AMERICAN ACADEMY OF OPHTHALMOLOGY®

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PO514: Safety and Tolerability of **Suprachoroidal Injection of CLS-AX** (axitinib injectable suspension) in nAMD Patients in a Phase 1/2a Study, OASIS

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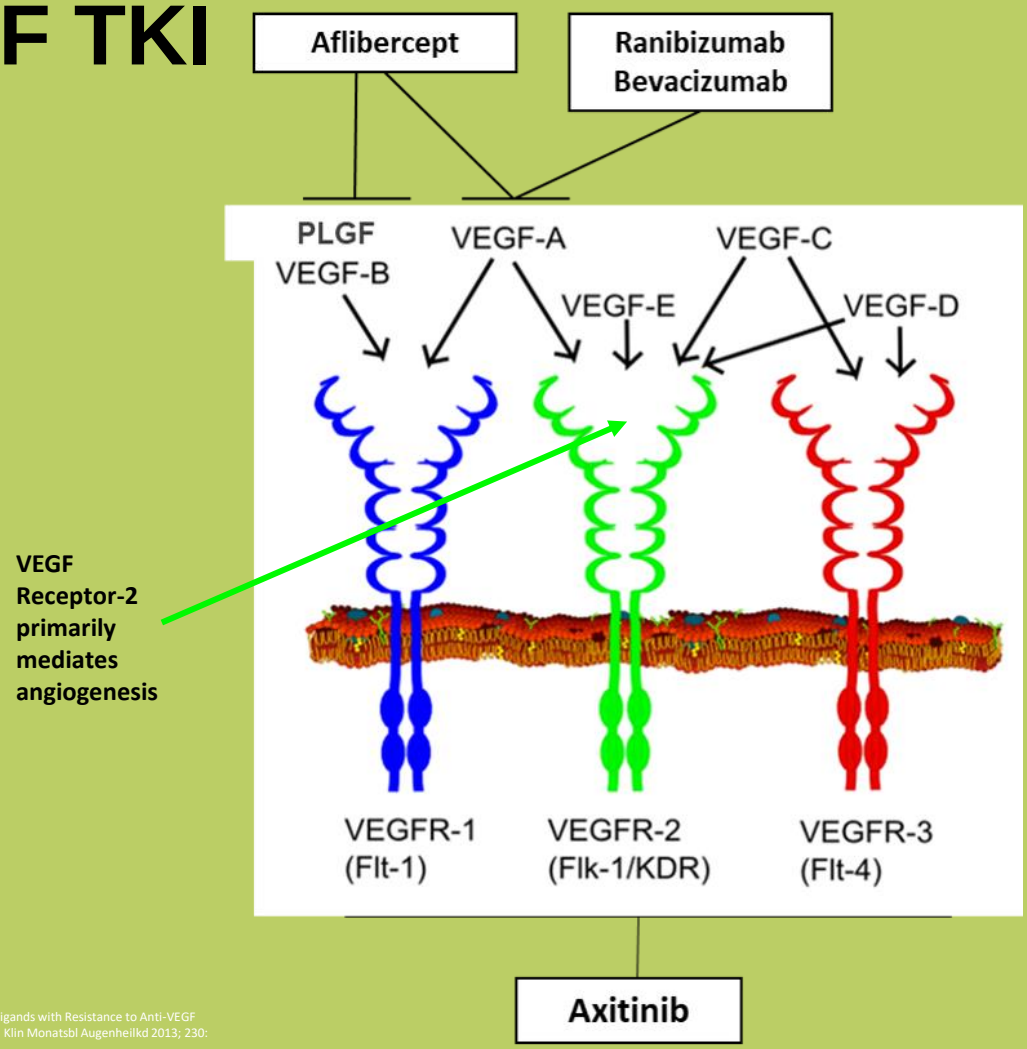
Axitinib: a Highly Potent, Pan-VEGF TKI to Treat Wet AMD

- 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 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
  - Better ocular cell biocompatibility than other TKIs[3]
  - More active 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.

CLS-AX for Suprachoroidal Use

Leveraging a Highly Potent Pan-VEGF Inhibitor with Suprachoroidal Delivery

CLS-AX

(axitinib injectable suspension)

High potency pan-VEGF inhibition of TKI

Proprietary suspension formulation

Delivery via a proprietary microinjector

Axitinib is a tyrosine kinase inhibitor (TKI) | 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.

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
- 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

2 mg aflibercept dosed at screening

CLS-AX dosed at baseline (1 Month post screening)

Note: aflibercept is dosed via intravitreal injection (IVT); CLS-AX is dosed via suprachoroidal injection | clinicaltrials.gov NCT# 04626128, NCT05131646

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 (33.9-54.7)**	**67 (6.8-102.1)**	**36 (6.1-103.4)**	**53 (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

OASIS & 6-Month Extension Study Data

SAFETY DATA: Excellent Safety Profile at all doses and timepoints

No Serious Adverse Events

No Inflammation Adverse Events

No Vasculitis / vascular occlusion Adverse Events

No Treatment Emergent Adverse Events related to study treatment

- No dose limiting toxicities
- No vitreous “floaters” or dispersion of CLS-AX into the vitreous
- No retinal detachments
- No endophthalmitis
- No adverse events related to intraocular pressure

Source: Clearside data on file.

Extension Study: CLS-AX Demonstrated Reduction of Treatment Burden Across Cohorts

Observed Reduction in Treatment Burden

All Therapies Administered

Cohort	Number of Participants	Average # of injections 6 months prior to CLS-AX	Average # of injections 6 months post CLS-AX	% Reduction
4	5	5.2	1.2	**77**
3	7	4.9	0.7	**85**
2	2	5.0	1.0	80

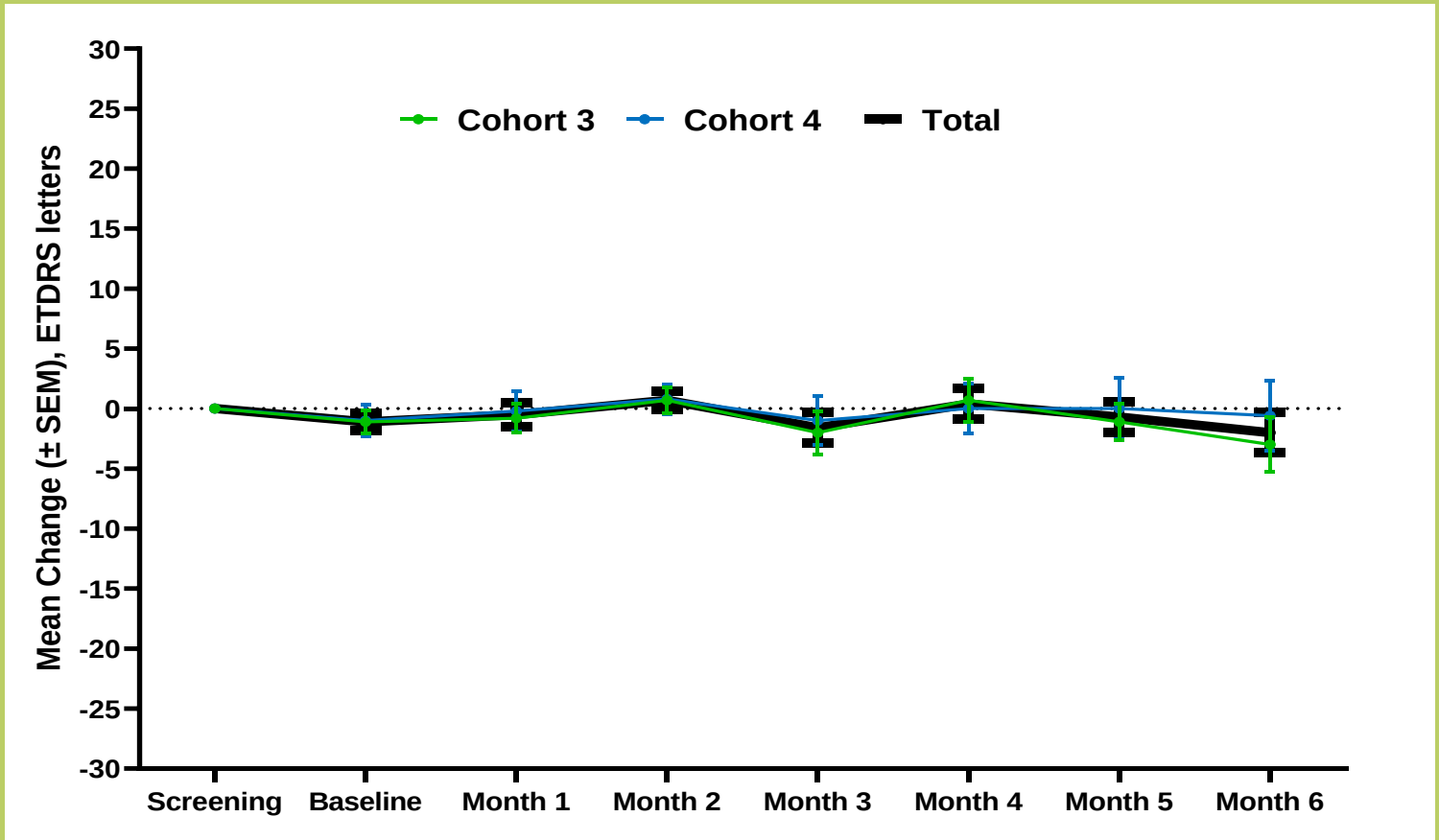
77 - 85% Reduction in Treatment Burden in Cohorts 3 and 4

Note:
Average # of injections 6 months priori to CLS-AX = # treatments six months prior to baseline in cohort / number of participants in cohort.
Average # of injections 6 months post CLS-AX = # treatments six months following CLS-AX / number of participants in cohort.
% Reduction = Average of individual reductions calculated as (after – before) / before × 100%.
Source: Clearside data on file.

Extension Study: Stable Visual Acuity

Cohorts 3 & 4

Mean Best Corrected Visual Acuity Letter Score, Change from Screening

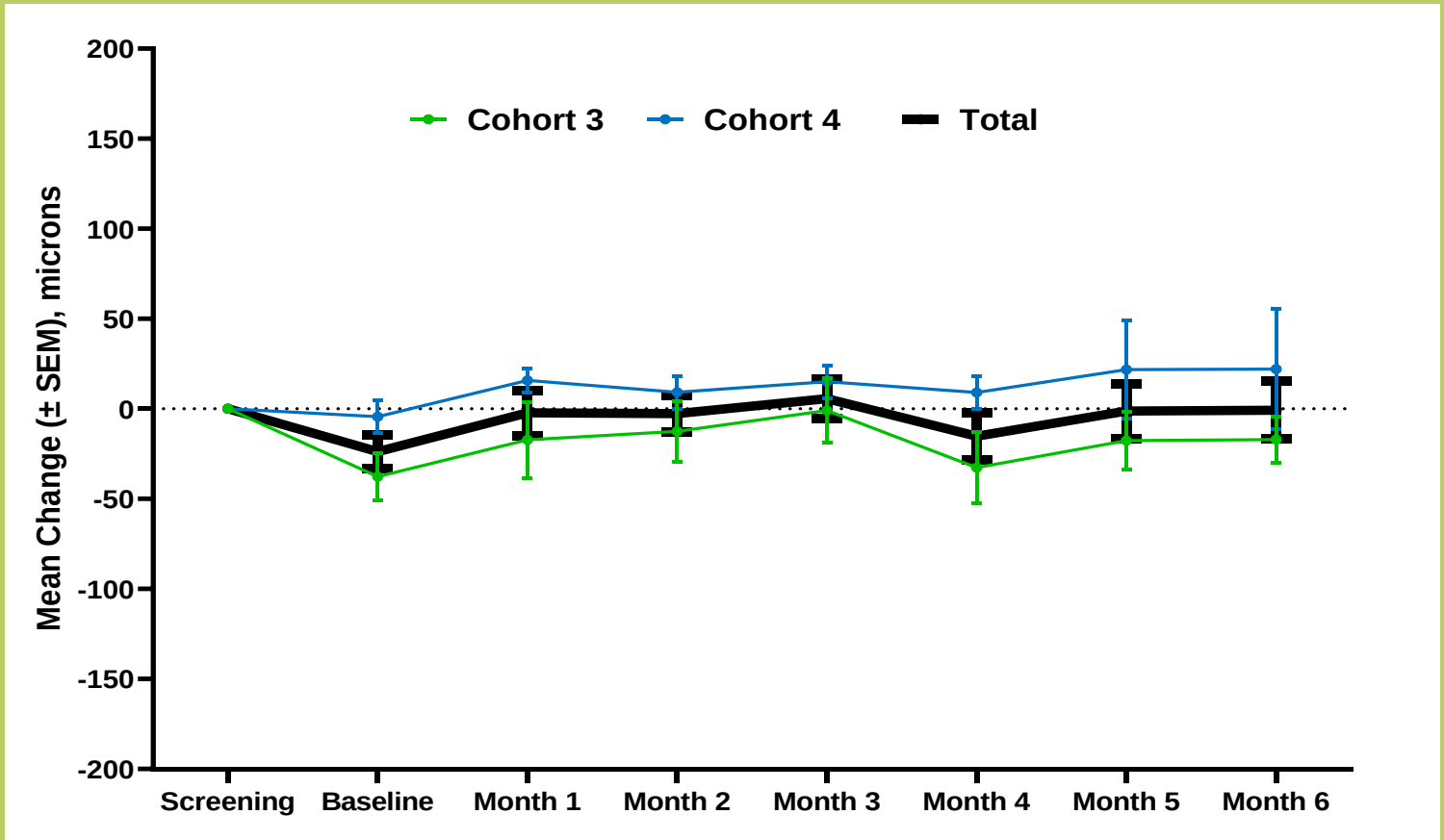


All Data, including post-supplemental therapy
Source: Clearside data on file.

Extension Study: Stable Central Subfield Thickness

Cohorts 3 & 4

Mean Central Subfield Thickness, Changing from Screening



All Data, including post-supplemental therapy
Source: Clearside data on file.

Key Takeaways

- **CLS-AX had an excellent safety profile at all doses** and timepoints, with no SAEs, no dose limiting toxicities, or AEs from inflammation
- **CLS-AX exhibited early signs of durability** and reduction in treatment burden
- **CLS-AX is being evaluated in a Phase 2b clinical trial**, ODYSSEY, for nAMD

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