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Safety and Tolerability of Suprachoroidal Axitinib Injectable Suspension, for Neovascular Age-related Macular Degeneration; Phase I/IIa Open-Label, Dose-Escalation Trial

Mark R. Barakat, MD,[1] *David Brown, MD,*[2] *Allen Hu, MD,*[3] *Rahul N. Khurana, MD,*[4] *Dennis Marcus, MD,*[5] *Joel Pearlman, MD, PhD,*[6] *Charles C. Wykoff, MD, PhD,*[2] *Barry Kapik, MS,*[7] *Thomas Ciulla, MD, MBA*[7,8]

Purpose: To evaluate the safety and tolerability of a single dose of axitinib injectable suspension (CLS-AX), a pan-anti-VEGF tyrosine kinase inhibitor (TKI), administered via suprachoroidal injection in patients with neovascular age-related macular degeneration (nAMD).

Design: Phase I/IIa, open-label, sequential dose escalation.

Participants: Anti-VEGF treatment-experienced patients with active subfoveal choroidal neovascularization secondary to nAMD.

Methods: The study included 4 cohorts (0.03, 0.10, 0.50, and 1.0 mg) of approximately 5 patients each enrolled in a dose-escalating fashion. Enrolled patients received intravitreal aflibercept (2 mg) followed by a single unilateral dose of CLS-AX 1 month later. All patients were followed monthly for 3 months with the option of an additional 3 months of extended follow-up for cohorts 2 to 4. End points included systemic and ocular safety and tolerability, visual acuity, retinal thickness, and need for aflibercept therapy.

Main Outcome Measures: The number of patients reporting treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), changes in ophthalmic examinations, and the number of patients qualifying for additional therapy for nAMD based on protocol-defined criteria.

Results: OASIS enrolled 27 patients with nAMD with mean age of 81 years, mean duration of nAMD diagnosis of 54 months, and between 5 and 90 prior anti-VEGF treatments. Twenty-six patients completed through 3 months, with 14 entering and completing the 3-month extension. No SAEs, drug-related TEAEs, or TEAEs leading to discontinuation were observed after CLS-AX administration; there were no adverse events related to ocular inflammation, vasculitis, intraocular pressure, or dispersion of drug into the vitreous or anterior chamber. Through 6 months, stable mean best-corrected visual acuity and stable mean central subfield thickness (CST) were observed, suggestive of TKI biologic effect. No aflibercept therapy was administered up to 3 months in 58% (15/26) of patients who completed 3 months of follow-up in OASIS. In the Extension, 57% (8/14) of patients went up to 6 months without receiving aflibercept therapy.

Conclusions: Up to 1.0 mg CLS-AX, a highly potent TKI targeted to the suprachoroidal space (SCS) via the SCS Microinjector, was well tolerated, with stable mean visual acuity and mean CST. A majority of patients followed for 6 months did not require aflibercept therapy.

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Neovascular age-related macular degeneration (nAMD) represents a leading cause of irreversible central vision loss in the industrialized world.[1,2] Central choroidal neovascularization (CNV) is driven by upregulated cytokines, including VEGF-A.[3] Standard care has historically involved monthly or bimonthly intravitreal (IVT) anti−VEGF-A injections,[4] but longer-term outcomes with these agents have been suboptimal.[5−7] Furthermore, clinical outcomes studies of anti-VEGF therapy, based on chart reviews, electronic medical records, or claims analyses, have reported poor visual outcomes, partly because of undertreatment, likely due to the significant

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treatment burden of frequent injections.[8–24] Consequently, there is an unmet need for more effective and longer acting therapies.

Axitinib is a second-generation receptor tyrosine kinase inhibitor (TKI), which stabilizes VEGF receptor (VEGFR)-1, VEGFR-2, and VEGFR-3 in inactive conformations at picomolar concentrations.[25] In 2012, axitinib was Food and Drug Administration-approved for treating advanced renal cell carcinoma.[25] Axitinib, a more highly potent TKI versus others assessed in ocular clinical trials, may demonstrate meaningful benefit in nAMD compared with current anti–VEGF-A agents, which focus on VEGF-A ligand blockade and are associated with upregulation of VEGF-C and VEGF-D,[26,27] potentially contributing to a ceiling of efficacy. Preclinical studies of axitinib in corneal, retinal, and choroidal models of angiogenesis support this potential role of axitinib in the treatment of nAMD, including more effective inhibition of angiogenic sprouts than a VEGF-A inhibitor.[28–33]

Microneedle-based suprachoroidal injection (suprachoroidal space [SCS] injection) is a minimally invasive, office-based procedure performed at the pars plana to administer therapeutics into the SCS adjacent to affected chorioretinal tissues.[34–39] Specifically, this delivery technique expands the SCS circumferentially and posteriorly to deliver drugs to the macula, as a natural pressure gradient drives injectate toward the posterior SCS (given that the intraocular pressure [IOP] > anterior SCS pressure > posterior SCS pressure).[40] This delivery approach targets therapy to diseased posterior ocular tissues while keeping it compartmentalized away from nondiseased tissues and entirely behind the visual field. The SCS injection via microneedle has been validated in a phase III clinical trial of a corticosteroid for the treatment of uveitic macular edema[41] and subsequent 2021 Food and Drug Administration approval of XIPERE (triamcinolone acetonide injectable suspension), for suprachoroidal use.

Axitinib delivered to the SCS via microneedle has shown efficacy and high levels of compartmentalization to posterior ocular tissues in preclinical models. In one pharmacokinetic study, a single SCS injection of axitinib suspension resulted in an 11-fold higher mean axitinib exposure in the posterior segment, compared with IVT injection, and there were sustained levels of axitinib in the retina and more posterior tissues throughout the duration of studies, up to 6 months.[42] Furthermore, suprachoroidally administered axitinib has demonstrated meaningful biologic effect in laser-induced CNV and retinal vascular leakage models in rats and pigs.[43]

Given the potential for axitinib delivered via SCS injection to decrease treatment burden in nAMD, a 3-month, multicenter, open-label, sequential dose-escalation phase I/IIa study (OASIS) of axitinib injectable suspension (CLS-AX) was conducted in nAMD (ClinicalTrials.gov identifier, NCT04626128). The results reported here represent the combined data from both OASIS and its extension study (Extension, ClinicalTrials.gov identifier, NCT05131646), a 3-month, noninterventional study in patients completing OASIS.

Methods

Study Design

OASIS and the Extension were conducted at 10 sites in the United States from December 2020 through January 2023. These studies adhered to the tenets of the Declaration of Helsinki and were conducted in accordance with the International Council for Harmonisation E6 Guidelines for Good Clinical Practice and applicable local, state, and federal laws. Institutional review board approval was obtained by all sites. The Health Insurance Portability and Accountability Act–compliant informed consent forms were approved by institutional review board, and informed consent was obtained from study patients. A Safety Monitoring Committee monitored safety and study conduct.

Participants

In OASIS, patients aged ≥50 years were eligible if they had nAMD and active subfoveal CNV of any lesion type in the study eye confirmed via central reading center (Merit contract research organization) assessments of fundus photographs, fluorescein angiography or spectral-domain OCT. Eligible patients had received ≥2 anti-VEGF treatments 1 to 4 months preceding the screening visit, with a meaningful response based on the investigator's opinion. Patients were required to have stable best-corrected visual acuity (BCVA) in the study eye, defined as vision between 20 and 75 letters (20/400 to 20/32 Snellen equivalent) at both the screening and baseline (day 1) visits, with ≤7 letters change between these visits.

Patients were excluded if the study eye had any active infection or disease other than nAMD or CNV due to causes other than AMD. Furthermore, patients were excluded if total lesion area was ≥30 mm^2, if the CNV component area was <50% of the total lesion area, or if subfoveal hemorrhage, subfoveal fibrosis, subfoveal atrophy, retinal pigment epithelial tear, or retinal angiomatous proliferation were present. If patients had any prior treatments for CNV other than IVT aflibercept, ranibizumab, bevacizumab, or brolucizumab, or had IOP of ≥25 mmHg or a cup-to-disc ratio of >0.8, they were excluded. Patients receiving one IOP-lowering medication were allowed to enroll if the IOP was <25 mmHg. Lens opacifications were allowed, provided they did not preclude retina and vitreous evaluation. Patients were not allowed topical ocular corticosteroids in the 10 days before baseline or any intraocular or periocular corticosteroid injections. Concomitant therapy of any drug considered toxic to the lens, retina, or optic nerve was exclusionary. To be eligible for enrollment into the Extension, patients had to have completed OASIS as part of cohorts 2, 3, or 4. The Extension was initiated after completion of cohort 1 and before patients completing cohort 2 of OASIS; therefore, cohort 1 patients were not eligible for participation in the Extension. Because the Extension protocol was approved during cohort 2, it was not possible to offer enrollment to all earlier patients. Complete inclusion and exclusion criteria are provided in the Supplementary Material (available at www.ophthalmologyscience.org).

Study Treatments

Study treatments consisted of 4 cohorts of increasing dosages of CLS-AX administered suprachoroidally to the study eye via the SCS Microinjector at doses of 0.03 mg (cohort 1), 0.10 mg (cohort 2), 0.50 mg (cohort 3), and 1.0 mg (cohort 4). At the screening visit, all eligible patients were administered an IVT injection of aflibercept 2 mg (50 µl), with patients returning to the clinic 4 weeks later at baseline to receive study treatment. Patients were

followed for up to 3 months, with no additional study treatments being administered.

At weeks 4, 8, 12, 16, 20, and 24, investigators determined if a patient qualified for additional therapy with IVT aflibercept, unless other therapy was medically necessary, based on protocol-defined criteria. These criteria included the following: (1) a loss of ≥10 letters in BCVA compared with the best prior BCVA that was attributed to intraretinal or subretinal fluid, (2) increased central subfield thickness (CST) of >75 μm from baseline, or (3) the presence of vision-threatening hemorrhage due to AMD.

Dose escalation proceeded after a review of the totality of safety data by the Safety Monitoring Committee, and after the Safety Monitoring Committee had made a recommendation regarding the next dose cohort.

Outcome Measures

The primary outcome included the number of patients experiencing treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) after administration of CLS-AX. Systemic safety was assessed by evaluating vital signs, clinical laboratory tests, 12-lead electrocardiograms, and medications. Ocular safety was assessed by evaluating IOP, BCVA, and outcomes obtained from slit-lamp biomicroscopy, indirect ophthalmoscopy, spectral-domain OCT, fundus photography, and fluorescein angiography.

Statistical Analysis

The sample size for OASIS was not statistically determined as this was a phase I/IIa study of CLS-AX delivered to the eye via SCS injection. Approximately 20 patients (5 per dose cohort) were planned.

The safety analysis population comprised all patients who received a dose of CLS-AX study drug, grouped according to the cohort into which they were enrolled. Analyses included all available observed data up to week 24, and missing data were not imputed.

The primary end points included the numbers of patients experiencing TEAEs and SAEs. For summarizing adverse events, reported terms were coded to standard terminology using the Medical Dictionary for Regulatory Activities System Organ Class and Preferred Terminology.

Changes in outcomes measures were calculated relative to the measurement taken before the administration of aflibercept at screening. Continuous outcomes were summarized using descriptive statistics, and categorical outcomes were summarized using counts and percentages.

The focus of the analysis was on estimation of the end points and not hypothesis testing. Therefore, no criteria value or type 1 error rate was predefined for declaring statistical significance.

This report presents safety and tolerability results >24 weeks for the full safety population. Although not designed to demonstrate or determine the efficacy of any of the single doses of CLS-AX used in the study, the biologic effect of CLS-AX >6 months on vision and ocular anatomic outcomes is described for those patients enrolled in cohorts 3 (0.50 mg) and 4 (1.0 mg), the 2 doses enrolling a meaningful number of patients into the Extension.

Results

Patient Disposition

Between December 15, 2020 and June 23, 2022, a total of 95 patients were consented and screened for participation in OASIS. Twenty-seven patients were deemed eligible and were administered an SCS injection of CLS-AX. Six patients were enrolled into cohort 1, 5 patients in cohort 2, and 8 patients each in cohorts 3 and 4. One patient in cohort 2 discontinued OASIS because of withdrawal of consent.

Fifteen patients completing OASIS consented and enrolled in the Extension, with 3 patients from cohort 2, 7 from cohort 3, and 5 patients from cohort 4 choosing to continue participation. One patient in cohort 2 discontinued the Extension shortly after consenting and before any additional follow-up assessments could be performed because of the withdrawal of consent.

All 27 patients receiving CLS-AX were included in the safety population (Table 1).

Demographics and Baseline Characteristics

Demographics and baseline study eye characteristics were well balanced across cohorts (Table 2), although there were some differences. Median age was 83.0 years, and the majority of patients were women (55.6%). All patients were White, and most (59.3%) patients were pseudophakic. Time since nAMD diagnosis ranged between 4.5 and 132.8 months, with patients receiving between 5 and 90 prior anti-VEGF injections for nAMD or 4.9 to 13.6 injections per year after adjusting for the duration of disease. The annualized number of anti-VEGF injections before CLS-AX administration on day 1 were a mean 8.5 to 12 injections across all cohorts. In the 6 months preceding study entry, 12 (44.4%) patients had received aflibercept, bevacizumab in 5 (18.5%) patients, and ranibizumab in 12 (44.4%) patients (Table 3). At study entry, patients recorded visual acuities of 28 to 75 letters (approximately 20/250 to 20/32 Snellen equivalent) and CST of 171 to 342 μm.

Safety

Adverse Events. Of 27 patients, 10 (37.0%) experienced at least one TEAE during the study, 8 (29.6%) patients experienced at least one event in the study eye (Table 4), none in the fellow eye, and 6 (22.2%) experienced at least one systemic event. There were no reports of death, SAEs, TEAEs related to CLS-AX or the injection procedure, or discontinuations due to an adverse event. The most frequently reported event (4 patients) was worsening of nAMD, representing a worsening of the underlying disease of the study population.

Additional Therapy

Patients were assessed at each visit to determine the need for aflibercept therapy (Fig 1). Fifteen of 27 (56%) patients went up to 3 months without needing additional therapy, with 10 (37%) requiring 1 aflibercept injection and 1 requiring 2 aflibercept injections (3.7%). Seven of the 12 patients needing aflibercept therapy were enrolled in cohorts 1 (0.03 mg) and 2 (0.10 mg), the lowest doses studied. Of the 12 aflibercept injections that were administered during the study, the criteria indicating the need for therapy included a loss of ≥10 letters in BCVA compared with the best prior measurement for 3

Table 1. Disposition

Disposition	Cohort 1	Cohort 2	Cohort 3	Cohort 4	All Patients
Patients screened, no.	12	18	37	28	95
Screen failures, no. (%)*	6 (50.0)	13 (72.2)	29 (78.4)	20 (71.4)	68 (71.6)
Received CLS-AX, no. (%)*	6 (50.0)	5 (27.8)	8 (21.6)	8 (28.6)	27 (28.4)
Completed OASIS, no. (%)†	6 (100)	4 (80.0)	8 (100)	8 (100)	26 (96.3)
Discontinued OASIS, no. (%)†	0	1 (20.0)	0	0	1 (3.7)
Withdrew consent, no. (%)‡	0	1 (100)	0	0	1 (100)
Entered extension, no. (%)†	0	3 (60.0)	7 (87.5)	5 (62.5)	15 (55.6)
Completed extension, no. (%)§	–	2 (66.7)	7 (100)	5 (100)	14 (93.3)
Discontinued extension, no. (%)§	–	1 (33.3)	0	0	1 (6.7)
Withdrew consent, no. (%)‡	–	1 (100)"	0	0	1 (100)
Safety population, no. (%)†	6 (100)	5 (100)	8 (100)	8 (100)	27 (100)

*Percentages are based on the total number of patients signing the informed consent form.
†Percentages are based on the total number of patients receiving CLS-AX.
‡Percentages are based on the number of patients discontinuing from the study.
§Percentages are based on the total number of patients entering the extension.
"Patient discontinued before the first follow-up visit during the extension.

injections, an increase from baseline in CST >75 μm for 7 injections, both BCVA loss and CST increase for 1 injection, and vision-threatening hemorrhage due to nAMD for 1 injection. However, masked reading center assessment showed that 8 of the 14 additional therapies administered during OASIS did not meet the protocol-defined criteria (represented as gold dots in Fig 1) and suggested that investigators sometimes treated for increased CST not meeting the >75 μm threshold or for unconfirmed hemorrhage.

Of the 14 patients followed into the Extension, 8 (57%) went up to 6 months without needing any additional therapy, with all 8 having been enrolled into the 2 higher dose cohorts (5 of 7 in cohort 3 [0.50 mg] and 3 of 5 in cohort 4

Table 2. Baseline Characteristics and Demographics

Characteristics	Cohort 1	Cohort 2	Cohort 3	Cohort 4	All Patients
No. of patients	6	5	8	8	27
Age, y					
Mean (range)	81.8 (66–93)	78.2 (65–90)	86.3 (75–97)	76.5 (66–83)	80.9 (65–97)
Median (IQR)	86.0 (22.0)	78.0 (18.0)	86.5 (6.5)	75.5 (8.0)	83.0 (14.0)
Women, no. (%)	2 (33.3)	3 (60.0)	5 (62.5)	5 (62.5)	15 (55.6)
White, no. (%)	6 (100)	5 (100)	8 (100)	8 (100)	27 (100)
Not Hispanic or Latino, no. (%)	6 (100)	5 (100)	8 (100)	8 (100)	27 (100)
BCVA, ETDRS letters					
Mean (range)	59.2 (28–75)	64.6 (51–73)	59.5 (37–75)	65.5 (50–75)	62.1 (28–75)
Mean Snellen equivalent	20/80	20/64	20/80	20/50	20/64
Median (IQR)	61.5 (21.0)	69.0 (10.0)	60.5 (24.5)	69.5 (17.0)	65.0 (18.0)
CST, μm					
Mean (range)	257.5 (214–304)	211.0 (190–237)	234.0 (171–312)	235.9 (184–342)	235.5 (171–342)
Median (IQR)	257.0 (83.0)	207.0 (13.0)	236.0 (68.5)	228.5 (39.0)	227.0 (57.0)
Presence of fluid, no. (%)					
Intraretinal only	0	1 (20.0)	0	1 (12.5)	2 (7.4)
Subretinal only	3 (50.0)	3 (60.0)	5 (62.5)	5 (62.5)	16 (59.3)
Pseudophakic, no. (%)	4 (66.7)	2 (40.0)	6 (75.0)	4 (50.0)	16 (59.3)
Duration of nAMD diagnosis, mo					
Mean (range)	50.13 (12.4–110.3)	49.78 (24.7–81.3)	66.64 (6.8–102.1)	48.21 (4.5–132.8)	54.39 (4.5–132.8)
Median (IQR)	47.05 (32.20)	54.30 (20.80)	80.60 (69.30)	30.20 (75.70)	54.50 (74.40)
Total number of prior nAMD treatments					
Mean (range)	26.8 (7–41)	24.2 (12–39)	37.0 (6–90)	28.8 (5–89)	29.9 (5–90)
Median (IQR)	29.0 (17.0)	19.0 (17.0)	31.0 (47.0)	28.0 (23.0)	27.0 (26.0)
Annualized number of prior nAMD treatments*					
Mean (range)	9.36 (6.3–12.7)	9.54 (5.4–12.2)	8.47 (4.9–11.8)	11.96 (8.9–13.6)	9.90 (4.9–13.6)
Median (IQR)	9.35 (4.71)	10.03 (1.34)	8.45 (4.92)	12.19 (1.94)	10.52 (3.65)

BCVA = best-corrected visual acuity; CST = central subfield thickness; IQR = interquartile range; nAMD = neovascular age-related macular degeneration.
*Defined as total number of injections in the study eye, up to and including screening, divided by the number of years diagnosed.

Table 3. Anti-VEGF Treatments 6 Months before Study Entry in the Study Eye

Anti-VEGF Treatment	Cohort 1 no. (%)	Cohort 2 no. (%)	Cohort 3*,† no. (%)	Cohort 4 no. (%)	All Patients no. (%)
No. of patients	6	5	8	8	27
Patients with any prior treatment	6 (100)	5 (100)	8 (100)	8 (100)	27 (100)
Aflibercept	1 (16.7)	2 (40.0)	5 (62.5)	4 (50.0)	12 (44.4)
Bevacizumab	1 (16.7)	1 (20.0)	2 (25.0)	1 (12.5)	5 (18.5)
Ranibizumab	4 (66.7)	2 (40.0)	3 (37.5)	3 (37.5)	12 (44.4)

*One patient in cohort 3 received both ranibizumab and bevacizumab.
†One patient in cohort 3 received both bevacizumab and aflibercept.

[1.0 mg]). During the extension portion of the study, 4 (28.6%) patients required 1 aflibercept injection, and 2 (14.3%) patients required 2 aflibercept injections. Of these 8 aflibercept injections administered during the Extension, 2 were administered because of a loss of ≥10 letters in BCVA compared with the best prior measurement, 4 injections were because of an increase from baseline in CST >75 μm, and 2 injections were due to vision-threatening hemorrhage due to nAMD. Six patients went longer than 6 months without requiring additional therapy.

A post hoc analysis of the patients enrolled into the Extension compared the average monthly number of IVT anti-VEGF injections in the 6 months before CLS-AX administration with the average monthly number of additional therapies administered afterward to estimate the reduction in treatment burden. Table 5 shows that reductions in treatment burden between 79% and 91% across the 3 cohorts were seen in patients receiving CLS-AX.

Intraocular Pressure

Median IOP at study entry was 14.0 mmHg, ranging from 9 to 20 mmHg. Three months after CLS-AX administration, patients had a median an IOP of 14.0 mmHg. Six months after administration of CLS-AX, median change from screening in IOP showed a 1.0-mmHg increase in cohort 2, and no change in cohorts 3 and 4.

There were no adverse events reported related to elevations in IOP preinjection or postinjection procedures, including the IVT injection at the screening visit and the suprachoroidal injection at baseline. All postinjection increases in IOP were transient, resolved spontaneously, and were related to the volume of drug injected, not the dose concentration. No interventions, including the use of new/additional IOP-lowering medications, were necessary.

Ocular Inflammation

Twenty-six out of 27 patients did not have any signs of inflammation during the first 3 months after CLS-AX administration. One patient was assessed as having 1+ anterior chamber cells per Standardization of Uveitis Nomenclature criteria (6−15 cells in 1×1-mm slit beam at the highest illumination) at week 8 that resolved by week 12. One patient was noted as having trace vitreous haze at week 20 that resolved by week 24. Neither instance resulted in treatment or classification as an adverse event by the investigator. Inflammation was absent for all other patients.

Visual Acuity

Mean change from screening in BCVA at 3 months varied between the 2 later cohorts of patients, with a 3.1-letter loss in cohort 3 (0.50 mg) and a gain of 0.5 letters in cohort 4 (1.0 mg) (Fig 2). Mean change at 6 months showed a 3.0-letter loss in cohort 3 and a 0.6-letter loss in cohort 4. No patients lost >15 letters from screening at any time.

To ensure that additional therapies were not driving BCVA stability, a post hoc analysis was conducted in which all BCVA measurements assessed after the administration of

Table 4. Ocular Adverse Events in the Study Eye

System Organ Class Preferred Term	Cohort 1 no. (%)	Cohort 2 no. (%)	Cohort 3 no. (%)	Cohort 4 no. (%)	All Patients no. (%)
No. of patients	6	5	8	8	27
Patients with ≥1 ocular AE	1 (16.7)	4 (80.0)	2 (25.0)	1 (12.5)	8 (29.6)
Overall no. of AEs	1	5	4	1	11
Eye disorders					
Conjunctival hemorrhage	1 (16.7)	0	1 (12.5)	0	2 (7.4)
Conjunctival edema	0	0	1 (12.5)	0	1 (3.7)
Macular degeneration	0	2 (40.0)	0	1 (12.5)	3 (11.1)
Neovascular age-related macular degeneration	0	0	1 (12.5)	0	1 (3.7)
Retinal hemorrhage	0	1 (20.0)	1 (12.5)	0	2 (7.4)
Subretinal fluid	0	1 (20.0)	0	0	1 (3.7)

Reported adverse events counted by Medical Dictionary for Regulatory Activities System Organ Class and Preferred Terminology.
AE = adverse event.

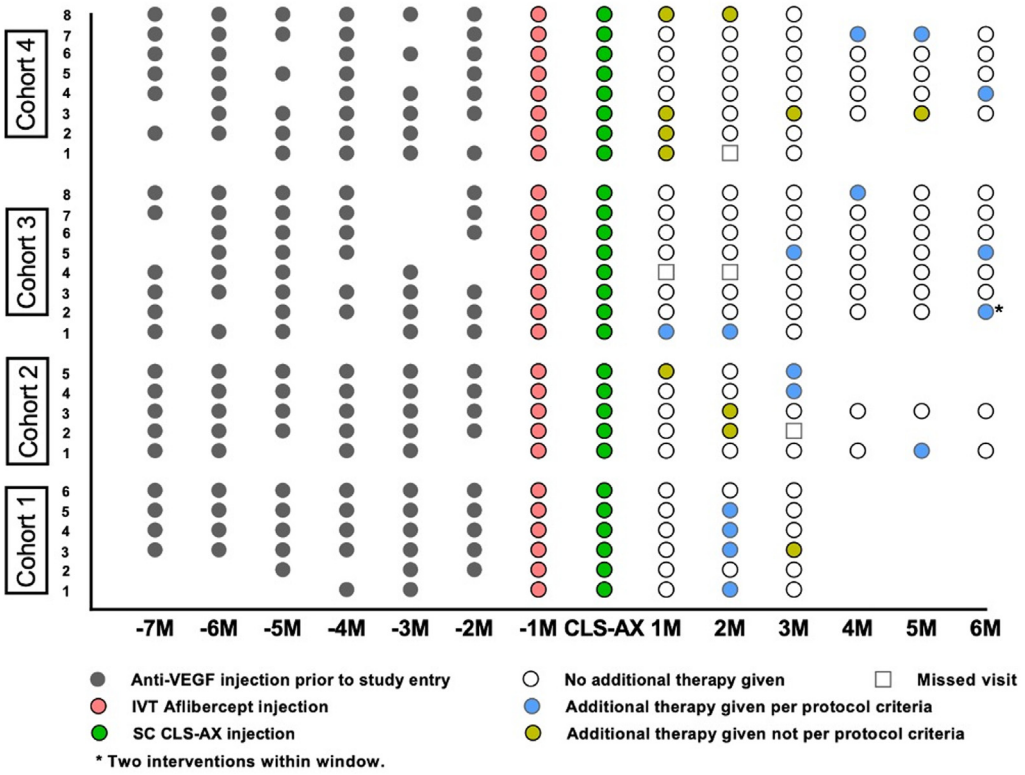

Figure 1. Swim lane plot showing prior intravitreal (IVT) anti-VEGF injections, IVT aflibercept at screening, suprachoroidal CLS-AX (axitinib injectable suspension) injection at baseline, and postbaseline additional treatments for signs of neovascular age-related macular degeneration.

additional therapy was excluded. In this "responder analysis," mean change in BCVA at 6 months was a loss of 0.3 letters in cohort 3 (n = 4) and a 3.3-letter gain in cohort 4 (n = 3).

CST

Three months after administration of CLS-AX, retinal thickness was stable with no meaningful change (reduction in mean change from screening of 2.9 μm in cohort 3 [0.50 mg], and an increase of 1.5 μm in cohort 4 [1.0 mg]) (Fig 3). Similar results were noted at 6 months, with a 17.1-μm reduction in cohort 3 and a 22.0-μm increase in cohort 4. A post hoc "responder analysis," which excluded CSTs after additional therapy, showed a mean decrease of 17.0 μm at 6 months in cohort 3 (n = 4) and a 58.0-μm increase in cohort 4 (n = 3).

Case Studies

Figure 4 shows the spectral-domain OCT images over time for patient 2 of cohort 3 (0.50 mg). This patient had received 89 IVT anti-VEGF injections before enrolling into OASIS and had persistent subfoveal fluid 1 month after receiving aflibercept 2 mg at screening. Subretinal fluid was resolved 4 months after CLS-AX administration with stable BCVA and improved CST. At month 5, BCVA remained stable despite new intraretinal fluid, and at month 6, there was further progression, for which additional treatment was administered.

Table 5. Reduction in Treatment Burden

	Cohort 2 (N = 2)	Cohort 3 (N = 7)	Cohort 4 (N = 5)	Total (N = 14)
Median number of injections before CLS-AX administration	5	5	5	5
Median number of injections after CLS-AX administration	1	0	0	0.5
Average monthly injections before CLS-AX administration	0.83	0.76	0.87	0.83
Average monthly injections after CLS-AX administration	0.17	0.07	0.17	0.12
Percentage reduction	79.5	90.8	80.5	0.86

Average monthly injections calculated as the number of treatments in the 6 months before/after CLS-AX / (number of patients × 6). Percentage reduction calculated as (after − before)/before × 100%.
CLS-AX = axitinib injectable suspension.

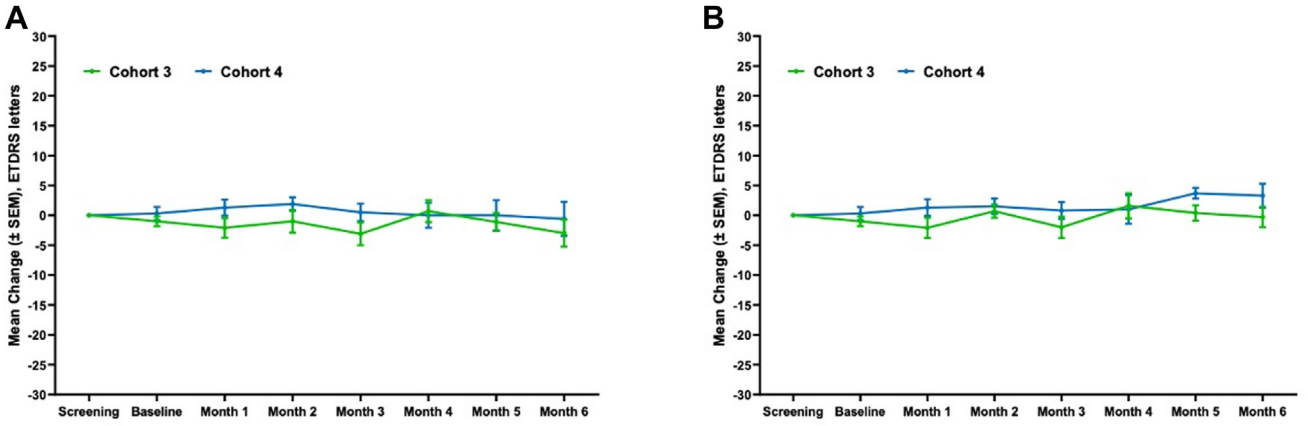

Figure 2. Line plots of mean ± SEM change from screening in ETDRS best-corrected visual acuity (BCVA) letter score for cohorts 3 and 4. **A**, All data. **B**, Excludes data after the administration of additional treatment per protocol-defined criteria. Mean BCVA at screening was 59.5 letters for cohort 3 and 65.5 letters for cohort 4. SEM = standard error of the mean.

Discussion

OASIS was a phase I/IIa, single-dose, escalation study of CLS-AX delivered via suprachoroidal injection, with primary end points focused on safety. In OASIS, CLS-AX demonstrated a positive safety profile in all 4 cohorts, with no SAEs, TEAEs related to study treatment, dose-limiting toxicities, or adverse events related to inflammation, vasculitis, or vascular occlusion. These results are not unexpected, as axitinib is an already-approved, well-characterized small molecule, with less potential risk of immunogenicity than a novel biologic agent or gene therapy. Furthermore, the SCS injection procedure is a commercially accepted office-based procedure after the launch of XIPERE. In OASIS, there were no observed incidents of drug migration or vitreous "floaters." There were no retinal detachments, endophthalmitis, and no adverse events related to IOP.

OASIS enrolled heavily anti-VEGF treatment-experienced patients with active disease at screening, confirmed by an independent reading center. Across the 4 cohorts, mean time since nAMD diagnosis was >4 years, and mean number of prior anti-VEGF injections was >24. Enrolling active treatment-experienced patients with nAMD facilitates observation of possible signs of biologic effect while minimizing false signals. In OASIS, CLS-AX showed preliminary signs of durability. Specifically, in the Extension study, 67% of cohorts 3 and 4 patients went 6 months or longer without additional treatment, and 50% of cohorts 3 and 4 patients exited the 6-month study without needing additional treatment. Similarly, there was a 77% to 85% reduction in treatment burden in cohorts 3 and 4 over 6 months, compared with the treatments administered 6 months before CLS-AX administration. These results are consistent with preclinical studies, in which 1 mg axitinib injected suprachoroidally demonstrated mean axitinib levels in the retina 3 to 5 log orders higher than the in vitro IC50 value (0.2 ng/ml, VEGFR2 autophosphorylation inhibition assay), supporting therapeutic levels for 6 months after a single dose.[42]

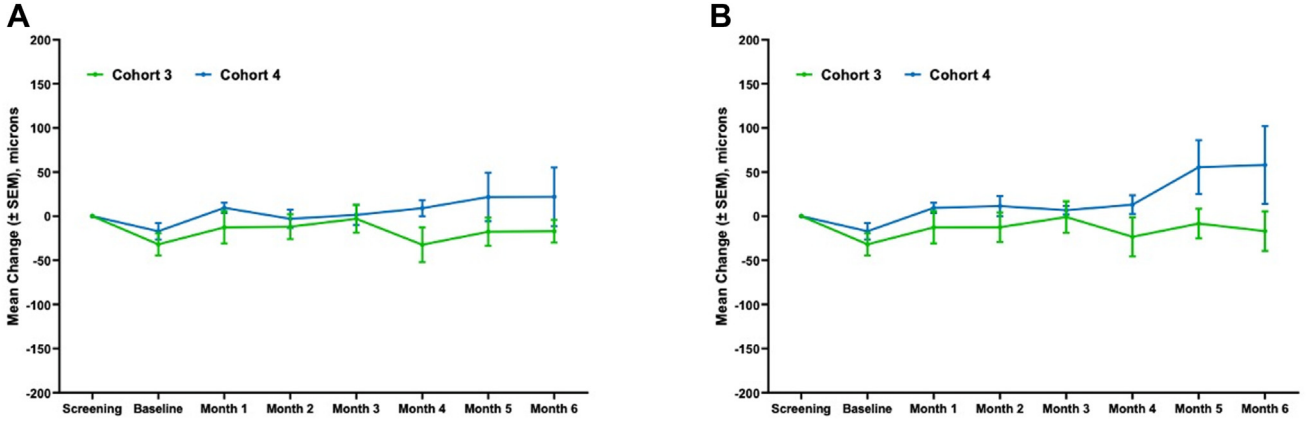

Figure 3. Line plots of mean ± SEM change from screening in central subfield thickness (CST) via spectral-domain OCT for cohorts 3 and 4. **A**, All data. **B**, Excludes data after the administration of additional treatment per protocol-defined criteria. Mean CST at screening was 177.1 μm for cohort 3 and 201.5 μm for cohort 4. SEM = standard error of the mean.

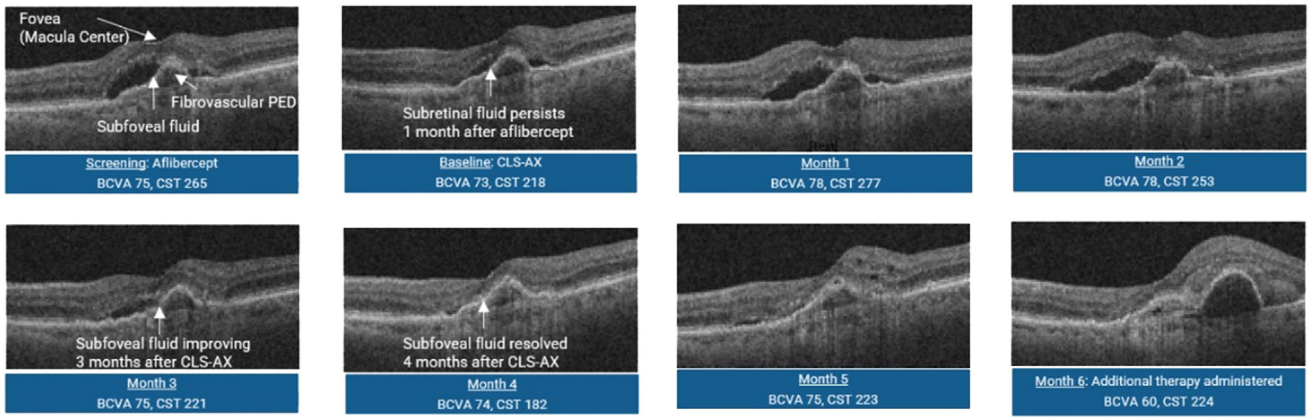

Figure 4. Case study of participant 2 of cohort 3 (0.50 mg). BCVA = best-corrected visual acuity; CLS-AX = axitinib injectable suspension; CST = central subfield thickness; PED = pigment epithelial detachment.

Importantly, these results may compare favorably with other currently marketed and investigational intravitreally injected biologic agents.

Axitinib injectable suspension also showed preliminary signs of biologic effect in these anti-VEGF treatment-experienced patients. Of note, at baseline, although there was reading center confirmation of either subretinal or intraretinal fluid in the central subfield, the mean CSTs were not elevated, reflective of the treatment-experienced nature of the study population, and this creates a floor effect with a propensity to worsen in nAMD. Nevertheless, in the Extension, through 6 months, there was stable mean CST and stable BCVA, even after excluding data after aflibercept therapy, to ensure additional therapies were not driving this stability. As demonstrated in the case study, there were also anatomical signs of biologic effect on OCT imaging. These data on biologic effect are not completely unexpected, given the high potency pan-VEGF receptor blockade of axitinib,[25] a TKI, which may be differentiated from focused VEGF-A ligand blockade of most current agents, as well as the supportive data from preclinical studies.[28–33,42,43] Furthermore, the high levels of drug targeting affected choroid-retina associated with SCS delivery may further leverage efficacy, particularly in anti-VEGF treatment-experienced patients.[42]

OASIS, a phase I/IIa study using CLS-AX, has multiple limitations, including the small number of patients enrolled into each cohort, the highly treatment-experienced nature of the study patients, which may limit potential clinical improvement, the lack of a control group, and lack of inferential statistics. Another limitation of this study involves the implementation of retreatment criteria, which may not accurately reflect retreatment criteria in clinical practice settings. Nevertheless, OASIS represents a successful, phase I/IIa clinical trial of CLS-AX administered suprachoroidally via the SCS Microinjector in patients with nAMD. It demonstrated an excellent safety profile across all doses and time points with no dose-limiting toxicities. Patients receiving CLS-AX 0.50 and 1.0 mg showed stable mean BCVA and OCT imaging overall, suggestive of TKI biologic effect. Visual improvement was not anticipated, as these patients were in the plateau phase of management. Results from OASIS and Extension support further evaluation of CLS-AX in a phase II trial as a potential alternative to existing anti-VEGF therapies to maintain or improve long-term outcomes in nAMD and reduce treatment burden. The phase IIb ODYSSEY study will assess the safety and efficacy of CLS-AX 1.0 mg administered under a flexible dosing regimen in patients with nAMD >9 months.

Footnotes and Disclosures

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[1] Retina Macula Institute of Arizona, Scottsdale, Arizona.

[2] Retina Consultants of Texas, Houston, Texas.

[3] Cumberland Valley Retina Consultants, Hagerstown, Maryland.

[4] Northern California Retina Vitreous Associates, Mountain View, California.

[5] Southeast Retina Center, PC, Augusta, Georgia.

[6] Retina Consultants Medical Group, Sacramento, California.

[7] Clearside Biomedical, Inc., Alpharetta, Georgia.

[8] Midwest Eye Institute, Indianapolis, Indiana.

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HUMAN SUBJECTS: Human subjects were included in this study. These studies adhered to the tenets of the Declaration of Helsinki and were conducted in accordance with the International Council for Harmonisation E6 Guidelines for Good Clinical Practice and applicable local, state, and federal laws. Institutional Review Board approval was obtained by all sites. The Health Insurance Portability and Accountability Act-compliant informed consent forms were approved by Institutional Review Board, and informed consent was obtained from study patients.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Kapik, Ciulla

Data collection: Barakat, Brown, Hu, Khurana, Marcus, Pearlman, Wykoff, Kapik, Ciulla

Analysis and interpretation: Barakat, Brown, Hu, Khurana, Marcus, Pearlman, Wykoff, Kapik, Ciulla

Obtained funding: Kapik, Ciulla

Overall responsibility: Kapik, Ciulla

Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **CNV** = choroidal neovascularization; **CST** = central subfield thickness; **IOP** = intraocular pressure; **IVT** = intravitreal; **nAMD** = neovascular age-related macular degeneration; **SAE** = serious adverse event; **SCS** = suprachoroidal space; **TEAE** = treatment-emergent adverse event; **TKI** = tyrosine kinase inhibitor.

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Correspondence:
Mark R. Barakat, MD, 20201 N Scottsdale Healthcare Dr, Ste 100, Scottsdale, AZ 85255. E-mail: mark.barakat@gmail.com.

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