Safety and Tolerability Study of Suprachoroidal Injections of CLS-AX in Neovascular AMD Patients with Persistent Activity Following Anti-VEGF Therapy: OASIS Phase 1/2a Clinical Trial 6-Month Extension Study Results

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Financial Disclosures

CLINICAL RESEARCH

Allegro Ophthalmics; Allergan; Genentech Inc; Ionis; IVERIC Bio; Novartis Pharmaceuticals; Regeneron Pharmaceuticals Inc; RegenXBio

CONSULTANT

Allegro Ophthalmics; Allergan; Aviceda Therapeutics; Clearside Biomedical; EyeBio; Eyedaptic; Genentech Inc; Glaukos Corporation; InflammX Therapeutics; IVERIC Bio; jCyte; Novartis Pharmaceuticals; Regeneron Pharmaceuticals Inc; ReVana Therapeutics; Ripple Therapeutics; Theravance Biopharma

SPEAKERS BUREAU

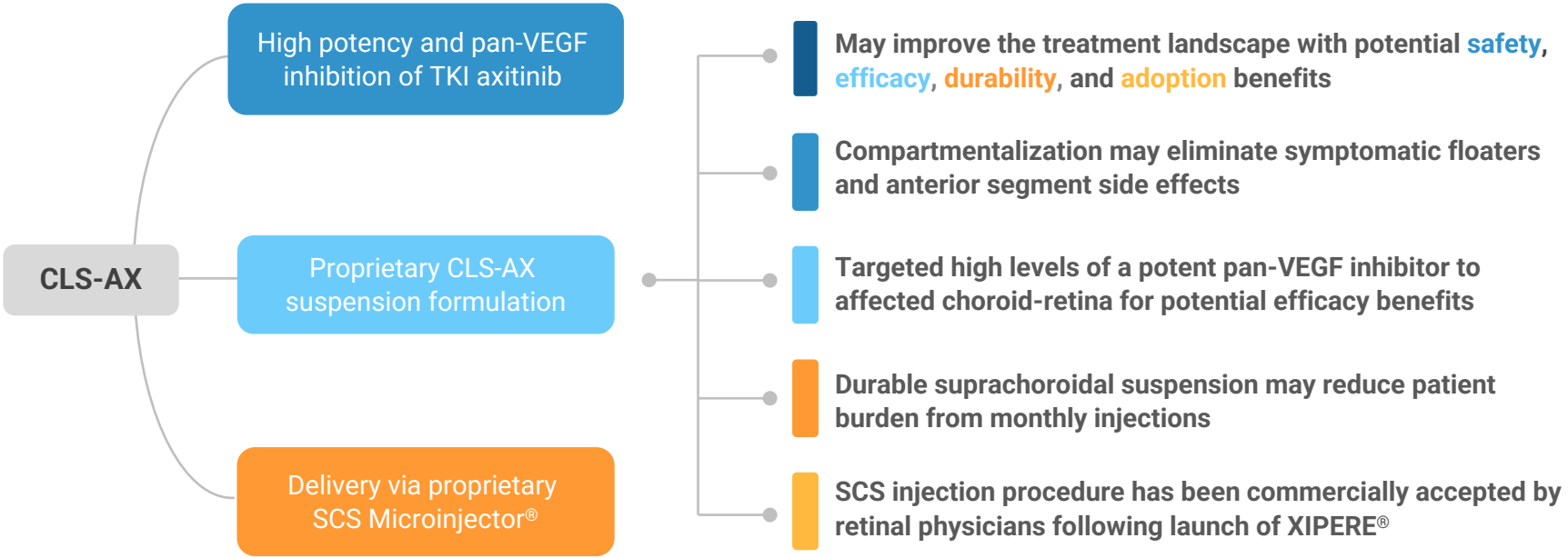
Allergan; Genentech Inc

CLS-AX for nAMD

Rationale for suprachoroidal delivery of a tyrosine kinase inhibitor (TKI)

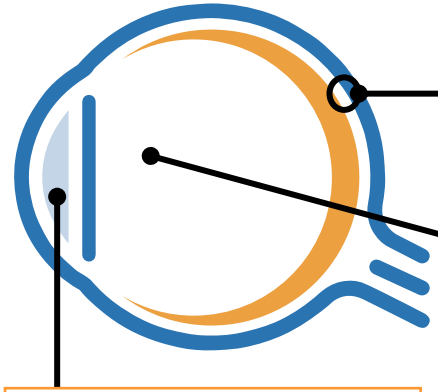
CLS-AX (axitinib injectable suspension) for Suprachoroidal Use

Leveraging a Highly Potent Small Molecule Pan-VEGF Inhibitor (MW 386) with Suprachoroidal Delivery



Axitinib is a tyrosine kinase inhibitor (TKI) | XIPERE® (triamcinolone acetonide injectable suspension), for suprachoroidal use has received U.S. FDA Approval. Please see Important Safety Information for XIPERE® in the Full Prescribing Information: https://www.bauschhealth.com/Portals/25/Pdf/PI/XIPERE-PI.pdf. | Source: 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.

CLS-AX Injected Suprachoroidally Provides Targeted Delivery Relative to Intravitreal Injection at Same Dose



11x SCS vs IVT
Retina / RPE-choroid-sclera

0.003X SCS vs IVT
Vitreous humor

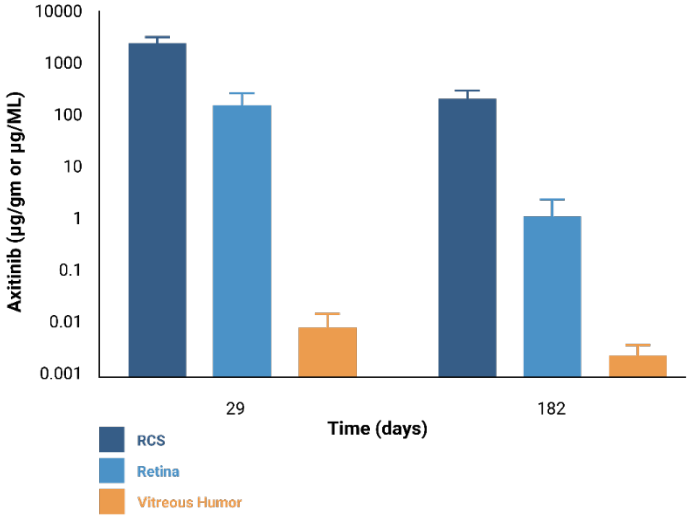
Plasma
CLS-AX at or below level of detection

Aqueous Humor
CLS-AX at or below level of detection

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

CLS-AX has Potential for Meaningful Durability CLS-AX Levels to 6 Months

High Retina Levels: Sufficient to block VEGF pathway
Low Plasma Levels: <1 ng/mL



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

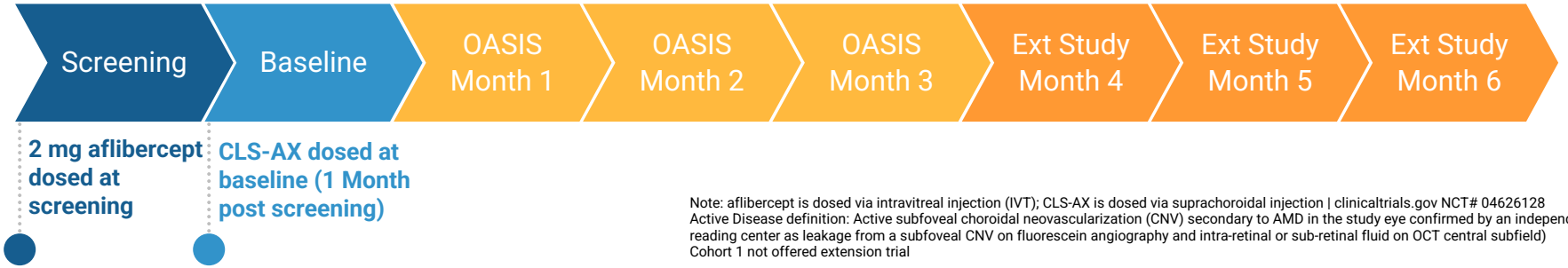
Sources: Viral S. Kansara, Leroy W. Muya, Thomas A. Ciulla; Evaluation of Long-Lasting Potential of Suprachoroidal Axitinib Suspension Via Ocular and Systemic Disposition in Rabbits. *Trans. Vis. Sci. Tech*. 2021;10(7):19.
Abbreviations: SCS: Suprachoroidal Space | IVT: Intravitreal Injection | PK: Pharmacokinetic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

OASIS Results: Safety, Durability, & Treatment Burden Reduction

OASIS and Extension Study: CLS-AX Phase 1/2a Clinical Trial in Treatment-Experienced Wet AMD Patients with Active Disease at Screening

TRIAL DESIGN AND OBJECTIVES

- **Open-label study** with a primary endpoint to evaluate safety and tolerability of escalating single doses of CLS-AX administered through suprachoroidal injection following IVT aflibercept
- Wet AMD patients with ≥2 anti-VEGF treatments in the prior 4 months, reading center confirmation of persistent active disease
- Dose-escalation of CLS-AX (in mg): Cohort 1 at 0.03; Cohort 2 at 0.1; Cohort 3 at 0.5; Cohort 4 at 1.0
- Secondary endpoints: visual function, ocular anatomy, and need for additional treatment
- Monthly assessment for additional treatment with aflibercept: loss from best measurement of ≥10 letters in BCVA with exudation; increase in CST >75 microns; a vision-threatening hemorrhage
- **Extension study:** A total of 6 months' follow-up for patients in Cohorts 2, 3, & 4 who chose to continue for an additional 3 months



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)
Cohort 1 not offered extension trial

OASIS Enrolled Heavily anti-VEGF Treatment-Experienced Wet AMD Patients

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

Why target this patient population instead of treatment naïve or patients with controlled disease?

- Patients have a high need for effective therapy with lower treatment burden
- Minimizes the risk of false signals of biologic effect
- Facilitates assessment for biological effect in a difficult-to-treat nAMD patient population
- Facilitates assessment of an appropriate dose, based on safety and biologic effect
- Represents a significant number of patients in clinical practice, with >30% sub-responders
- Supports future clinical trials

Desired outcomes in this heavily treated patient population:

- Demonstrate safety and tolerability of CLS-AX
- Maintain stability of visual acuity and central subfield thickness with lower treatment burden

Enrolling difficult to treat anti-VEGF sub-responders allowed observation of possible signs of biologic effect while minimizing false signals

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)

Extension Study: Demographics and Wet AMD History

Wet AMD Disease Characteristics	COHORT 2: 0.1 mg	COHORT 3: 0.5 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)**
Number of anti-VEGF injections reported prior to CLS-AX administration on Day 1, mean (range)	**23.0 (12-34)**	**38.9 (6-90)**	**33.2 (6-89)**	**34.6 (6-90)**
Annualized number of anti-VEGF injections prior to Enrollment, mean (range)	**8.81 (5.4-12.2)**	**8.84 (4.9-11.9)**	**12.01 (10.5-13.1)**	**9.97 (4.9-13.1)**

Source: Clearside data on file.
Cohort 2 data calculated with number of patients with available data. Cohorts 3 & 4 data calculated with number of participants.

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

3-Month & 6-Month Extension Study Data

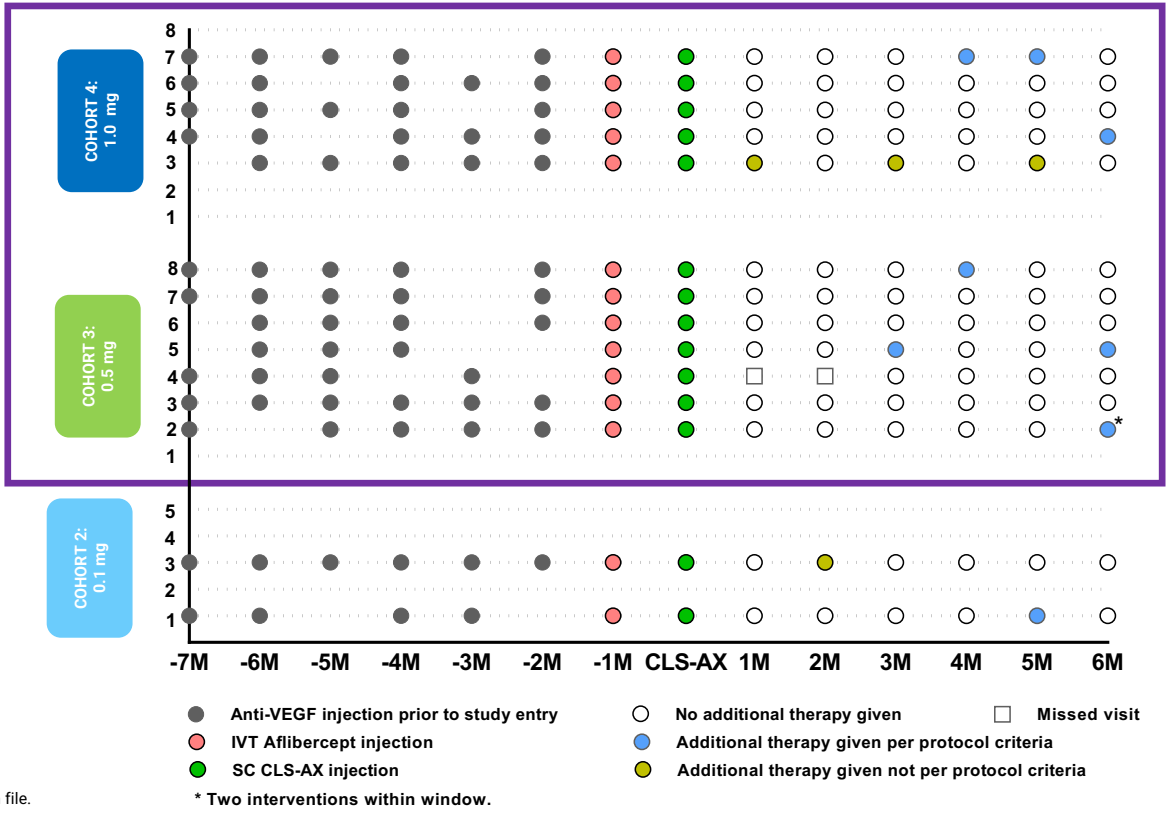
SAFETY DATA

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 (6 Month Data): Prior Anti-VEGF Therapies and All Additional Therapies



DURABILITY

Cohorts 3 & 4

No Additional Therapy

≥ 3 Months: 11/12 (92%)
≥ 4 Months: 10/12 (83%)
≥ 6 Months: 8/12 (67%)
> 6 Months: 6/12 (50%)

Source: Clearside data on file.

Extension Study (6 Month): CLS-AX Demonstrated Reduction of Treatment Burden Across Cohorts

Observed Reduction in Treatment Burden
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 Treatment Burden
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

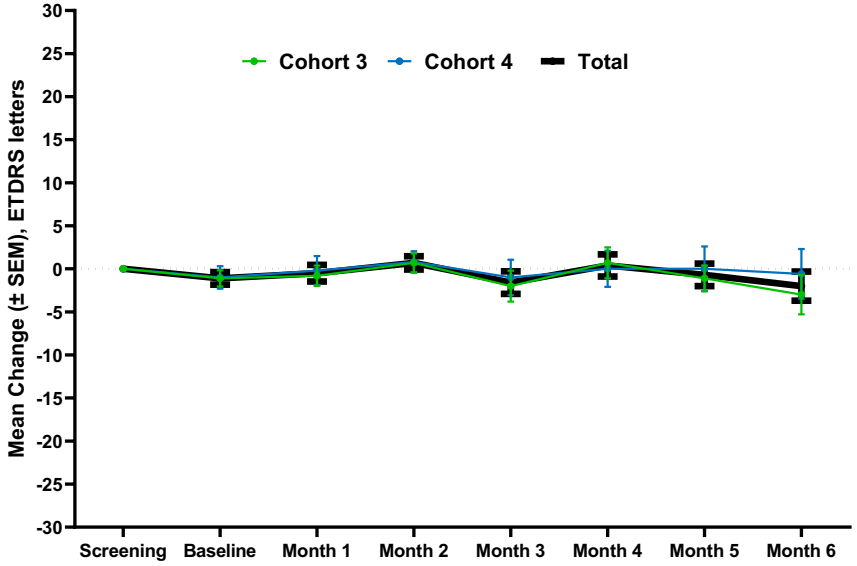
77 – 85% Reduction in Treatment Burden in Cohorts 3 and 4

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.

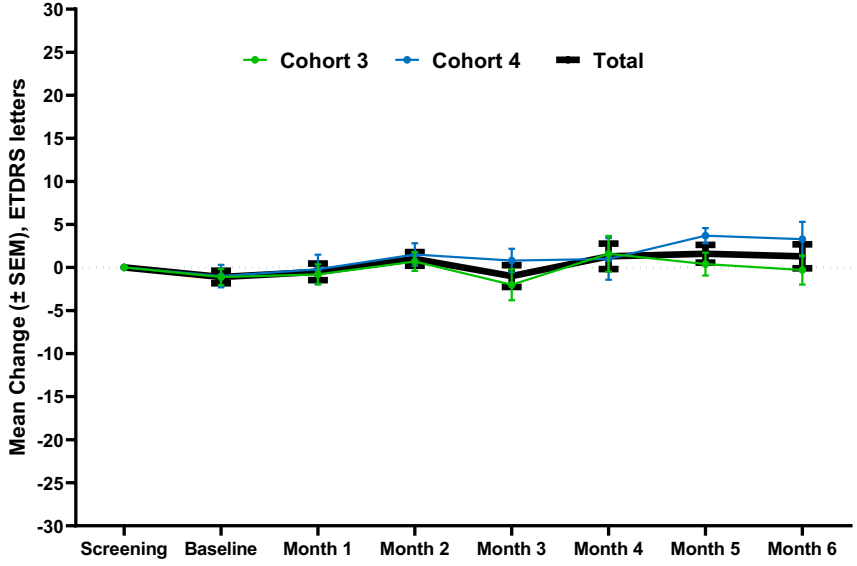
Extension Study (6 Month): Stable Visual Acuity

Mean Best Corrected Visual Acuity Letter Score, Change from Screening

All Data



Excluding Data After Additional Treatment

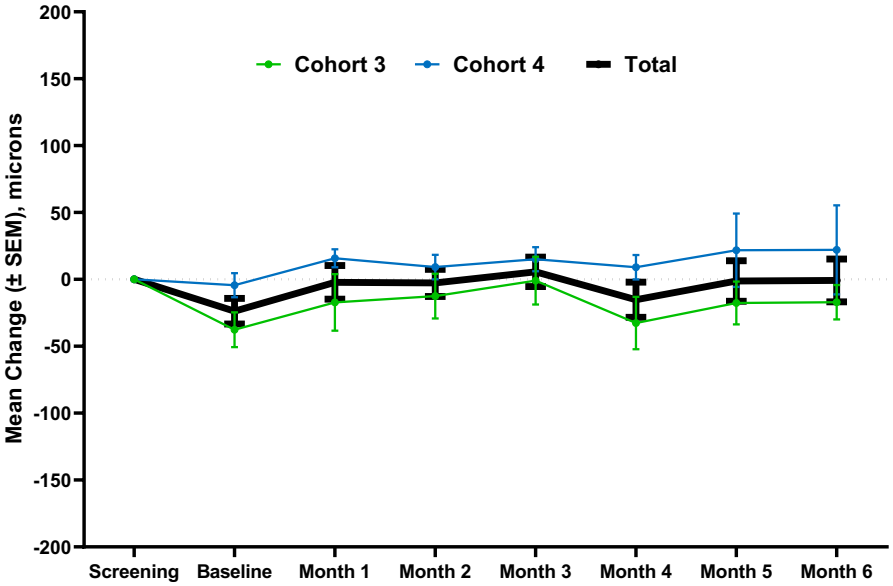


Source: Clearside data on file.

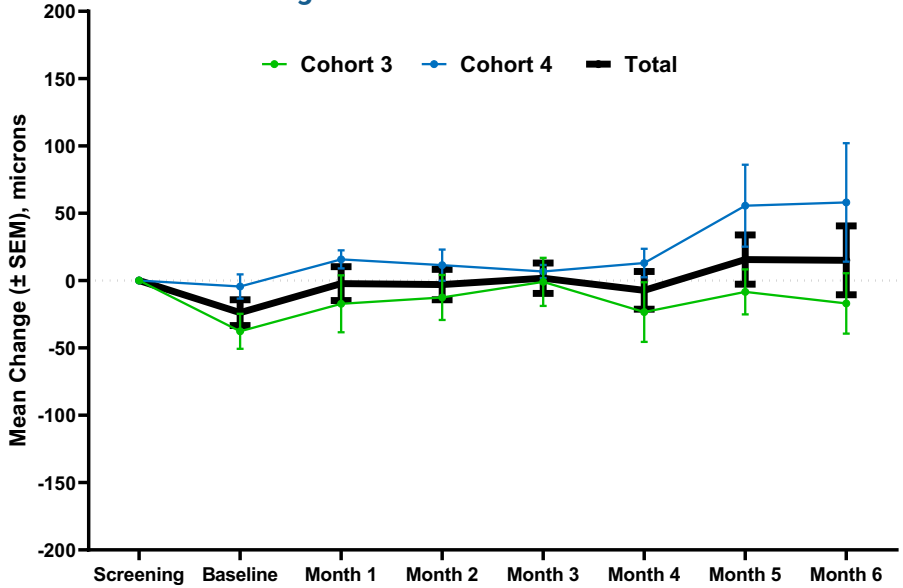
Extension Study (6 Month): Stable Central Subfield Thickness

Mean Central Subfield Thickness, Change from Screening

All Data



Excluding Data After Additional Treatment

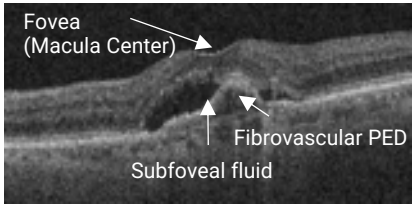


Source: Clearside data on file.

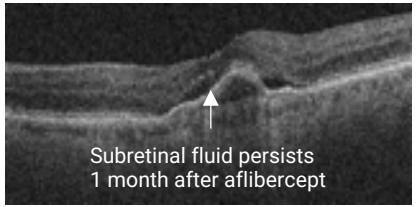
6 Month Case Study:
A Biological Effect Following CLS-AX in Anti-VEGF Sub-responder

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

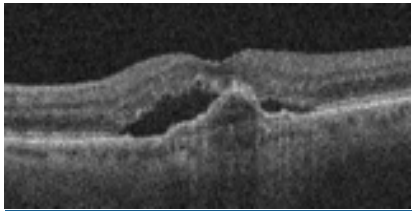
Subretinal fluid gradually resolves through 4 months after CLS-AX with stable BCVA and improved CST



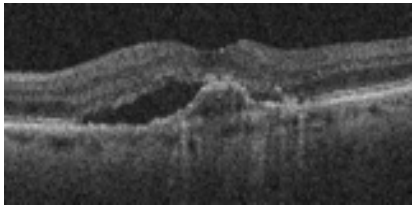
Screening: Aflibercept
BCVA 75, CST 265



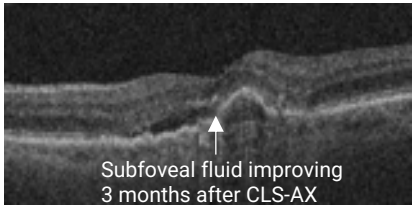
Baseline: CLS-AX
BCVA 73, CST 218



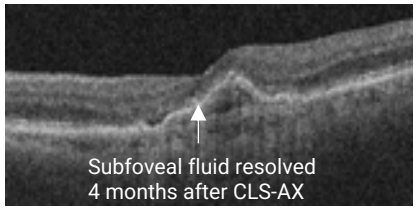
Month 1
BCVA 78, CST 277



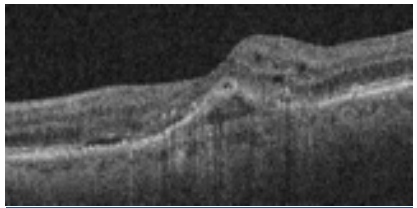
Month 2
BCVA 78, CST 253



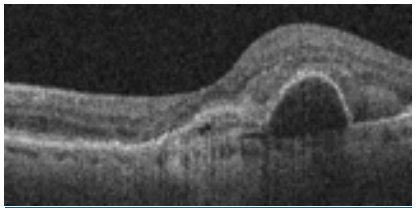
Month 3
BCVA 75, CST 221



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. | Previous treatments prior to screening.

ODYSSEY
CLS-AX
Phase 2b
Clinical Trial

UCI Center for Translational Vision Research

The Gavin Herbert Eye Institute
University of California, Irvine · School of Medicine

ODYSSEY Phase 2b Trial in Treatment-Naïve Wet AMD Participants

Randomized, Double-Masked, CLS-AX Maintenance vs Faricimab Maintenance

Trial Objectives:

Stable visual acuity with reduced treatment burden/better durability

Number of Participants:

Total of 110 patients
(55 in each arm)

- Key inclusion criteria:
  - Treatment naïve wet AMD participants
  - Subfoveal CNV secondary to wet AMD
  - Best Corrected Visual Acuity (BCVA) of 78–24 letters*
- Primary endpoint: Mean change in BCVA
- Key secondary endpoints:
  - Mean change in Central Subfield Thickness (CST)
  - Treatment burden reduction as measured by total anti-VEGF injections over trial duration
- Monthly disease activity assessments: Beginning 2 months after last faricimab loading dose to determine if retreatment is needed
- Retreatment criteria: Decrease in BCVA, increase in CST, or new macular hemorrhage (per faricimab Phase 3 trial retreatment criteria#)

* Inclusive (20/32–20/320 approximate Snellen equivalent)
# Increase ≥75 µm in CST compared with the lowest CST value recorded at either of the previous 2 scheduled visits, **or** Increase >50 µm in CST compared with the average CST value over the previous 2 scheduled visits, **or** Decrease ≥5 letters in BCVA compared with the average BCVA value over the previous 2 scheduled visits, owing to nAMD disease activity (as determined by the Investigator), **or** Decrease ≥10 letters in BCVA compared with the highest BCVA value recorded at either of the previous 2 scheduled visits, owing to nAMD disease activity (as determined by the Investigator), **or** Presence of new macular hemorrhage (as determined by the Investigator), owing to nAMD disease activity.

OASIS (3 Month) and Extension Study (6 Month) Cohorts 3 and 4: Promising CLS-AX Safety Data, Durability and Biologic Effect

SAFETY DATA

- Excellent safety profile at all doses and timepoints
- No Serious Adverse Events
- No dose limiting toxicities
- No Adverse Events (AEs) from inflammation
- No AEs related to intraocular pressure

DURABILITY

- In OASIS, to 3 months:
  - ≥72% reduction in treatment burden
- In Extension Study, to 6 months:
  - ≥77% reduction in treatment burden
  - Patients not requiring additional therapy:
    - ≥ 3 Months: 11/12 (92%)
    - ≥ 4 Months: 10/12 (83%)
    - **≥ 6 Months: 8/12 (67%)**
    - **> 6 Months: 6/12 (50%)**

BIOLOGIC EFFECT

- Stable mean Best Corrected Visual Acuity (BCVA)
- Stable mean Central Subfield Thickness (CST)
- On optical coherence tomography (OCT), anatomical signs of tyrosine kinase inhibitor (TKI) biologic effect were observed in anti-VEGF treatment-experienced sub-responders

NEXT STEPS

- Expect to initiate Phase 2b clinical trial in Q1 2023 with primary endpoint readout anticipated in mid-2024

Source: Clearside data on file.

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