OASIS Phase 1/2a Clinical Trial Safety Results

December 21, 2021

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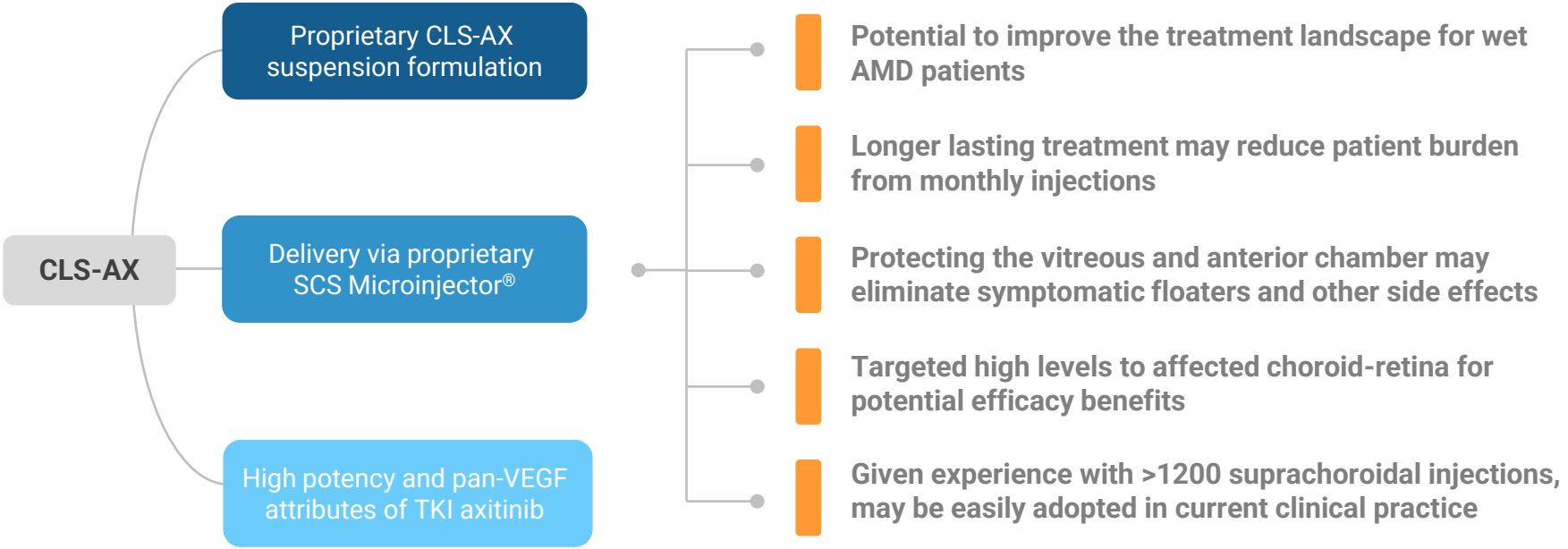
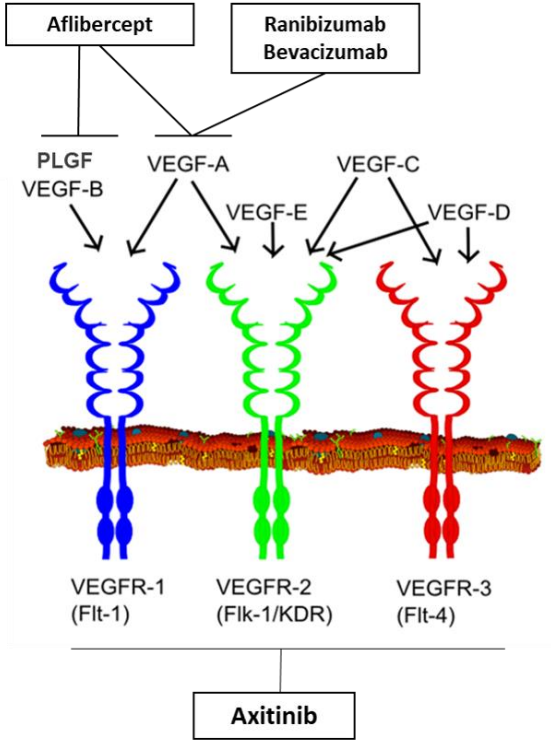
CLS-AX (axitinib injectable suspension) for Suprachoroidal Use



Axitinib is a tyrosine kinase inhibitor (TKI)

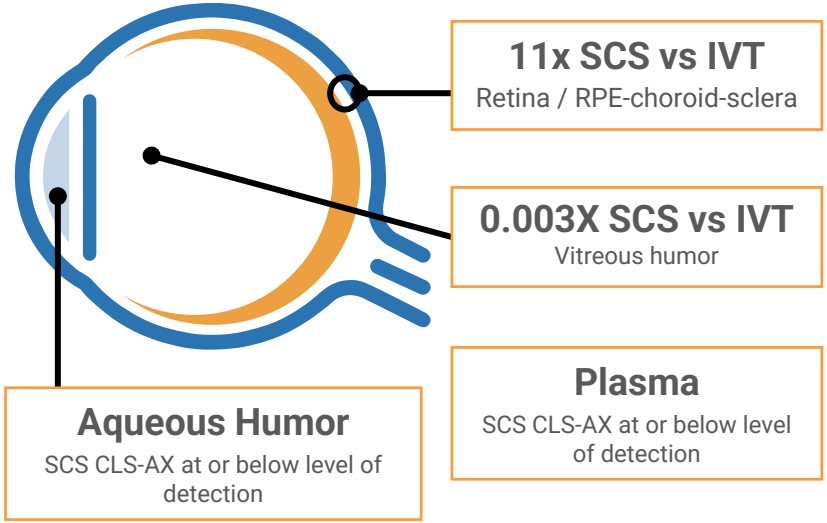
Axitinib: a Highly Potent, Pan-VEGF TKI to Treat Wet AMD

- Axitinib's intrinsic pan-VEGF inhibition through receptor blockade
  - Approved treatments are focused VEGF-A inhibitors
- Inhibits **VEGFR-1**, **VEGFR-2**, **VEGFR-3** receptors
  - More effective 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
  - Better ocular cell biocompatibility than other TKIs[3]
  - More effective than other TKIs for experimental corneal neovascularization in preclinical models
- Preclinical data showed axitinib inhibition and regression of 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. 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.

Suprachoroidal CLS-AX Demonstrated Targeted Delivery in Preclinical Models



Provides Targeted Delivery Relative to Intravitreal Injection at Same Dose

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

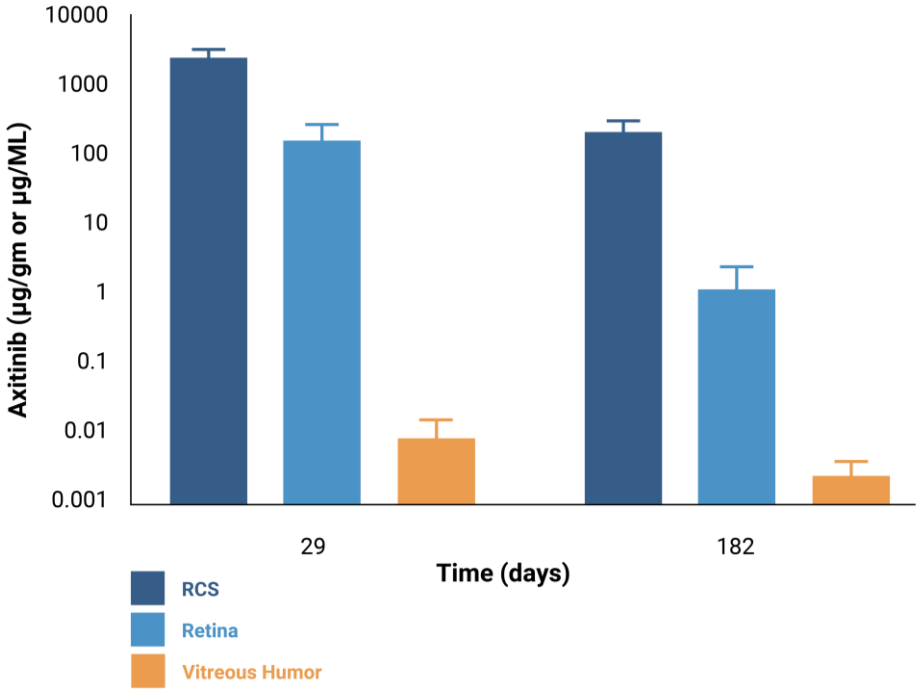
1-wk rabbit PK studies

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. doi:

Abbreviations: SCS: Suprachoroidal Space | IVT: Intravitreal Injection | PK: Pharmacokinetic | RPE: Retinal pigment epithelium

CLS-AX has Potential for Meaningful Durability

Therapeutic Levels > IC50 for 6 months after 1.05 mg/eye SCS Injection in Rabbits



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

- On day 182, mean axitinib levels in the RPE-choroid-sclera (199 µg/gm) and in the retina (1.1 µg/gm) were 3-5 log orders higher than the in-vitro IC50 value (0.2 ng/mL, VEGFR2 autophosphorylation inhibition assay).
- Based on this IC50 value, therapeutic levels were achieved in the RPE-choroid-sclera and retina for 6 months after a single suprachoroidal injection of axitinib in rabbits.

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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. doi:
Abbreviations: RCS: RPE-choroid-sclera| | RPE: Retinal pigment epithelium

CLS-AX Phase 1/2a Clinical Trial in Wet AMD

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
- 3 Cohorts of 5 patients each: n=15
- Dose-escalation of CLS-AX (in mg): Cohort 1 at 0.03; Cohort 2 at 0.10; Cohort 3 planned at 0.50
- Secondary endpoints: visual function, ocular anatomy, and need for additional treatment
- 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

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

Wet AMD History

Wet AMD Disease Characteristics	COHORT 1: 0.03 mg (N=6)	COHORT 2: 0.10 mg (N=5)
No. of participants	6	5
Bilateral wAMD, n	0	4
Mean duration of wAMD diagnosis (range), months	50.13 (12.4-110.3)	49.78 (24.7-81.3)
Mean duration since first wAMD treatment (range), months	50.08 (12.4-110.3)	49.70 (24.7-81.1)
Total mean number of wAMD treatments prior to screening (range)	25.8 (6-40)	23.2 (11-38)
wAMD treatments administered prior to Screening, n (%) [No. of injections]		
Aflibercept	1 (16.7%) [29]	2 (40.0) [16]
Bevacizumab	1 (16.7%) [6]	2 (40.0) [21]
Ranibizumab	4 (66.7%) [114]	4 (80.0) [79]
Blinded therapy	1 (16.7%) [6]	0
Total number of wAMD treatments prior to Screening (within 3 years), n (%)		
3-6	1 (16.7)	0
7-12	0	1 (20.0)
13-18	1 (16.7)	2 (40.0)
>18	4 (66.7)	2 (40.0)
Mean (range)	22.5 (6-33)	21.6 (11-33)

Source: Clearside data on file.

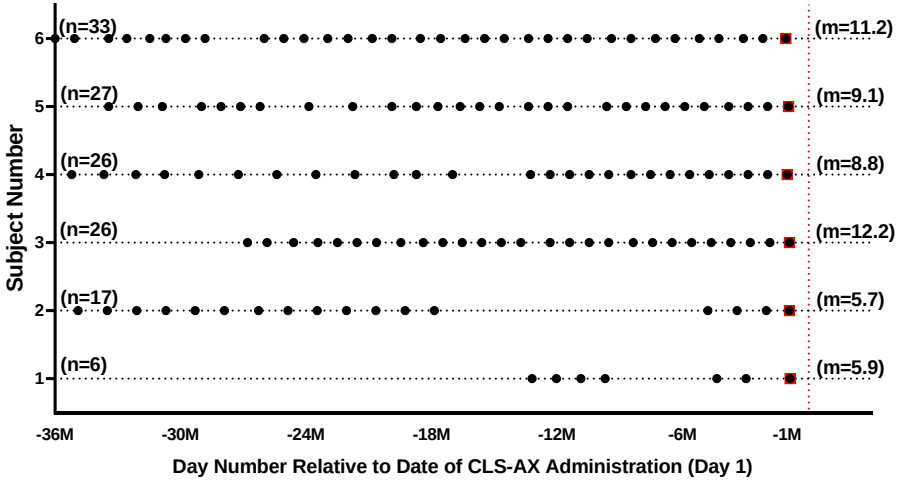
Demographics and Characteristics at Baseline

CHARACTERISTICS	COHORT 1: 0.03mg (N=6)	COHORT 2: 0.10mg (N=5)
No. of participants	6	5
Mean age (range), years	81.8 (66-93)	78.2 (65-90)
Women, no. (%)	2 (33.3)	3 (60.0)
Mean baseline best corrected visual acuity (range), letters	59.0 (29-74)	65.6 (52-75)
Mean central subfield retinal thickness (range), µm	231.2 (208-294)	209.4 (184-227)
Mean total lesion area (range), mm2	6.252 (3.58-9.58)	7.712 (1.06-18.02)

Source: Clearside data on file.

Anti-VEGF Treatments up to 3 Years Prior to Screening

COHORT 1: 0.03 mg

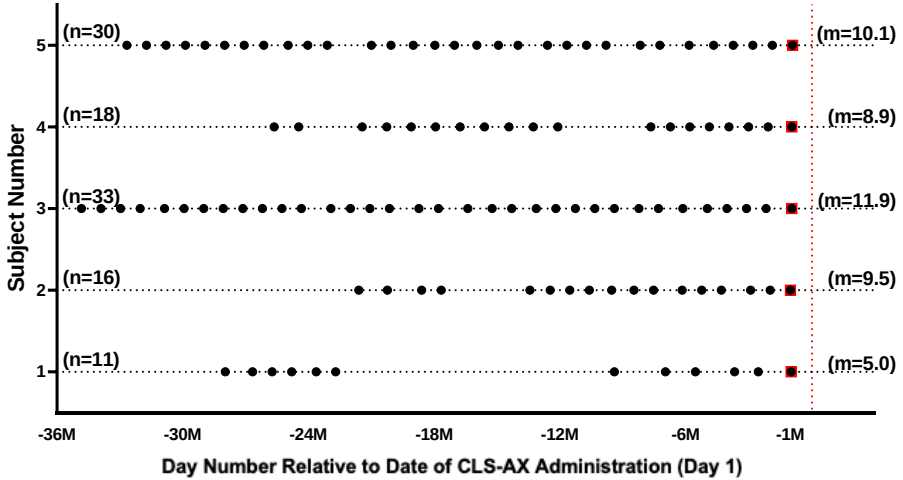


● Prior wAMD Treatment ■ IVT Aflibercept (Screening, Visit 1)

(n=) Total number of wAMD treatments prior to Screening

(m=) Mean number of wAMD treatments prior to Screening per year

COHORT 2: 0.10 mg



● Prior wAMD Treatment ■ IVT Aflibercept (Screening, Visit 1)

(n=) Total number of wAMD treatments prior to Screening

(m=) Mean number of wAMD treatments prior to Screening per year

Source: ADLS (CLSD ADaM), ADPTRT (CLSD ADaM)

Injection Procedure Questionnaire Responses

INJECTING PHYSICIAN QUESTION	COHORT 1: 0.03 mg (N=6)	Cohort 2: 0.10 mg (N=5)
Were you able to inject all contents of the syringe? **YES, n (%)**	6 (100)	5 (100)
Needle length used to perform procedure: 900 µm needle, **n (%)**	6 (100)	5 (100)
IF 900 µm NEEDLE WAS USED: Were adjustments in the syringe positioning/alignment required during this procedure? **NO, n (%)**	6 (100)	5 (100)
Did you have to remove the needle and reinsert that same needle into a new location during this procedure? **NO, n (%)**	6 (100)	5 (100)
Did you feel adequately prepared to give an injection based on the training you received? **YES, n (%)**	6 (100)	5 (100)
How do you rate the force necessary to complete the injection? **ACCEPTABLE, n (%)**	6 (100)	5 (100)
Were you able to perform the injection based on the training you received? **YES, n (%)**	6 (100)	5 (100)

Safety Overview

COHORT 1: 0.03 mg

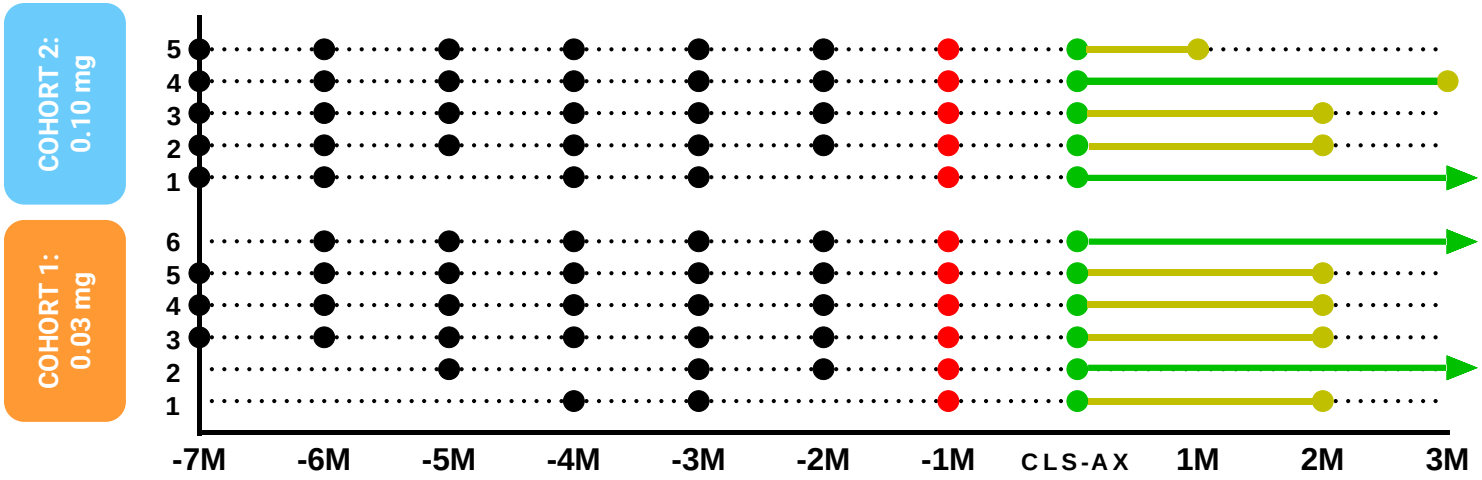
- **No study suspension or stopping rules were met**
- **No Serious Adverse Events (SAEs)**
- No treatment emergent adverse events (TEAEs) related to aflibercept, CLS-AX or suprachoroidal injection procedure
- No dispersion of investigational product into the vitreous
- No adverse events related to intraocular pressure (IOP), inflammation, or vasculitis

COHORT 2: 0.10 mg

- **No study suspension or stopping rules were met**
- **No Serious Adverse Events (SAEs)**
- No treatment emergent adverse events (TEAEs) related to aflibercept, CLS-AX or suprachoroidal injection procedure
- No dispersion of investigational product into the vitreous
- No adverse events related to intraocular pressure (IOP), inflammation, or vasculitis

Source: Clearside data on file.

6 Month Prior Anti-VEGF Therapies and Time to Additional Therapy



- SC CLS-AX injection
- IVT Aflibercept injection
- Anti-VEGF injection prior to study entry
- Additional IVT anti-VEGF injection

Time to Additional Therapy	Number (%) of Participants
≥ 3 months	4 (36.4%)
2 months	6 (54.5%)
1 month	1 (9.1%)

Source: ADLS (CLSD ADaM), ADPTRT (CLSD ADaM), ADRM (CLSD ADaM)

Reason for Retreatment

COHORT	SUBJECT	RETREATMENT VISIT	REASON FOR RETREATMENT
COHORT 1: 0.03 mg (N=6)	5	2 months post CLS-AX	BCVA
	4	2 months post CLS-AX	CST
	3	2 months post CLS-AX	CST
	1	2 months post CLS-AX	BCVA
COHORT 2: 0.10 mg (N=5)	5	1 month post CLS-AX	CST – retreatment criteria not met according to independent reading center
	4	3 months post CLS-AX	BCVA
	3	2 months post CLS-AX	Hemorrhage – no hemorrhage observed by the independent reading center; retreatment criteria not met
	2	2 months post CLS-AX	CST – retreatment criteria not met according to independent reading center

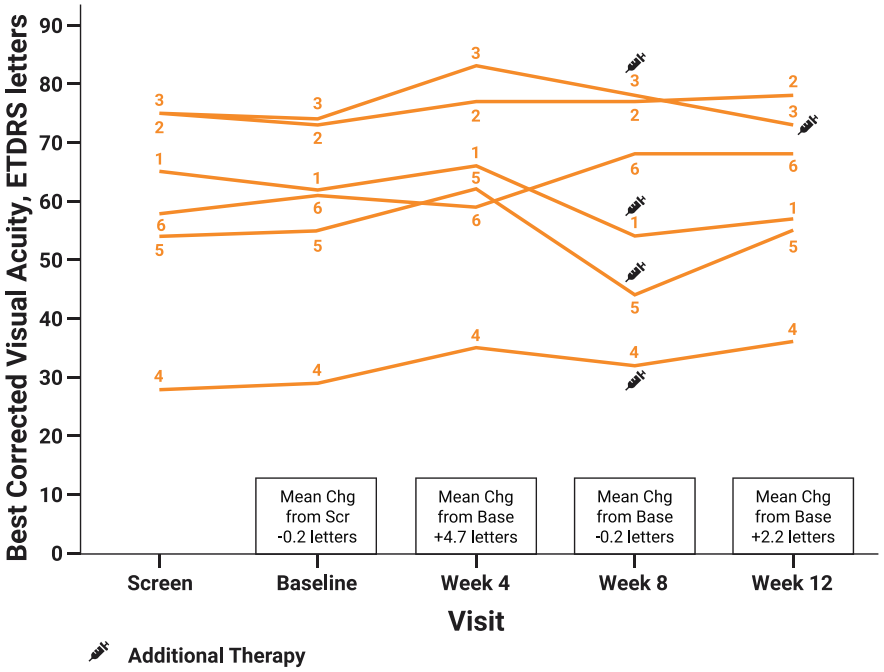
Protocol based Assessment for additional aflibercept treatment:

- loss from best measurement of ≥10 letters in BCVA with exudation
- increase in CST >75 microns
- a vision-threatening hemorrhage

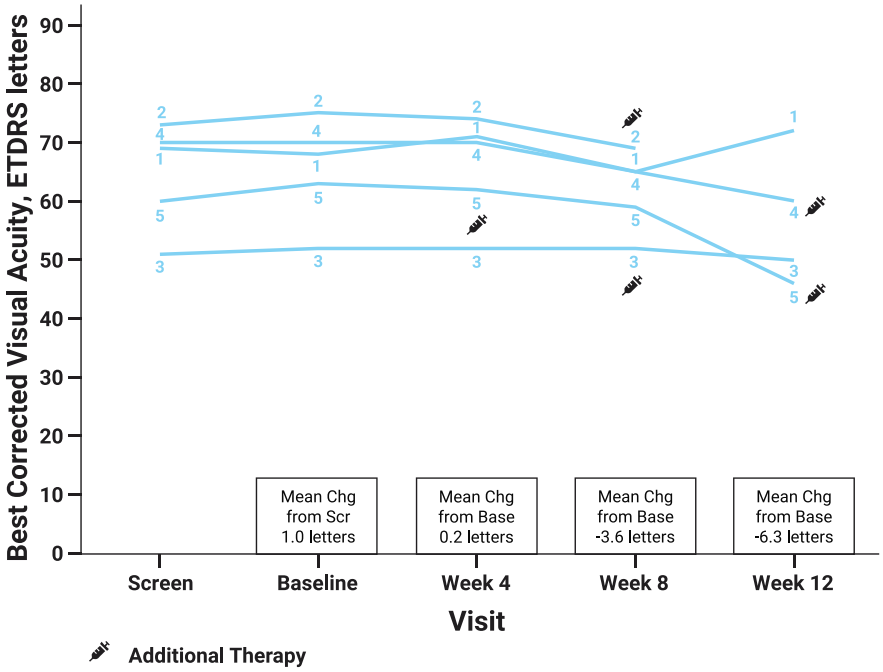
Source: Clearside data on file.

Individual Best Corrected Visual Acuity Letter Score, by Visit

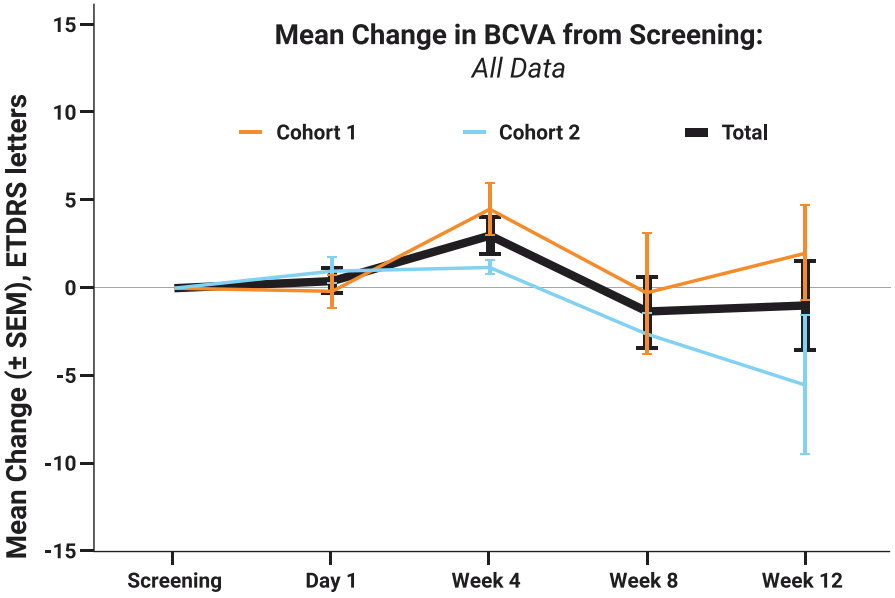
COHORT 1: 0.03 mg



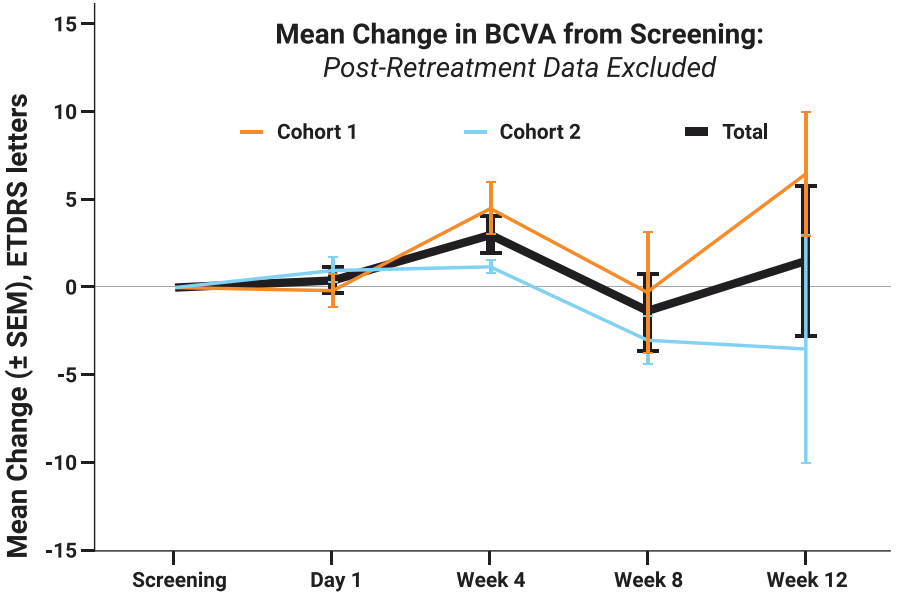
COHORT 2: 0.10 mg



Mean Best Corrected Visual Acuity Letter Score, Change from Screening



Cohort	Screening	Baseline	Week 4	Week 8	Week 12
Cohort 1, n	6	6	6	6	6
Cohort 2, n	5	5	5	5	4*

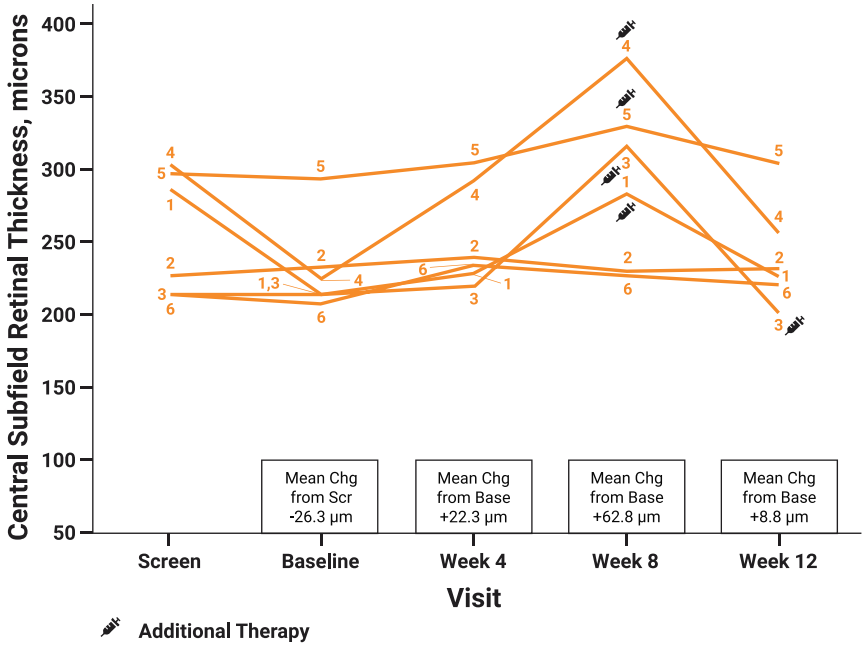


Cohort	Screening	Baseline	Week 4	Week 8	Week 12
Cohort 1, n	6	6	6	6	2
Cohort 2, n	5	5	5	4	2

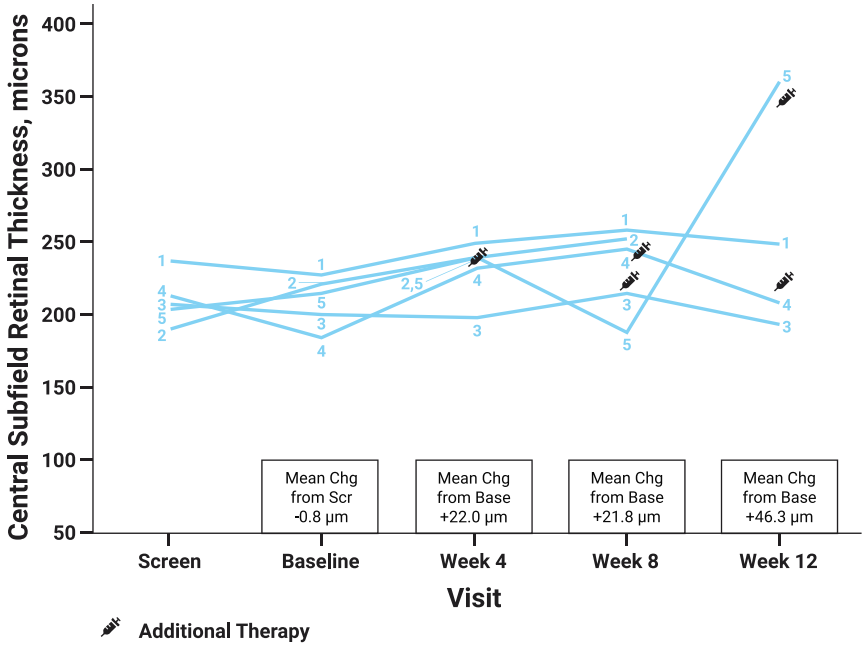
*Cohort 2 subject 2 discontinued after receiving additional therapy | Source: Clearside data on file.

Individual Central Subfield Thickness, by Visit

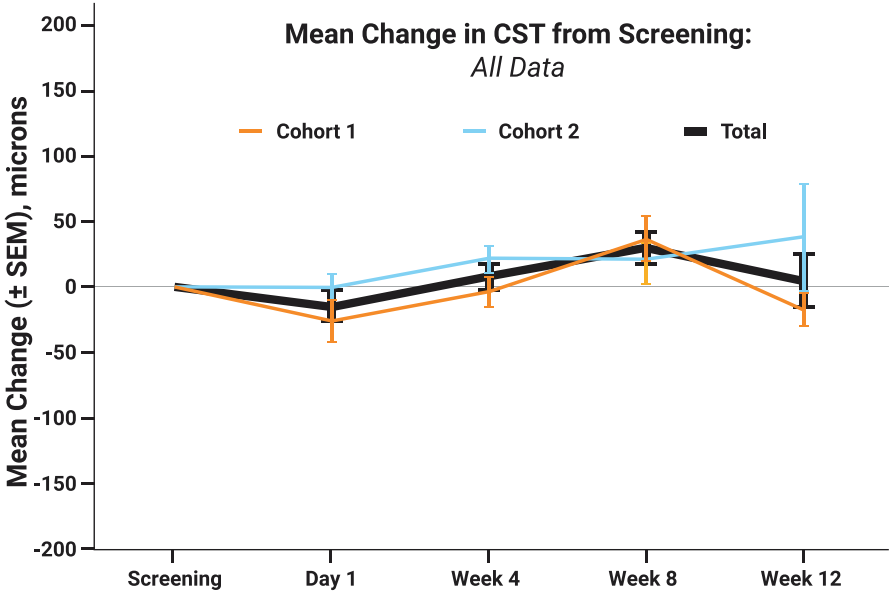
COHORT 1: 0.03 mg



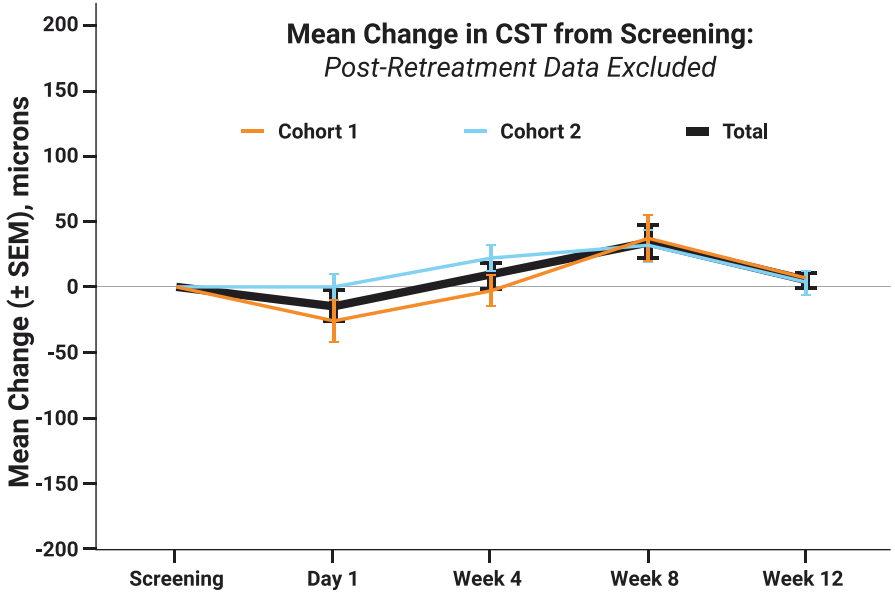
COHORT 2: 0.10 mg



Mean Change Central Subfield Thickness, Change from Screening



Cohort	Screening	Baseline	Week 4	Week 8	Week 12
Cohort 1, n	6	6	6	6	6
Cohort 2, n	5	5	5	5	4*



Cohort	Screening	Baseline	Week 4	Week 8	Week 12
Cohort 1, n	6	6	6	6	2
Cohort 2, n	5	5	5	4	2

*Cohort 2 subject 2 discontinued after receiving additional therapy | Source: Clearside data on file.

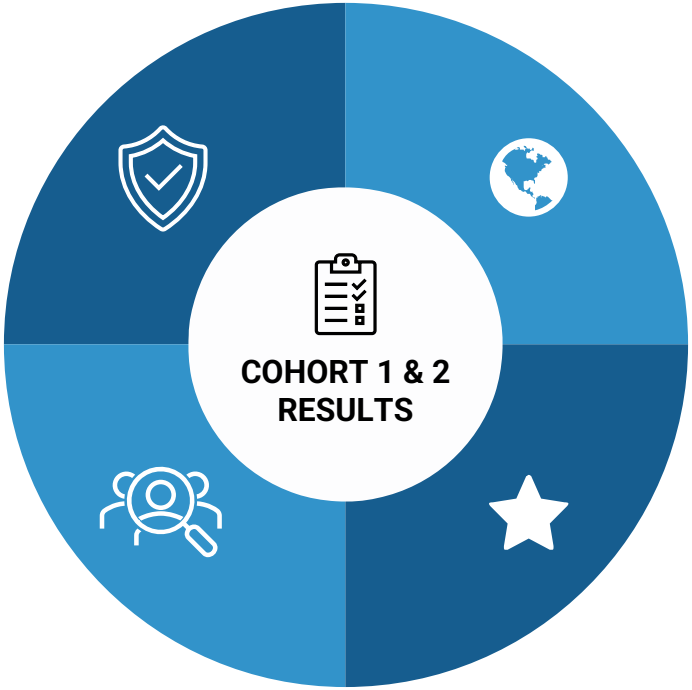
OASIS Cohort 1 & 2 Results Support Advancing to Cohort 3

SAFETY

- CLS-AX well tolerated with no dose limiting toxicities
- No dispersion of investigational product into the vitreous
- No adverse events related to intraocular pressure (IOP), inflammation, or vasculitis

ANATOMIC EFFECTS

Stable disease activity (based on CST), on average, over three months even after excluding patients who were retreated



VISUAL ACUITY

Stable visual acuity, on average, over three months even after excluding patients who were retreated

DURABILITY POST CLS-AX IN HEAVILY PRE-TREATED PATIENTS

- 4/11 (36%) of patients did not require additional therapy for ≥ 3 months
- 6/11 (55%) of patients did not require additional therapy for 2 months
- 1/11 (9%) patient was retreated at 1 month

Source: Clearside data on file.

Protocol Dosing Change for Cohort 3

- Given that this is the first time a tyrosine kinase inhibitor has been injected suprachoroidally in humans, we initiated OASIS with a low dose to establish a foundation for safety.
- **The lack of dose limiting toxicities in Cohorts 1 and 2, along with preclinical toxicology studies, support greater dose escalation than previously planned.**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