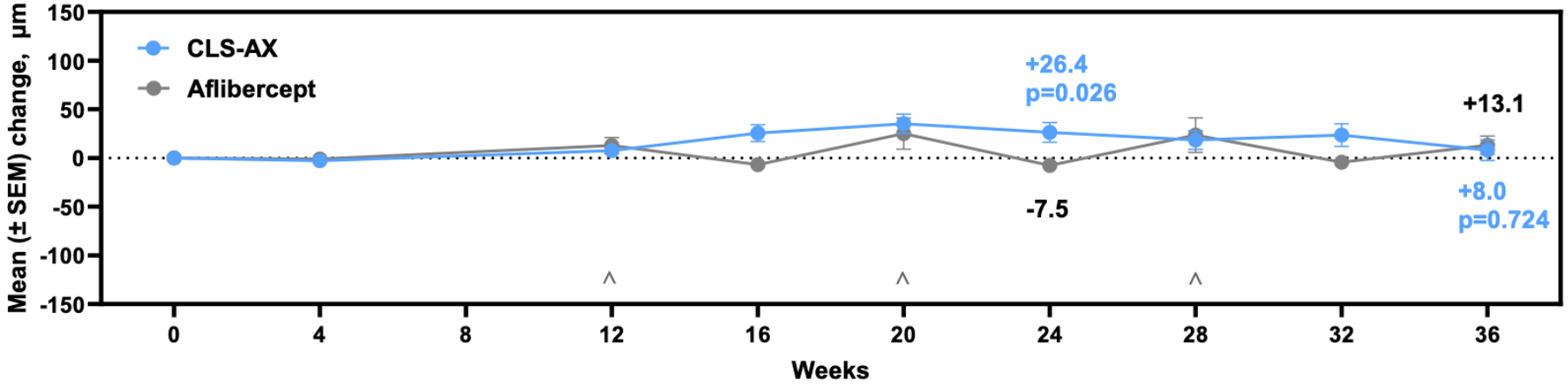
Within 2 letters from Baseline at Week 24 and Week 36 in CLS-AX arm



CST

Stable anatomical control

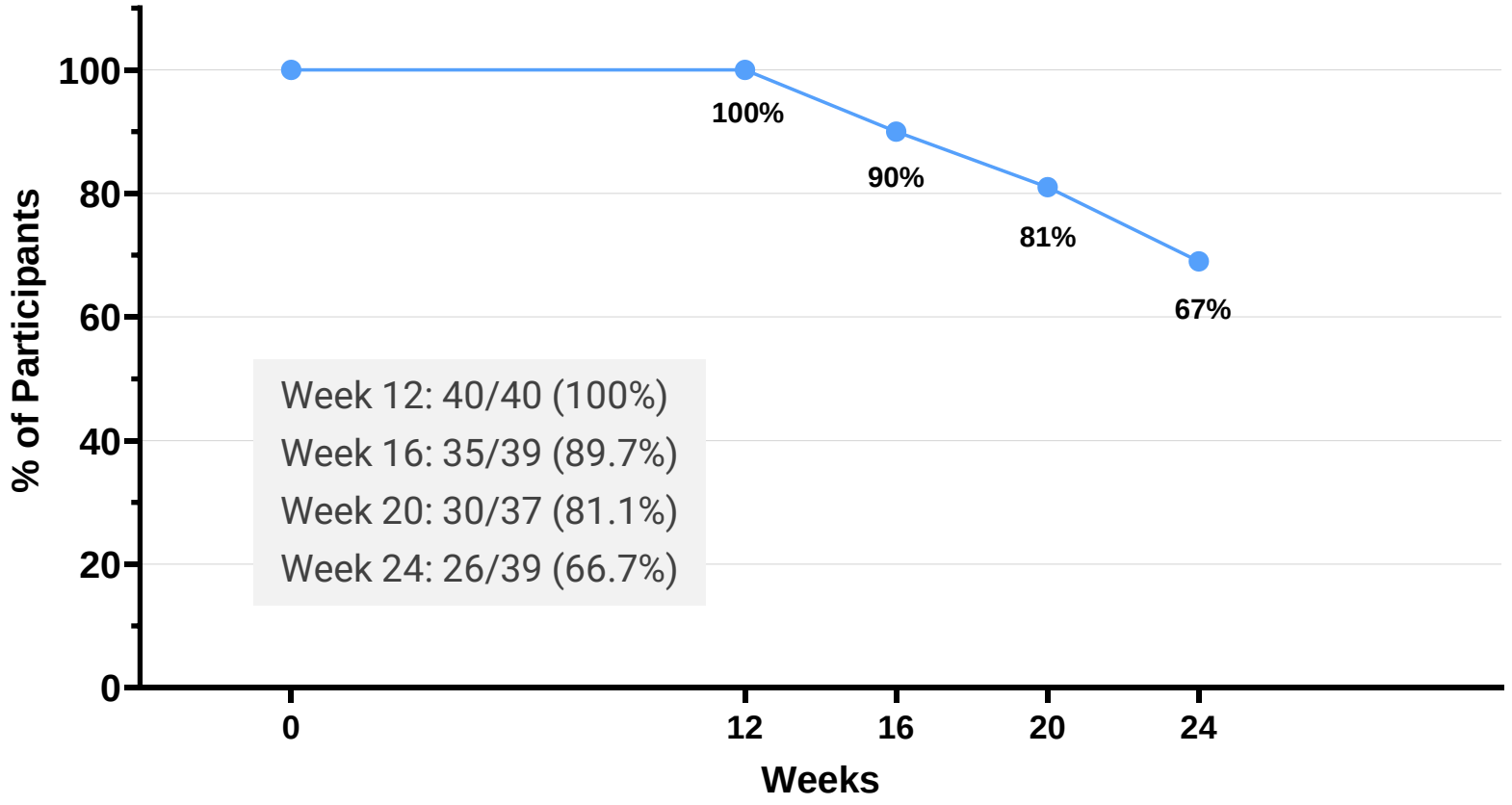
Reduces fluctuation



^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



Results Comparable to Other TKI Programs Beginning Phase 3 Trials

6 Month Injection-Free Rate:

67%

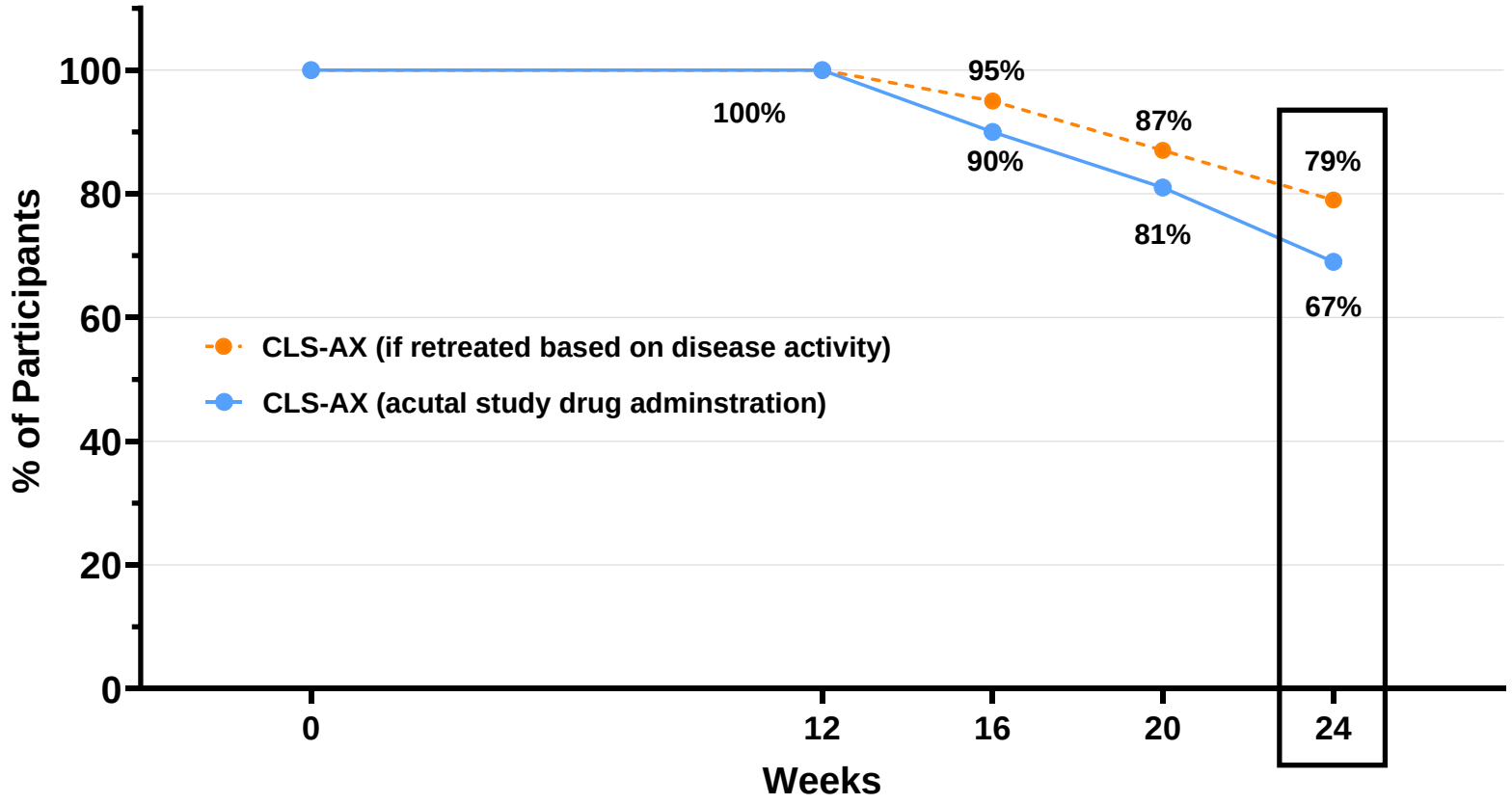
Reduction of Injection Frequency:

84%

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.
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.

More Participants May Have Been Intervention Free at Every Time Point if DAA Criteria Strictly Applied

No Participants Met the DAA Criteria Per Reading Center Confirmation at Week 24, but They Received Mandatory Re-Dosing Per the Protocol



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

DAA = Disease Activity Assessment. Actual treatments compared to reading center confirmation. Active disease-free rate calculation: if participant had active disease at a study visit, those were reflected in the count at the following study visit. N = number of participants assessed at a study visit; n = number of participants active disease-free up to a visit. Active disease presence based on BCVA and CSRT as graded by the central reading center.

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 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
- Four cases of intraocular inflammation all deemed clinically mild by the Safety Review Committee
  - Two cases had minimal clinical signs that resolved
  - Two cases were potentially related to drug administration
  - In all four cases, the inflammation was no longer detected at or before Week 36

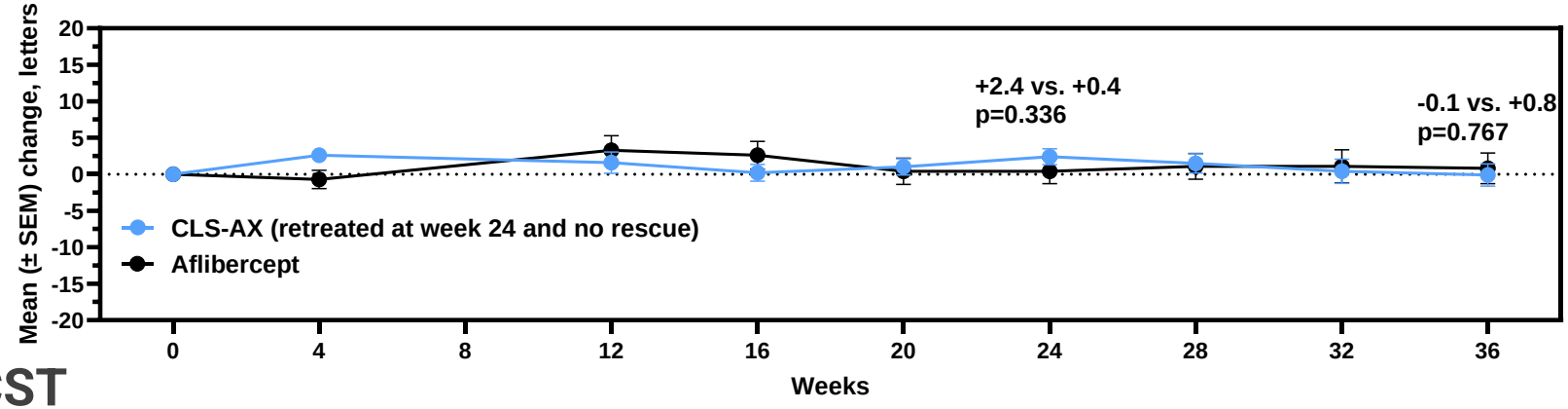
Abbreviations: AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Sub-Group Analysis 1: Patients Re-Dosed with CLS-AX at Week 24 Only

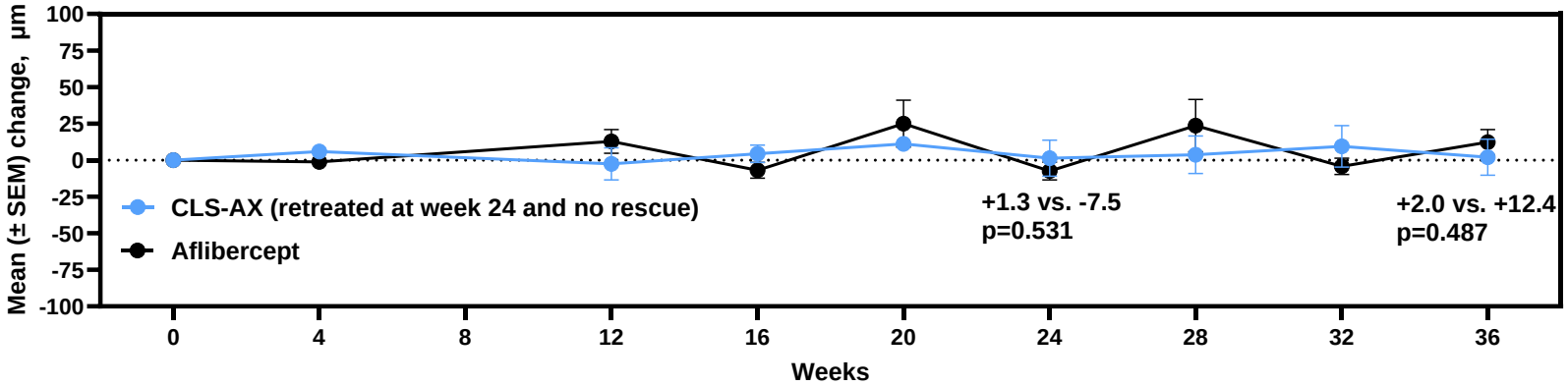
Did not require aflibercept rescue or CLS-AX re-dosing prior to Week 24

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**

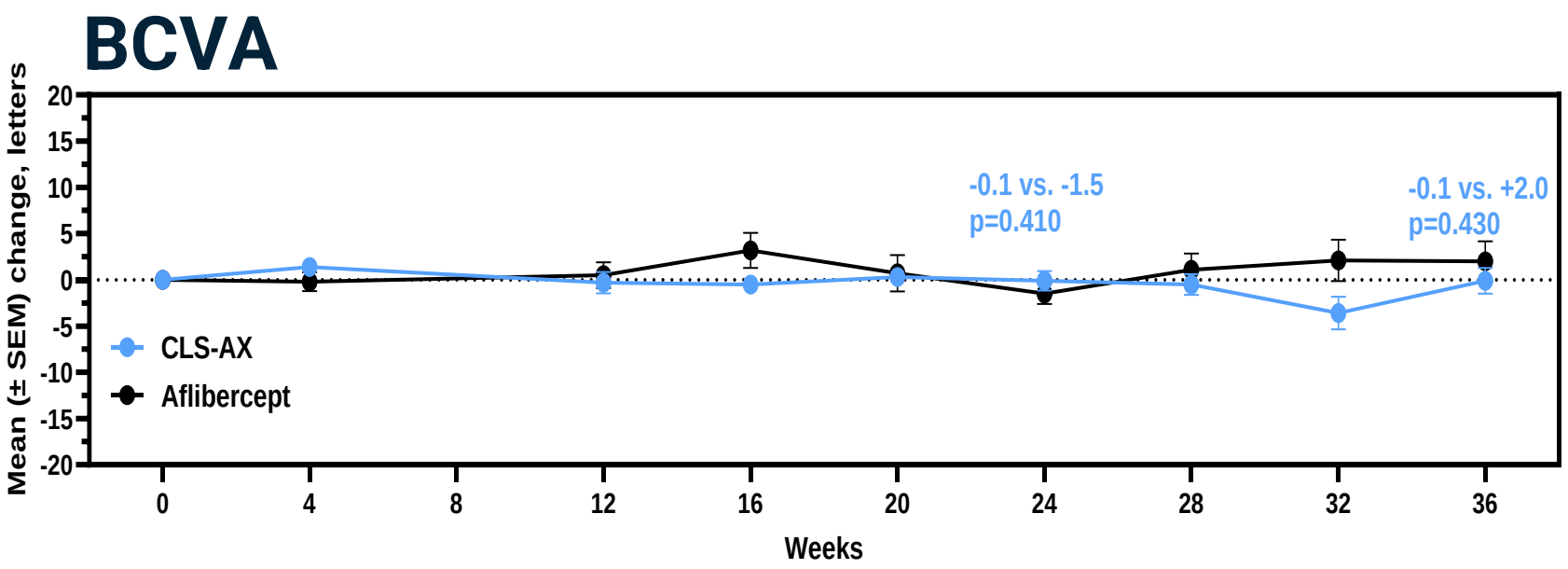
In the planned Phase 3 program, by targeting treatment naïve or the more general wet AMD population, there may be an even greater percentage reaching 6-months without rescue or re-dosing.

CLEARSIDE BIOMEDICAL

Abbreviations: BCVA, best corrected visual acuity; CSRT, 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.

Sub-Group Analysis 2:
Elimination of data on any observed ≥10 letter change in BCVA without OCT changes

Supports CLS-AX Phase 3 Trial Design That Excludes Participants with Non-disease Related Changes in Visual Acuity Prior to Randomization



Sub-Group Analysis Excluding Observations with ≥10 Letter Change from the Previous Visit in BCVA Without a Corresponding 50 Micron Change in CST

Key Insights for Phase 3 Planning

Elimination of observations of ≥10 letter changes prior to randomization may:

- **Reduce BCVA variability unrelated to Wet AMD activity**
- **Better ensure data reflects real world treatment practices**

Abbreviations: BCVA, best corrected visual acuity; CST, central subfield retinal thickness; SEM, standard error of the mean.
Excluded observations with a BCVA loss from the previous visit of 10 letters or more without a CST increase from the previous visit of 50 microns or more, or a BCVA gain from the previous visit of 10 letters or more without a CST decrease from the previous visit of 50 microns or more. P-values are based on a 2-sample t-test.

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

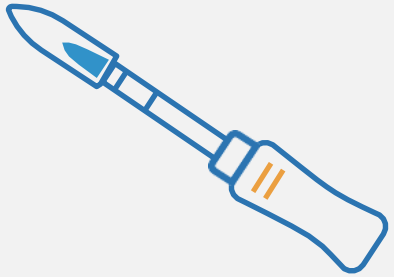
Phase 3 Program Summary

- Two pivotal, non-inferiority trials with treatment naïve participants
- Two arms with ~225 participants per arm: CLS-AX 1mg vs aflibercept 2mg
- Eliminate participants with non wAMD visual acuity variability prior to randomization
- Similar to Phase 3 trial design of EYLEA HD and VABYSMO in maintenance phase
- Employ more “real world” clinical practice re-dosing criteria for CLS-AX
- CLS-AX flexible dosing should be important differentiation vs other TKI programs
- End-of-Phase 2 Meeting expected in Q1 2025
- Expect to initiate both trials in 2H 2025

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

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