Safety and Tolerability of CLS-AX via Suprachoroidal Injection in nAMD Patients with Persistent Activity Following Anti-VEGF Therapy

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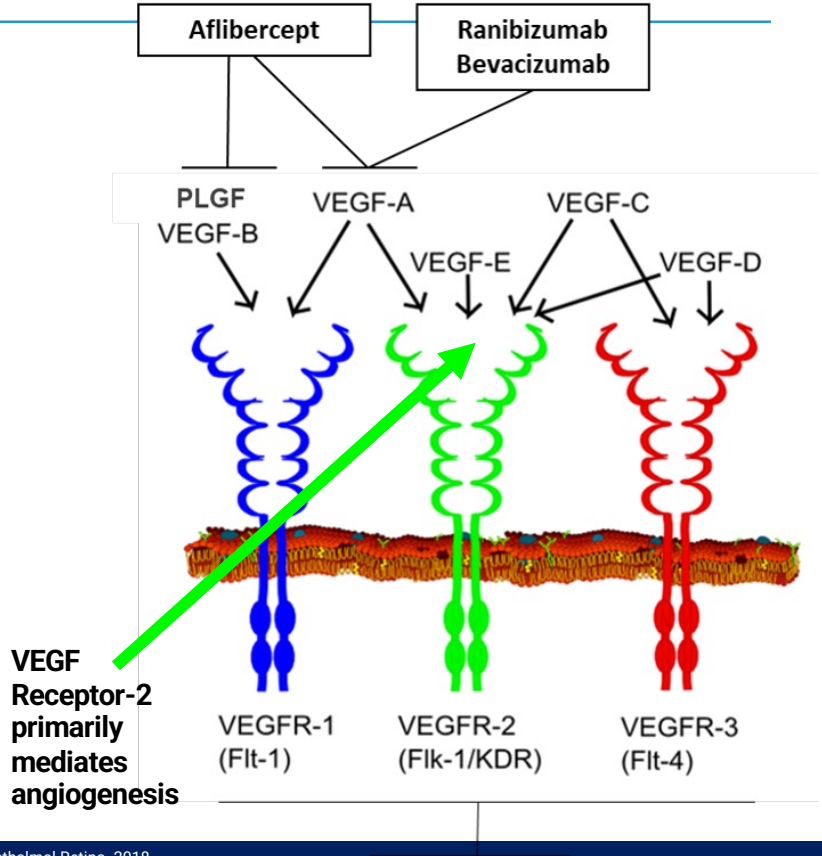
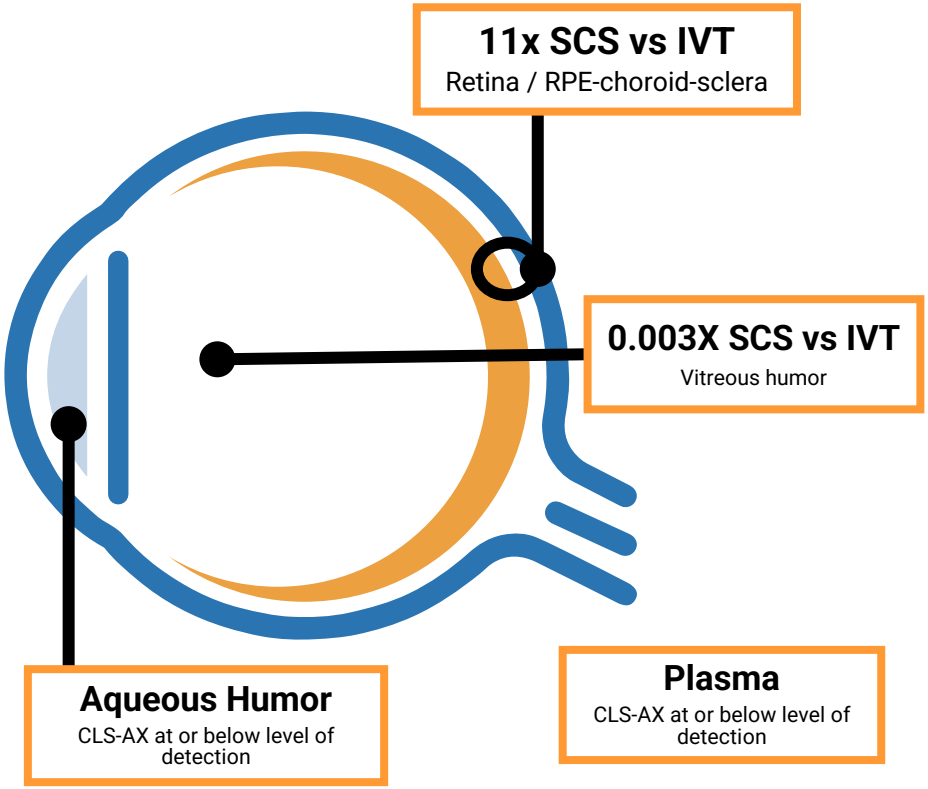
CLS-AX Delivered with Proprietary Microinjector for Wet AMD

Axitinib: a Highly Potent, Pan-VEGF TKI to Treat Wet AMD

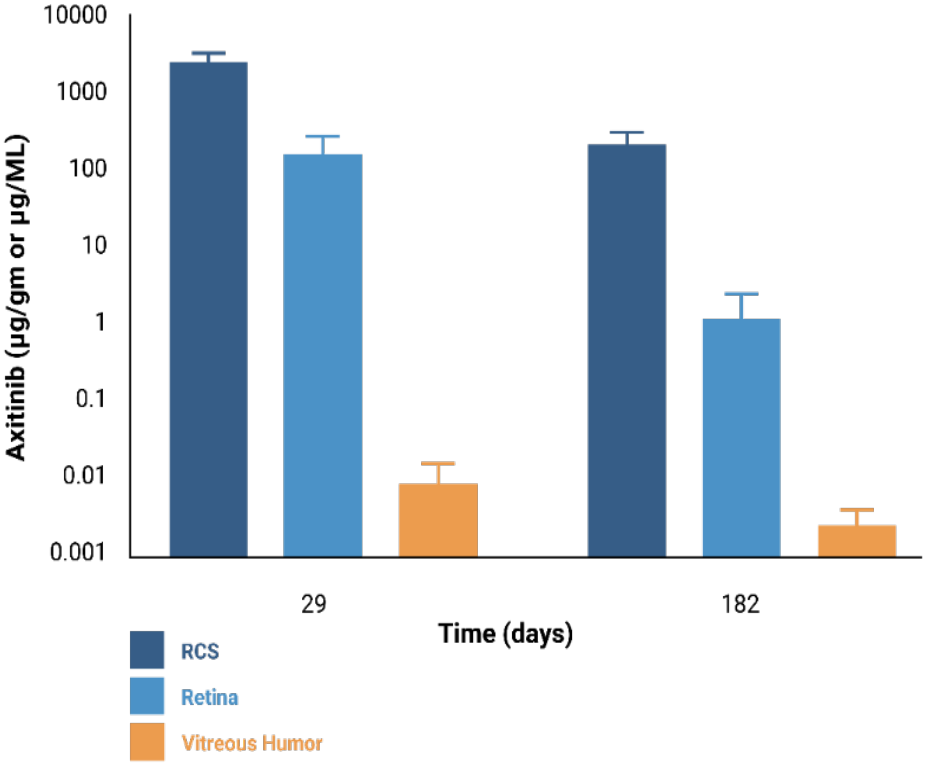
- Inhibits **VEGFR-1**, **VEGFR-2**, **VEGFR-3** receptors
  - More active than anti-VEGF-A in *in-vitro* angiogenesis model[1-2]
- Highly potent tyrosine kinase inhibitor (TKI)
  - >10x more potent than other TKIs in preclinical studies



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. Theile et al. Multikinase Inhibitors as a New Approach in Neovascular Age-Related Macular Degeneration (AMD) Treatment: In Vitro Safety Evaluations of Axitinib, Pazopanib and Sorafenib for Intraocular Use. Klin Monatsbl Augenheilkd 2013; 230: 247-254. | Image by Mikael Häggström, used with permission. Häggström, Mikael (2014). "Medical gallery of Mikael Häggström 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.008. ISSN 2002-4436. Public Domain.



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



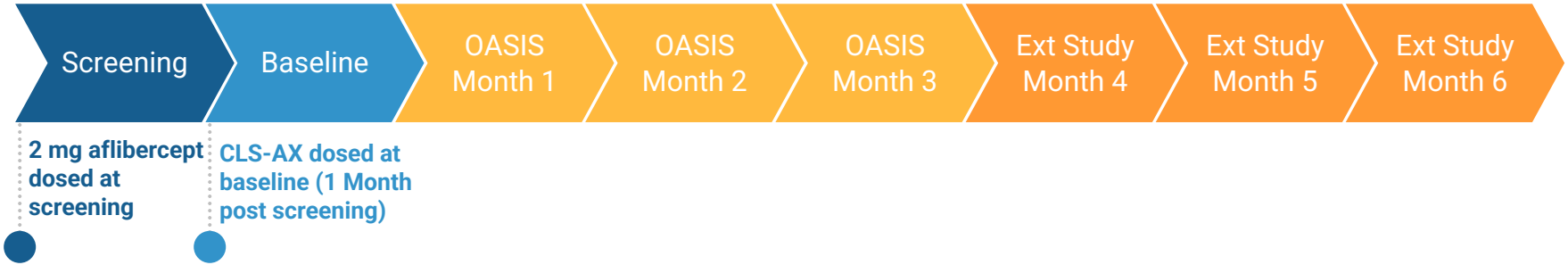
Rabbit toxicology study with single bilateral suprachoroidal injection of axitinib, 1.05 mg/eye (n=4 eyes/ timepoint)

Sources: Viral S. Kansara, Leroy W. Muya, Thomas A. Ciulla; Evaluation of Long-Lasting Potential of Suprachoroidal Axitinib Suspension Via Ocular and Systemic Disposition in Rabbits. *Trans. Vis. Sci. Tech.* 2021;10(7):19.
Abbreviations: SCS: Suprachoroidal Space | IVT: Intravitreal Injection | PK: Pharmacokinetic | RPE: Retinal pigment epithelium I RCS: RPE, Choroid, Sclera

OASIS and Extension Study

TRIAL DESIGN AND OBJECTIVES

- Open-label study with a primary endpoint to evaluate safety and tolerability
- Wet AMD patients with ≥2 anti-VEGF treatments in the prior 4 months
- Dose-escalation of CLS-AX
- Monthly assessment for additional treatment with aflibercept
- 6-Month follow-up after CLS-AX via a 3-month Extension Study



Note: aflibercept is dosed via intravitreal injection (IVT); CLS-AX is dosed via suprachoroidal injection | clinicaltrials.gov NCT# 04626128

Active Disease definition: Active subfoveal choroidal neovascularization (CNV) secondary to AMD in the study eye confirmed by an independent reading center as leakage from a subfoveal CNV on fluorescein angiography and intra-retinal or sub-retinal fluid on OCT central subfield)

OASIS and Subsequent Extension Study Enrolled Heavily anti-VEGF Treatment-Experienced Wet AMD Patients

Patients were sub-responders with active disease at screening confirmed by reading center

Wet AMD Disease Characteristics	COHORT 2: 0.10 mg	COHORT 3: 0.50 mg	COHORT 4: 1.0 mg	Total
No. of participants	2	7	5	14
Mean age (range), years	74.0 (70-78)	87.9 (81-97)	79.6 (74-83)	82.9 (70-97)
Mean baseline best corrected visual acuity (range), letters	60.0 (52-68)	59.0 (37-74)	71.2 (69-74)	63.5 (37-74)
Mean baseline central subfield retinal thickness (range), µm	213.5 (200-227)	201.9 (175-238)	214.8 (197-234)	208.1 (175-238)
Mean duration of wAMD diagnosis (range), months	**44.30 (33.9-54.7)**	**67.29 (6.8-102.1)**	**36.42 (6.1-103.4)**	**52.98 (6.1-103.4)**

Core et at. Predominantly Persistent Intraretinal Fluid in the Comparison of Age-related Macular Degeneration Treatments Trials. Ophthalmol Retina. 2022 Sep;6(9):771-785. | Waldstein et al. Morphology and visual acuity in aflibercept and ranibizumab therapy for neovascular age-related macular degeneration in the VIEW trials. Ophthalmology 2016;123:1521-1529.

Active Disease definition: Active subfoveal choroidal neovascularization (CNV) secondary to AMD in the study eye confirmed by an independent reading center as leakage from a subfoveal CNV on fluorescein angiography and intra-retinal or sub-retinal fluid on OCT central subfield)

CLS-AX Demonstrated a Positive Safety Profile in All Four Cohorts

OASIS & Extension Study Data (Through 6 Months)

SAFETY DATA

Excellent Safety Profile at all doses and timepoints

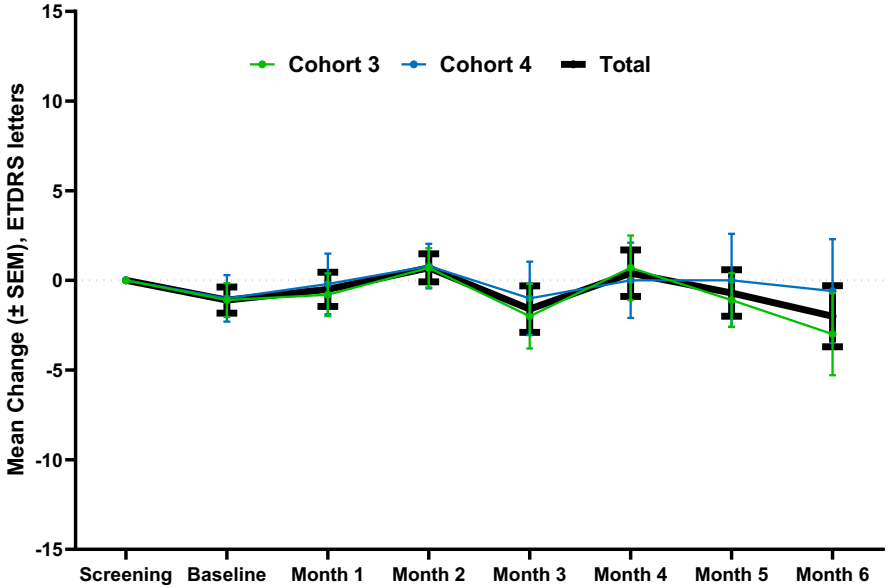
- No serious adverse events (SAEs)
- No treatment emergent adverse events (TEAEs) related to study treatment
- No dose limiting toxicities
- No adverse events related to inflammation, vasculitis or vascular occlusion
- No vitreous “floaters” or dispersion of CLS-AX into the vitreous
- No retinal detachment
- No endophthalmitis
- No adverse events related to intraocular pressure

Source: Clearside data on file.

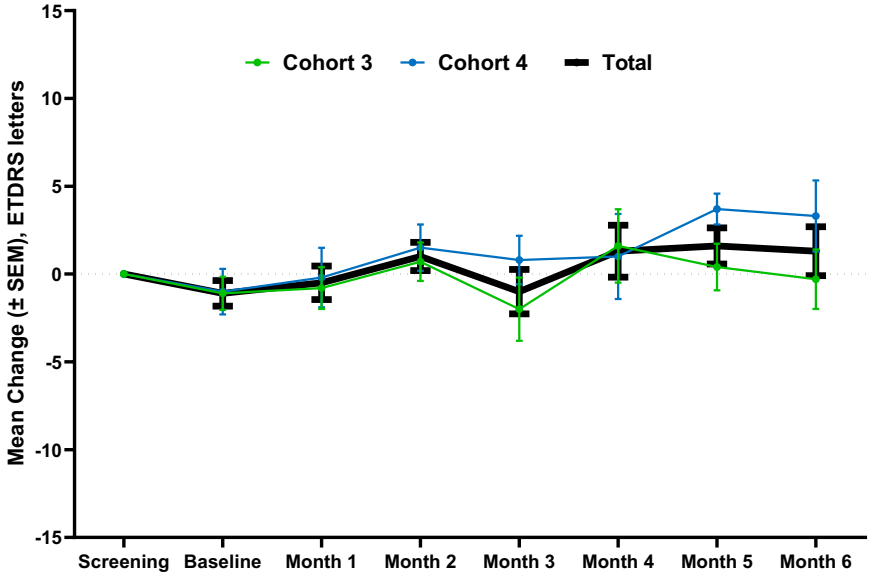
Extension Study: Stable Visual Acuity

Mean Best Corrected Visual Acuity Letter Score, Change from Screening

All Data



Excluding Data After Additional Treatment

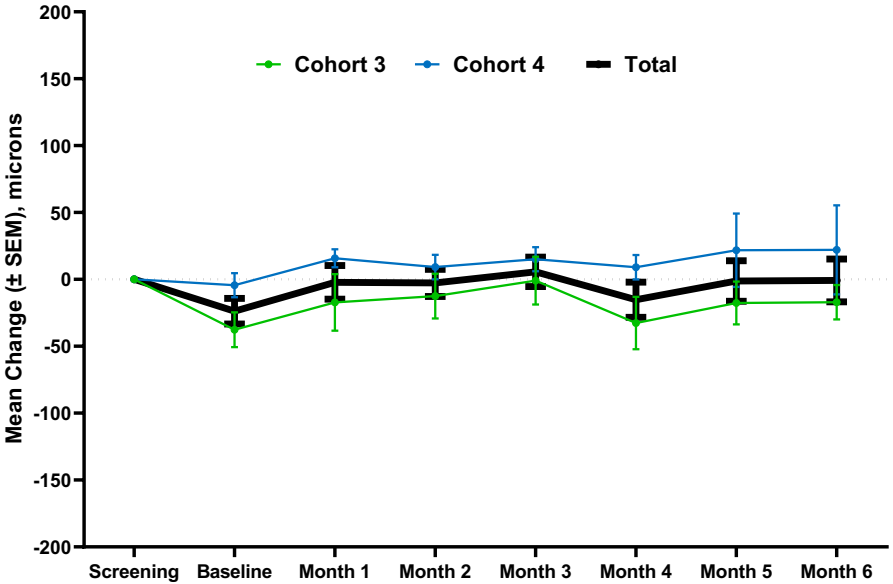


Source: Clearside data on file.

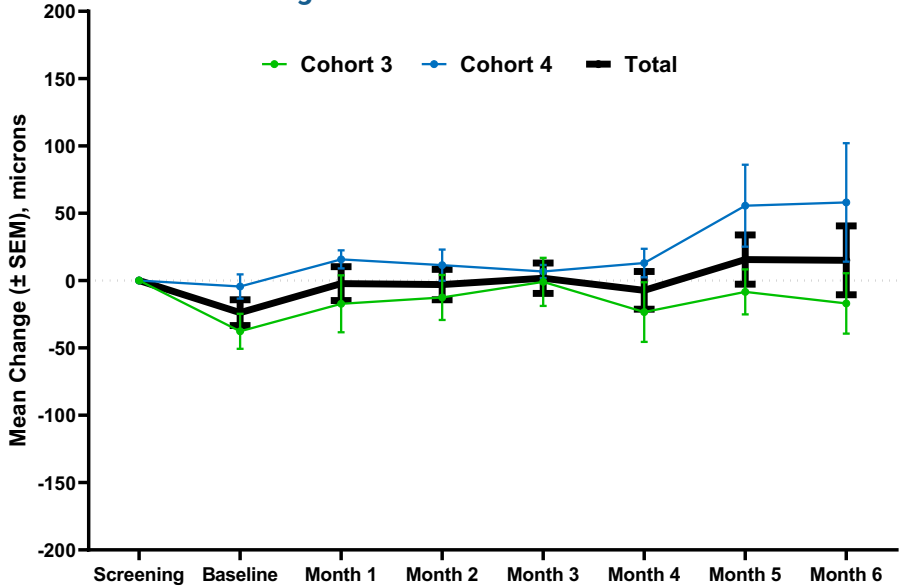
Extension Study: Stable Central Subfield Thickness

Mean Central Subfield Thickness, Change from Screening

All Data



Excluding Data After Additional Treatment



Source: Clearside data on file.

Extension Study:
CLS-AX Treatment Across Cohorts

Observed Reduction in Injection Frequency
All Therapies

Cohort	Number of Participants	Avg Monthly Injections Before CLS-AX Administration	Avg Monthly Injections After CLS-AX Administration	% Reduction
4	5	0.87	0.20	**77.0**
3	7	0.81	0.12	**85.2**
2	2	0.83	0.17	79.5

Observed Reduction in Injection Frequency
Therapies Per Protocol Criteria

Cohort	Number of Participants	Avg Monthly Injections Before CLS-AX Administration	Avg Monthly Injections After CLS-AX Administration	% Reduction
4	4	0.83	0.13	**84.3**
3	7	0.81	0.12	**85.2**
2	1	0.67	0.17	74.6

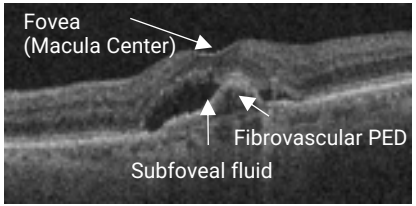
77 – 85% Reduction in Injection Frequency in Cohorts 3 and 4

Note: Average Monthly Injections Before CLS-AX Administration = # treatments six months prior/ 6.
Average Monthly Injections After CLS-AX Administration = # treatments / # months of follow-up.
% Reduction = Average of individual reductions calculated as (after – before) / before × 100%.
Source: Clearside data on file.

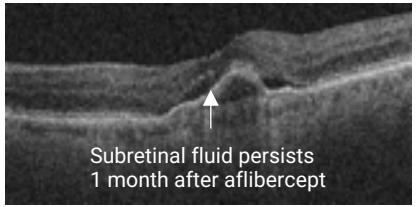
6 Month Case Study:
CLS-AX Demonstrated Biologic Effect in anti-VEGF Sub-responder

Cohort 3, Subject 2: 89 prior anti-VEGF injections with persistent subfoveal fluid 1 month after aflibercept at screen

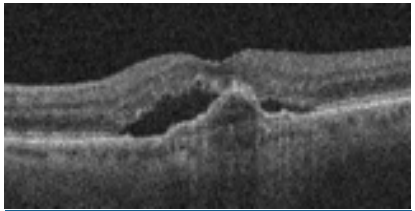
Subretinal fluid gradually resolves through 4 months after CLS-AX with stable BCVA and improved CST



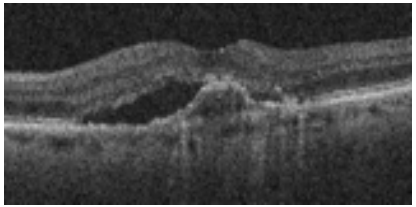
Screening: Aflibercept
BCVA 75, CST 265



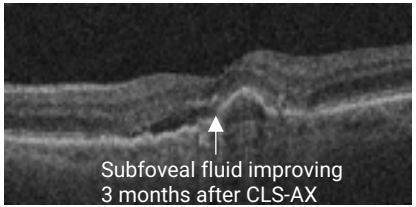
Baseline: CLS-AX
BCVA 73, CST 218



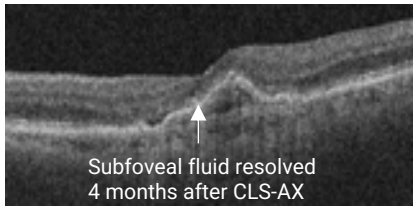
Month 1
BCVA 78, CST 277



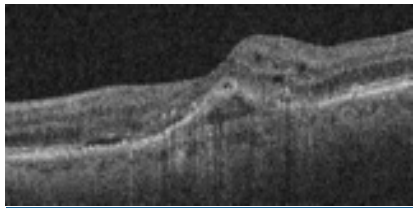
Month 2
BCVA 78, CST 253



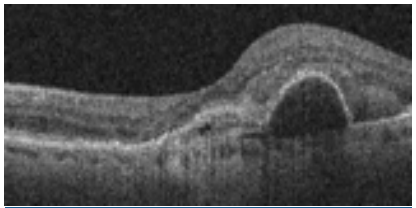
Month 3
BCVA 75, CST 221



Month 4
BCVA 74, CST 182



Month 5
BCVA 75, CST 223



Month 6: Additional therapy administered
BCVA 60, CST 224

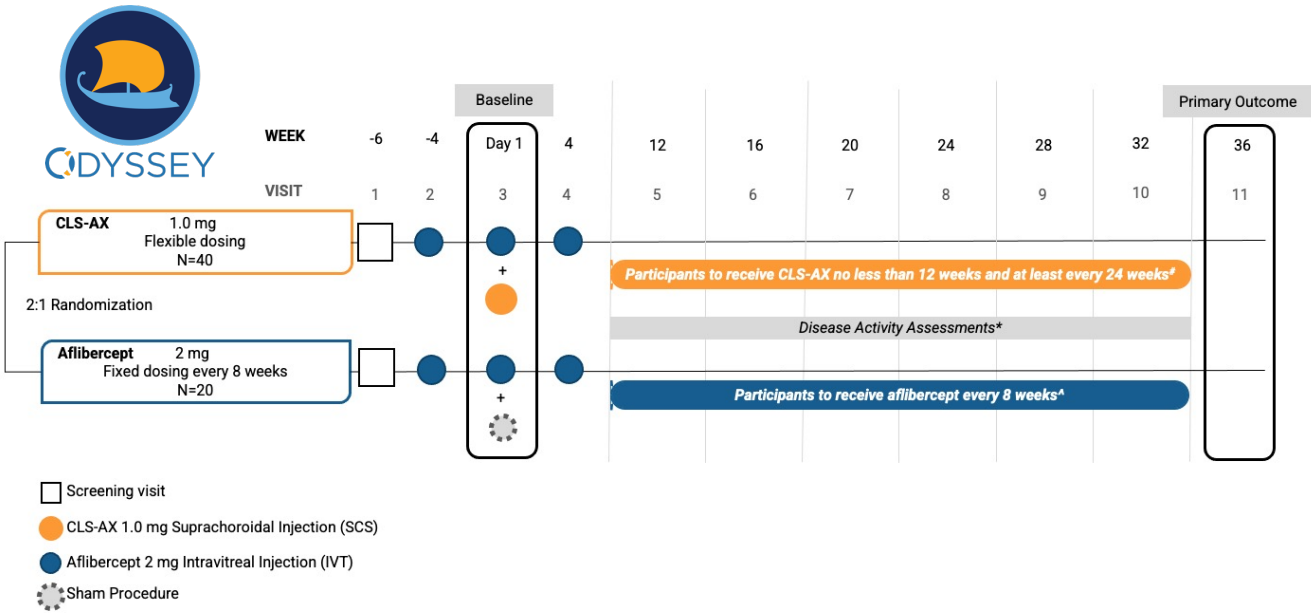
Source: Clearside data on file

ODYSSEY Ph 2b Trial: Treatment Experienced nAMD Participants with Active Disease

Randomized, Double-Masked, Parallel-Group, Active-Controlled Multicenter Trial

Trial Objectives:

- **Primary outcome:** Mean change in BCVA from Baseline to Week 36; safety & tolerability
- **Secondary outcomes:**
  - Other changes in visual function and ocular anatomy, such as CST
  - Need for supplemental treatment
  - Treatment burden as measured by total injections over trial duration



* 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.

CLS-AX administered via SCS Injection for nAMD was safe and well-tolerated

Key Takeaways

- CLS-AX had an excellent safety profile at all doses and timepoints, with no SAEs, no dose limiting toxicities, and AEs from inflammation
- CLS-AX exhibited early signs of durability and reduction in treatment burden
- CLS-AX is being evaluated in a Phase IIb clinical trial, ODYSSEY, for nAMD

Financial Disclosures

- Available upon request