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Phase I DAVIO Trial: EYP-1901 Bioerodible, Sustained-Delivery Vorolanib Insert in Patients With Wet Age-Related Macular Degeneration

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Purpose: To evaluate safety and tolerability of EYP-1901, an intravitreal insert containing vorolanib, a pan−VEGF receptor inhibitor packaged in a bioerodible delivery technology (Durasert E™) for sustained delivery, in patients with wet age-related macular degeneration (wAMD) previously treated with anti-VEGF therapy.

Design: Phase I, multicenter, prospective, open-label, dose-escalation trial.

Participants: Patients with wAMD and evidence of prior anti-VEGF therapy response.

Methods: Patients received a single intravitreal injection of EYP-1901.

Main Outcome Measures: The primary objective was to evaluate safety and tolerability of EYP-1901. Secondary objectives assessed biologic activity of EYP-1901 including best-corrected visual acuity (BCVA) and central subfield thickness (CST). Exploratory analyses included reduction in anti-VEGF treatment burden and supplemental injection-free rates.

Results: Seventeen patients enrolled in the 440 μg (3 patients), 1030 μg (1 patient), 2060 μg (8 patients), and 3090 μg (5 patients) dose cohorts. No dose-limiting toxicity, ocular serious adverse events (AEs), or systemic AEs related to EYP-1901 were observed. There was no evidence of ocular or systemic toxicity related to vorolanib or the delivery technology. Moderate ocular treatment-emergent AEs (TEAEs) included reduced visual acuity (2/17) and retinal exudates (3/17). One patient with reduced BCVA had 3 separate reductions of 17, 18, and 16 letters, and another had a single drop of 25 letters. One severe TEAE, neovascular AMD (i.e., worsening/progressive disease activity), was reported in 1 of 17 study eyes but deemed unrelated to treatment. Mean change from baseline in BCVA was −1.8 letters and −5.4 letters at 6 and 12 months. Mean change from baseline in CST was +1.7 μm and +2.4 μm at 6 and 12 months. Reduction in treatment burden was 74% and 71% at 6 and 12 months. Of 16 study eyes, 13, 8, and 5 were injection-free up to 3, 6, and 12 months.

Conclusion: In the DAVIO trial (ClinicalTrials.gov identifier, NCT04747197), EYP-1901 had a favorable safety profile and was well tolerated in previously treated eyes with wAMD. Measures of biologic activity remained relatively stable following a single EYP-1901 injection. These preliminary data support ongoing phase II and planned phase III trials to assess efficacy and safety.

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Age-related macular degeneration (AMD) is a leading cause of blindness among adults aged ≥50 years in high-income regions.[1] It may lead to a profound loss of central visual function, which is necessary for reading and driving.[2] About 10% of AMD cases consist of neovascular or wet AMD (wAMD) in which angiogenesis is inappropriately stimulated, resulting in choroidal neovascularization (CNV) with accompanying vascular leakage into the retina, leading to lower visual acuity.[3] Choroidal neovascularization is subdivided into 3 types based on the source of retinal invasion: type 1 develops when proliferation occurs below the retinal pigment epithelium, type 2 develops when proliferation occurs above the retinal pigment epithelium, and type 3 develops when there is intraretinal neovascularization.[4] The treatment of wAMD was greatly enhanced by the introduction of anti−VEGF therapies in the form of biologics that are administered locally via intravitreal injection. These therapies, including bevacizumab, ranibizumab, aflibercept, faricimab, and brolucizumab, bind VEGF-A and in some cases VEGF-B, placental growth factor, and angiopoetin-2.[5] These treatments reduce vascular hyperpermeability by blocking the downstream VEGF pathway, preventing the formation of CNV and reducing macular edema.[6]

Current anti-VEGF therapies can considerably improve vision for a period of time in approximately 25% to 50% of

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patients.[7–10] However, the treatment effect tends to diminish over long periods, particularly in real-world practice as compared with clinical trials.[7–12] This can partly be attributed to the burden of treatment on patients with wAMD, who are typically advanced in age, and on their caregivers.[13,14] Achieving efficacy with anti-VEGF treatment in wAMD is often accomplished with a high frequency of injections, typically ranging from 1 to 4 months.[15,16] Adherence to a rigid intravitreal schedule is challenging, and some physicians opt for a pro re nata or treat-and-extend approach to ease the treatment and visit burden while maintaining treatment benefits, usually measured by visual acuity and anatomic response on OCT.[15] However, adherence to treatment visits is still a challenge, as demonstrated by undertreatment with anti-VEGF therapies across patients with wAMD.[14] Some patients with wAMD discontinue treatment and this is associated with poor visual outcomes.[17,18] Nonadherence may be due to a perceived lack of efficacy or treatment burden. Patients of low socioeconomic status may find it especially challenging to attend frequent treatment visits, as adults aged ≥40 years with moderate or severe visual impairment in the United States (US) are less likely to have yearly eye doctor visits if their annual income is <$35,000, perhaps due to prohibitive out-of-pocket costs.[19] There is also the increasing burden on clinics and the health care system as a whole to consider, with increasing demand due to an aging population and the recent introduction of intravitreal treatment for geographic atrophy, a condition in many patients with advanced dry AMD.[19,20]

The need for new therapeutic strategies that can reduce treatment frequency and visit burden and facilitate visual gains over the long-term in patients with wAMD has been widely acknowledged.[3,11,14,21] Sustained drug release may reduce the burden of care and stabilize central subfield thickness (CST), which is a challenge with currently approved therapies that can cause variability in CST leading to suboptimal visual and anatomic outcomes and possibly fibrosis.[22,23]

The phase I, multicenter, 12-month DAVIO Trial of a new sustained-delivery therapy, EYP-1901 (vorolanib in Durasert E™) was designed with this in mind. EYP-1901 is a bioerodible, sustained-delivery intravitreal insert designed to release microgram levels of a multikinase pan−VEGF receptor inhibitor, vorolanib, into the vitreous chamber constantly over several months. An oral formulation of vorolanib was previously studied in the phase II APEX Trial in patients with wAMD, which suggested its efficacy in wAMD.[24] The intravitreal insert formulation design of EYP-1901 is based on Durasert® technology, which is currently being used in 4 US Food and Drug Administration−approved ophthalmic therapies: ganciclovir (Vitrasert®) and 3 fluocinolone acetonide intravitreal products (Retisert® [Bausch & Lomb], Iluvien® [Alimera Sciences], and Yutiq® [Alimera Sciences]). EYP-1901 uses a bioerodible formulation of Durasert®, referred to as Durasert E™. The insert was designed to deliver consistent therapeutic levels of vorolanib in the vitreous for approximately 9 months. This technology presents an opportunity to lower the treatment burden with a potential twice-yearly in-office injection of an insert that dissolves completely over time. The objective of the DAVIO Trial was to demonstrate the safety, tolerability, and preliminary evidence of biologic activity of EYP-1901 in patients who were previously treated with anti-VEGF therapy.

Methods

Ethical Considerations

The study was registered at www.ClinicalTrials.gov (identifier, NCT04747197) and performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice according to the International Conference on Harmonization, as well as applicable regulatory requirements. Approvals from institutional review boards or ethical committees were obtained (Advarra Institutional Review Board, Wills Eye Hospital Institutional Review Board). Written informed consent was obtained from each patient before enrollment and before any study-related procedure was performed, according to US Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a] and 21 CFR 50.25[b]).

Study Population

Patients were considered eligible for participation in the study if they were diagnosed with wAMD in the study eye and were ≥50 years of age at the time of screening. They must have received ≥3 prior injections with the same anti-VEGF agent (including bevacizumab, ranibizumab, or aflibercept) in the 6 months prior to the screening visit, in the study eye. Patients must have received the last anti-VEGF treatment within 7 to 10 days prior to day 0 (dosing day). They must have demonstrated response to that treatment in the study eye prior to enrollment, with stable or improved response at day 0 defined as CST unchanged, reduced, or increased no >50 μm compared to the CST observed at screening just prior to the last anti-VEGF injection. Patients must have had best-corrected visual acuity (BCVA), using ETDRS charts, of 25 letters (Snellen equivalent, 20/320) to 85 letters (Snellen equivalent, 20/20). All subtypes of wAMD CNV lesions were permissible, including classic CNV, occult CNV, or lesions with some classic CNV component, or retinal angiomatous proliferation lesions.

Key exclusion criteria were history of vitrectomy surgery, submacular surgery, or other surgical intervention for AMD in the study eye; subretinal hemorrhage (size >50% or >1 disc area, 2.54 mm^2) involving the center of the fovea of the study eye at the screening visit; subfoveal fibrosis or scarring >50% of the total lesion, or atrophy in the study eye, confirmed by a central reading center; CNV in either eye due to other causes such as ocular histoplasmosis, trauma, or pathologic myopia that would have potentially compromised vision in the study eye, confirmed by the central reading center; any concurrent intraocular condition in the study eye (e.g., cataract or glaucoma) that, in the opinion of the investigator, would either require surgical intervention during the study to prevent or treat visual loss that might result from that condition or affect interpretation of the study results; active intraocular inflammation (grade trace or above) in the study eye; history of vitreous hemorrhage or rhegmatogenous retinal detachment or treatment for retinal detachment or macular hole (stage 3 or 4) in the study eye; history of idiopathic or autoimmune-associated uveitis in either eye; active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye; and history of glaucoma-filtering surgery, tube shunt placement, microinvasive glaucoma surgery, or corneal transplantation in the study eye.

Notably, patients were not excluded based on fluid levels or CST-based criteria.

Study Design

The study was a phase I, multicenter (11 sites in the US), prospective, open-label, dose escalation trial. It evaluated safety, tolerability, and preliminary evidence of biologic activity following a single intravitreal injection of the EYP-1901 insert in eyes with wAMD and evidence of prior response to anti-VEGF therapy. The study was conducted from January 2021 to May 2022. The study duration was 48 weeks, and the study consisted of a patient screening phase and a sequential dose-escalation phase. All patients in the study received EYP-1901, and both patients and investigators were not masked. According to the study protocol, 3 successive dose cohorts were planned to be enrolled in the dose-escalation phase, and depending on toxicity, up to 26 patients could have been enrolled during this phase. Cohort 1 (3 patients) was to receive the 440 μm dose, Cohort 2 (5 patients) was to receive the 2060 μm dose, and Cohort 3 (5 patients) was to receive the 3090 μm dose. Depending on the findings of the dose-escalation phase, an optional cohort extension may have been added.

A major protocol deviation occurred during administration of EYP-1901 to 4 patients in Cohort 3, each enrolled at a different site. Investigators experienced difficulties with the injector related to the advancement of the plunger as it pushed the 3 inserts (1030 μg each) through the needle. As a result, only 2 of the 3 inserts were delivered in 3 patients (05-009, 08-003, 12-001), and 1 of 3 inserts was delivered in another patient (07-001). In all 4 cases, the undelivered inserts remained in the needle. The first 3 patients were reassigned to the mid-dose group (2060 μg total dose) for analysis by actual dose cohort, and the fourth patient was reassigned to an unplanned low-mid dose cohort (i.e., receiving 1 insert of 1030 μg). Additional patients were enrolled in Cohort 3 until the planned number of 5 patients received the 3090 μm dose. The injector issues that caused the deviation have been resolved in the subsequent phase II DAVIO 2 trial, and the device continues to be in development.

Patients received a single intravitreal administration of EYP-1901 in the study eye on day 0 using a preloaded applicator, 7 to 10 days following their last anti-VEGF injection. Follow-up examinations were conducted on day 7, 14, 28, and then every 4 weeks through week 48 following EYP-1901 injection. Administration of additional Food and Drug Administration-approved anti-VEGF treatment for wAMD (e.g., ranibizumab or aflibercept; not brolucizumab) or off-label bevacizumab was allowed at the investigator's discretion if a patient had a new or worsening vision-threatening hemorrhage since day 0 due to wAMD, an increase in CST of >75 μm from day 0, or a loss of ≥ 10 ETDRS letters from day 0 with intraretinal or subretinal fluid and/or hemorrhage judged to be the cause of BCVA loss. If these criteria were not met, the investigator could still determine the need for administering anti-VEGF injection in the best interest of the patient's welfare. Repeat administration following the first anti-VEGF intervention was allowed if any of the above criteria were met again at any subsequent study visit.

Study Objectives

The primary objective of this study was to evaluate the safety and determine the maximum tolerated dose of the EYP-1901 intravitreal insert for the treatment of patients with wAMD, based on ocular treatment-emergent adverse events (TEAEs) in the study and fellow eye, as well as nonocular adverse events (AEs), including clinical laboratory findings. Secondary objectives were changes in BCVA, CST (using spectral-domain OCT [SD-OCT]), central retinal lesion thickness on SD-OCT, height of subretinal fluid on SD-OCT, the proportion of patients with no detectable intraretinal fluid or cysts, total lesion area by fluorescein angiography, and total CNV area by fluorescein angiography; the proportion of patients receiving anti-VEGF injections at each time point through 6 months; median time to first additional (supplemental) anti-VEGF injection; ocular exposure to EYP-1901 measured using aqueous humor levels; and systemic exposure to EYP-1901 measured using plasma levels. Posthoc exploratory analyses were conducted to evaluate reduction in treatment burden and supplemental injection-free rate.

Study Assessments

Safety assessments included the incidence and severity of TEAEs reported after the screening visit, clinical laboratory evaluations (e.g., hematology, serum chemistry, coagulation, and urinalysis), safety data collected from ocular examinations and intraocular pressure measurements, vital sign measurements, electrocardiograms, and the use of anti-VEGF and concomitant medications. Secondary endpoints were evaluated during monthly follow-up examinations assessing BCVA and CST.

Preenrollment and postenrollment treatment burden, defined as the number of injections during the 12-month period before or after the EYP-1901 injection, were derived for each patient. Preenrollment treatment burden was based on historical anti-VEGF injection records. Patients who were treated for <12 months prior to study enrollment had their 12-month treatment burden normalized based on the number of injections they received and the time period during which they received those injections (e.g., if the patient received 3 injections during the preceding 6-month period, their preenrollment treatment burden was normalized to 6 injections during the 12-month preenrollment period). Postenrollment treatment burden was based on additional injections administered during the study, following the standard-of-care anti-VEGF injection at study start. The reduction in treatment burden between pre- and postenrollment was expressed as a percentage at 6 and 12 months. On-study injection-free rates up to each visit were also calculated.

No formal sample size calculations were performed. The sample size was considered reasonable to determine the safety profile of escalating doses of EYP-1901 in patients with wAMD. All patients who received EYP-1901 were planned to be included in all analyses. All safety, tolerability, and secondary and exploratory parameters were reported using descriptive summary statistics. No inferential statistical analysis was planned.

Results

Patient Population and Baseline Characteristics

Seventeen patients were enrolled in the study and received a single injection of EYP-1901 in 1 eye (hereafter, the study eye). Patients were assigned to 1 of 4 cohorts based on their received dose: 440 μg cohort (1 insert; $n = 3$), 1030 μg cohort (1 insert; $n = 1$), 2060 μg cohort (2 inserts; $n = 8$), 3090 μg cohort (3 inserts; $n = 5$). Baseline characteristics (Table 1) were comparable across the treatment groups. Thirteen patients (76%) were women. The mean age was 77.4 years, median time from wAMD diagnosis to enrollment was 17 months, mean BCVA was 69 letters, and mean CST was 299 μm. The mean (normalized) number of anti-VEGF injections received by patients was

Table 1. Patient Baseline Characteristics

Characteristic	Single-Dose EYP-1901 (N = 17)
Age, y, mean (range)	77.4 (67–94)
Female, n (%)	13 (76)
BCVA, ETDRS letters, mean (range)	69 (38–85)
CST, μm, mean (range)	299 (204–441)
Time from wAMD diagnosis to enrollment, mo, median (range)	17 (4–74)
Number of anti-VEGF injections in the 12 months prior to enrollment, normalized,* mean (range)	8.6 (3–10)

BCVA = best-corrected visual acuity; CST = central subfield thickness; wAMD = wet age-related macular degeneration.
*Patients who were treated for <12 months prior to study enrollment had their 12-month treatment burden normalized based on the number of injections they received and the time period during which they received those injections (e.g., if the patient received 3 injections during the preceding 6-month period, their preenrollment treatment burden was normalized to 6 injections during the 12-month preenrollment period).

8.6 (every 6 weeks on average) during the 12 months prior to enrollment. All 17 patients were included in the safety analyses.

One patient withdrew from the study after the week 16 visit due to personal concerns related to traveling during the ongoing coronavirus disease 2019 pandemic. Subsequently, 218 days (approximately week 31) from administration of EYP-1901, the patient suffered a cardiac arrest at home, was transferred to the hospital, and was unable to be resuscitated. The cause of death was listed as diverticulitis, which was a preexisting condition reported in the patient's previous medical history prior to the start of the study that had resolved and was not being treated at the time of screening per the patient's own report. Because no additional data were collected after week 16, the study sponsor decided to exclude this patient from the secondary and exploratory analyses to avoid the potential to skew the data. As a result, all secondary and exploratory analyses included only the 16 patients who completed the study.

A subgroup of patients from the mid- and high-dose cohorts with minimal or no fluid at baseline, defined as CST values of ≤350 μm at screening (n = 9; CST, 205–298 μm) and minimal intraretinal or subretinal fluid reported in the study eye, was identified and analyzed separately.

Primary Objectives

Safety and Tolerability. Single intravitreal administrations of EYP-1901 were well tolerated up to the highest tested dose of 3090 μg (Table 2). There was no evidence of ocular or systemic toxicity related to vorolanib, and there were no toxicity or tolerance issues related to Durasert E™. No dose-limiting toxicity was observed in this study. There were 2 nonocular serious AEs (SAEs) reported during the study.

Ocular Safety. There were no unexpected TEAEs related to the intravitreal injection procedure. A total of 49 ocular TEAEs were reported for the study eye by 13 patients (76.5%), and 5 ocular TEAEs in the fellow eye (i.e., the untreated eye) were reported by 5 patients (29.4%). Six patients (35.3%) experienced ≥1 ocular TEAE in the study eye that was considered related to treatment. No TEAE in the fellow eye was considered related to treatment. No patients experienced an ocular SAE or TEAE leading to discontinuation or death. Most ocular TEAEs were mild. Moderate ocular TEAEs were experienced by 6 patients and included reduced visual acuity (defined as a decrease in BCVA of ≥15 letters from the previous BCVA measurement), corneal disorder, CNV, retinal exudates, and vitreous hemorrhage. One severe TEAE of neovascular AMD (defined as worsening or progressive disease activity) in the study eye was reported; this event was not related to study treatment and was resolving at the time of last contact.

The most common treatment-related TEAEs were conjunctival hemorrhage and neovascular AMD, experienced by 4 patients (23.5%) each. Most injection-related ocular TEAEs resolved without clinical sequelae. There were no vitreous floaters, endophthalmitis, retinal detachment, insert migration into the anterior chamber, retinal vasculitis, posterior or anterior segment inflammation, vascular occlusive events, or ischemic optic neuropathy observed throughout the study. Five patients had at most 1 TEAE in the fellow eye, and none were considered to be treatment-related.

Systemic Safety. No clinically relevant changes in vital sign parameters (e.g., systolic and diastolic blood pressure, pulse rate, and body temperature) were observed, and there were no treatment- or dose-related trends. Forty systemic, nonocular AEs were reported among 14 patients (82.4%). Nonocular TEAEs occurring in ≥2 patients (11.8%) included nasopharyngitis in 3 patients (17.6%) and coronavirus disease 2019, diverticulitis, and urinary tract infection in 2 patients (11.8%) each. The majority of nonocular TEAEs were mild or moderate. One nonocular TEAE, an increased laboratory value of γ-glutamyltransferase arising on day 58, was considered possibly treatment-related and mild. The patient also had elevated alanine aminotransferase and aspartate aminotransferase laboratory levels on day 261; these were considered mild and not related to study drug, and they resolved without any intervention.

No trends were observed relative to dose, and no systemic AE was judged by the investigators to be related to the study drug. Two patients (11.8%) had SAEs during the study, including pneumonia in 1 patient and diverticulitis in the other, the latter resulting in death. In both patients, these SAEs occurred >6 months after receiving EYP-1901 at a time point when the study drug was undetectable in plasma.

Secondary Objectives

BCVA. Patients in the DAVIO trial had a high treatment burden prior to the study with a median treatment frequency of every 6 weeks. A mean (range) BCVA change from baseline of +0.7 (−11 to +12), −5.2 (−51 to +10), −1.8

Table 2. Summary of Ocular TEAEs

TEAEs Through Study End, n (%)	EYP-1901 440 µg (n = 3)	EYP-1901 1030 µg (n = 1)	EYP-1901 2060 µg (n = 8)	EYP-1901 3090 µg (n = 5)	EYP-1901 Overall (N = 17)
Number of ocular TEAEs	9	0	16	24	49
Patients with ≥1 ocular TEAE	3 (100.0)	0 (0.0)	6 (75.0)	4 (80.0)	13 (76.5)
Patients with ≥1 ocular treatment-related TEAE	1 (33.3)	0 (0.0)	4 (50.0)	1 (20.0)	6 (35.3)
Patients with ≥1 ocular SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ocular TEAEs occurring in ≥2 patients					
Conjunctival hemorrhage	0 (0.0)	0 (0.0)	3 (37.5)	1 (20.0)	4 (23.5)
Neovascular AMD*	1 (33.3)	0 (0.0)	3 (37.5)	0 (0.0)	4 (23.5)
Retinal exudate	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)	3 (17.6)
Ocular discomfort	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.8)
Reduced visual acuity†	1‡ (33.3)	0 (0.0)	1§ (12.5)	0 (0.0)	2 (11.8)

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
*Defined as worsening or progressed disease activity.
†Defined as a decrease in BCVA of ≥15 letters from the previous BCVA measurement.
‡This patient experienced 3 separate drops in BCVA during the study: from 76 letters at week 8 to 59 letters at week 12, from 74 letters at week 16 to 56 letters at week 20, and from 72 letters at week 24 to 56 letters at week 28.
§This patient experienced a single drop in BCVA from 60 letters at week 8 to 35 letters at week 12.

(−38 to +8), and −5.4 (−45 to +10) ETDRS letters was observed at 4, 5, 6, and 12 months, respectively, following administration of EYP-1901 (Fig 1A). The mean (standard deviation) area under the curve for the observed change in BCVA from screening to end of study was −2.6 (8.4) letters/day. Among the 16 patients who completed the study, 6 (37.5%) had a loss of ≥5 letters from baseline in BCVA at 12 months, and 10 patients (62.5%) had a loss of <5 letters, no change, or a gain from baseline in BCVA at 12 months. Among 5 eyes that did not require anti-VEGF injection following EYP-1901 administration (31.3% of all 16 patients), the mean change in BCVA was +1.0 letter at 6 months and −2.6 letters at 12 months. Three eyes required anti-VEGF injection at 1 month following EYP-1901 administration; among the 13 that did not, the mean change in BCVA was −2.5 letters at 6 months and −2.7 letters at 12 months.

In the subgroup of 9 eyes that had minimal or no fluid at screening, the mean change in BCVA from baseline was −0.4 letters (range, −12 to +8) at 6 months and −2.2 letters (range, −17 to +10) at 12 months.

In the subgroup of 8 eyes that did not require supplemental injection up to 6 months after receiving EYP-1901, the mean change in BCVA from baseline was −0.4 letters (range, −12 to +7) at 6 months.

CST Using SD-OCT. A mean (range) CST change from baseline of +2.7 (−147 to +173), +60.5 (−91 to +227), +1.7 µm (−174 to +263), and +2.4 µm (−215 to +239) was observed at 4, 5, 6, and 12 months, respectively, following administration of EYP-1901 (Fig 1B). The mean (standard deviation) area under the curve for the observed change in CST from screening to end of study was +18.0 (54.8) µm/day. Among patients who completed the study, 6 (37.5%) had a mean change from baseline of <0 µm at 12 months, and 12 patients (75%) had a mean change of <50 µm at 12 months. Among the 5 eyes that did not require anti-VEGF injection, the mean change in CST was +0.4 µm at 6 months and −4.8 µm at 12 months. Among the 13 eyes that did not require anti-VEGF injection at 1 month, the mean change in CST was +20 µm at 6 months and +24 µm at 12 months.

In the subgroup of 9 eyes that had minimal or no fluid at screening, the mean change in CST from baseline was −1.0 µm (range, −93 to +44) at 6 months and +10.9 µm (range, −113 to +74) at 12 months.

In the subgroup of 8 eyes that did not require supplemental injection for rescue up to 6 months after receiving EYP-1901, the mean change in CST from baseline was +5.3 µm (range, −93 to +79) at 6 months.

Exploratory Analyses

Treatment Burden Reduction and Injection-Free Interval. When comparing the number of anti-VEGF injections before and after treatment with EYP-1901, the treatment burden was reduced by 74% at 6 months and 71% at 12 months (Fig 2). All eyes experienced a reduced treatment burden through month 6 and month 12, regardless of dose. The median time to first additional anti-VEGF treatment was 6.5 months. Thirteen eyes of 16 (81%) remained additional-injection free up to 3 months, 8 of 16 (50%) up to 6 months, and 5 of 16 (31%) up to 12 months (Fig 3A).

The subgroup of 9 eyes that had minimal or no fluid at screening remained additional-injection free up to 4 months (Fig 3B). Sixty-seven percent did not require an additional injection up to 6 months and 56% up to 12 months. The median time to first additional anti-VEGF treatment among these eyes was 12 months.

In the subgroup of 8 eyes that were additional-injection free 6 months after receiving EYP-1901, 63% remained injection free up to 12 months (Fig 3C). The median time to first additional anti-VEGF injection among these eyes was 12 months.

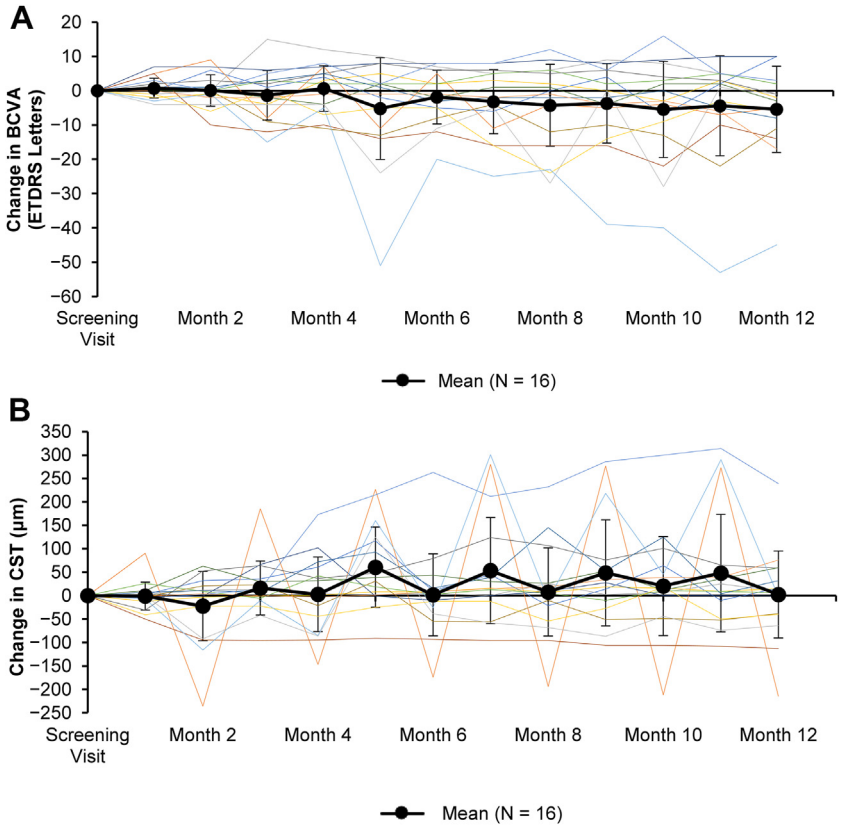

Figure 1. Spaghetti plots showing individual and mean change in **(A)** BCVA and **(B)** CST from the screening visit over 12 months following a single injection of EYP-1901. Error bars represent the standard deviation. BCVA = best-corrected visual acuity; CST = central subfield thickness.

Discussion

This is the first study in human eyes of a bioerodible, sustained-delivery formulation of vorolanib, EYP-1901, for the treatment of retinal disease. Sustained-delivery formulations are needed to complement currently approved therapies and increase the durability of anti-VEGF treatment efficacy for patients with wAMD and other retinal diseases, including diabetic retinopathy and diabetic macular edema, to decrease the treatment burden and thereby potentially improve both patient adherence and long-term outcomes.[3,13,21] The majority of retinal specialists participating in the 2023 American Society of Retina Specialists' Preferences and Trends membership survey considered the extended durability of treatment to be the most important potential benefit of a new therapy for wAMD.[25] A number of approaches have been developed for the intravitreal sustained delivery of therapies for retinal disease. One of these approaches is formulating drugs in biocompatible, biodegradable polymer materials to achieve sustained delivery of the drug in the eye as the materials gradually degrade.

Polymers used to package vorolanib in EYP-1901 are suitable materials for this purpose because they can be selectively modified for the intended release rate of the active drug.[26] Ocular inserts such as EYP-1901 occupy a small area of the vitreous and degrade over time as drug is released, and they are administered by in-office intravitreal injection. Currently used anti-VEGF drugs are large molecules that are difficult to incorporate into polymer formulations for sustained delivery. Small molecules such as antiangiogenic pan-VEGF receptor (VEGFR) inhibitors are better suited for release from polymers.

Vorolanib, a multikinase inhibitor derived from sunitinib with the intent of decreasing off-target effects,[27] potently inhibits all 3 VEGFRs (VEGFR-1, -2, and -3; manuscript in preparation) by competing with adenosine triphosphate for binding to the tyrosine kinase domain of VEGFR inside the cell membrane.[28] Vorolanib would therefore be expected to inhibit most VEGF pathway signaling, perhaps to a greater degree than current anti-VEGF drugs that each target only 1 form of VEGF and leave VEGFRs available to be activated by other forms of VEGF. Importantly, at clinically relevant doses vorolanib does not inhibit Tie2 (manuscript in preparation), a receptor tyrosine kinase that is inhibited by the angiogenic ligand angiopoeitin-2, which is released by endothelial cells in response to VEGFR-2 activity, is elevated in the aqueous humor of eyes with wAMD, and is targeted by the approved therapy faricimab.[29] Lack of activity against Tie2 may suggest

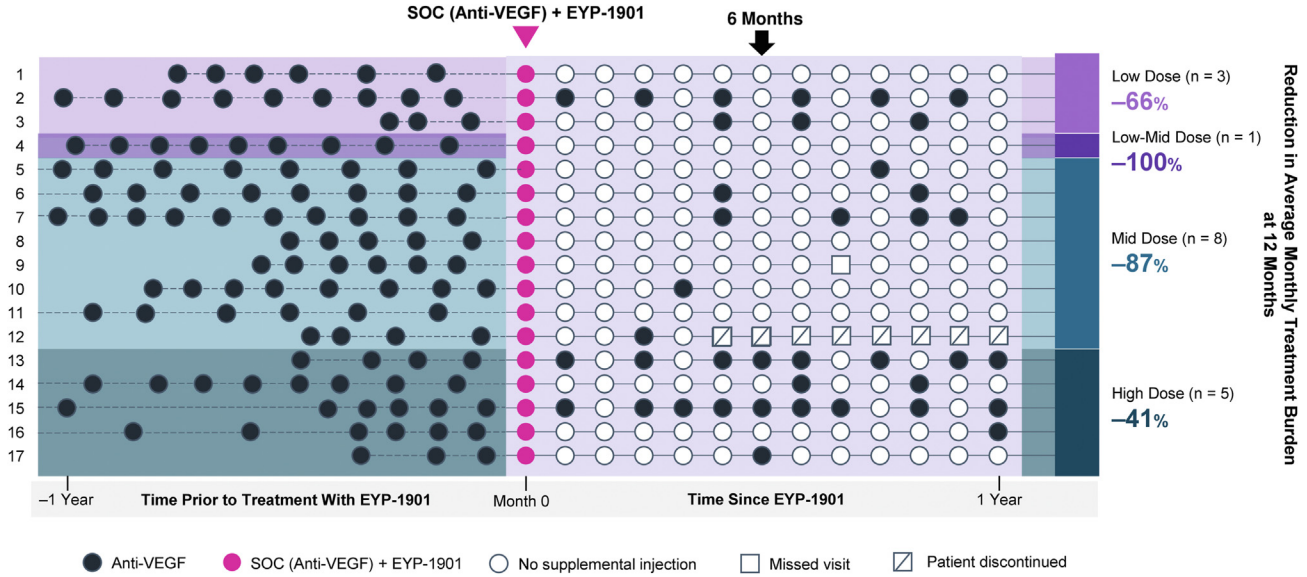

Figure 2. Anti-VEGF injections before and after treatment with EYP-1901 and reduction in average monthly treatment burden. The treatment burden calculations include injections for patient 12, who died during the study. SOC = standard of care.

additional benefit of vorolanib in wAMD as Tie2 activation promotes the maintenance of vascular stability.[29,30] Vorolanib also inhibits both platelet-derived growth factor receptors (platelet-derived growth factor-α and -β; data on file), which have a role in angiogenesis through stimulation of VEGF secretion by retinal microglia and Müller cells.[31]

Vorolanib was previously studied in oral formulations for patients with cancer[32–35] as well as patients with wAMD.[24,36] In the phase II APEX Trial in wAMD, oral vorolanib was noninferior to placebo in eyes receiving pro re nata anti-VEGF injections at 52 weeks, and it trended toward fewer pro re nata anti-VEGF injections compared with placebo.[24] Oral vorolanib also demonstrated a dose-dependent decrease in subretinal fluid on SD-OCT imaging at 52 weeks and protected fellow eyes from conversion to wAMD. The APEX Trial was stopped prematurely due to gastrointestinal and hepatobiliary AEs associated with oral vorolanib use such as elevated liver enzymes, and due to the fulfillment of the primary endpoint (noninferiority to placebo).[24] The APEX Trial demonstrated the potential benefit of vorolanib for the treatment of wAMD.

The primary objective of the DAVIO Trial was to demonstrate safety and tolerability of EYP-1901 after a single administration. EYP-1901 was developed as a localized, intravitreal, sustained-delivery formulation of vorolanib in an attempt to reduce the injection burden of wAMD treatment and also reduce systemic adverse effects of vorolanib. Intravitreal injections of EYP-1901 were well tolerated up to the highest dose of 3090 μg. No dose-limiting toxicities were observed in this study, and no ocular SAEs or serious drug-related systemic AEs were reported. The majority of ocular AEs were mild and expected.

A long-term therapy such as EYP-1901, with the potential to stabilize visual acuity and CST and minimize subretinal fluid accumulation over the course of ≥6 months, may have the most utility as a new maintenance treatment paradigm for eyes with wAMD. Physicians treating wAMD may not feel comfortable using a long-term therapy in eyes that are not yet stable because patients may not feel the need to return for monthly follow-up. For this reason, patients who were already stable on anti-VEGF therapy were recruited for the DAVIO Trial. As a result, instead of the rapid improvement seen with typical anti-VEGF clinical trials in a treatment-naive population, the maintenance of stable BCVA and CST was targeted and observed in this study.

This population of patients provided an opportunity to compare the treatment burden before and after initiation of EYP-1901. Undertreatment arising from the treatment burden of patients with wAMD impacts their visual acuity, which is often suboptimal in real-world settings compared with randomized clinical trials.[14] Treatment burden also creates a significant demand on health care resources, and therapies that reduce this burden while maintaining efficacy and safety may therefore lower the economic burden of wAMD.[37,38] In the DAVIO Trial, EYP-1901 treatment was associated with a 74% reduction in treatment burden at 6 months with a similar reduction at 12 months compared with preenrollment treatment burden. Examples of patients with high treatment burden before administration of EYP-1901 and long injection-free intervals following treatment are shown in Figure 4. Five eyes in this study did not require any injections during the 12-month study despite receiving regular anti-VEGF injections before treatment with EYP-1901. Such a reduction in treatment burden could be impactful in clinical settings by reducing the need for patient adherence to frequent intravitreal injections and decreasing operational pressure on physician practices. The widely acknowledged undertreatment of wAMD is at least partially a result of treatment

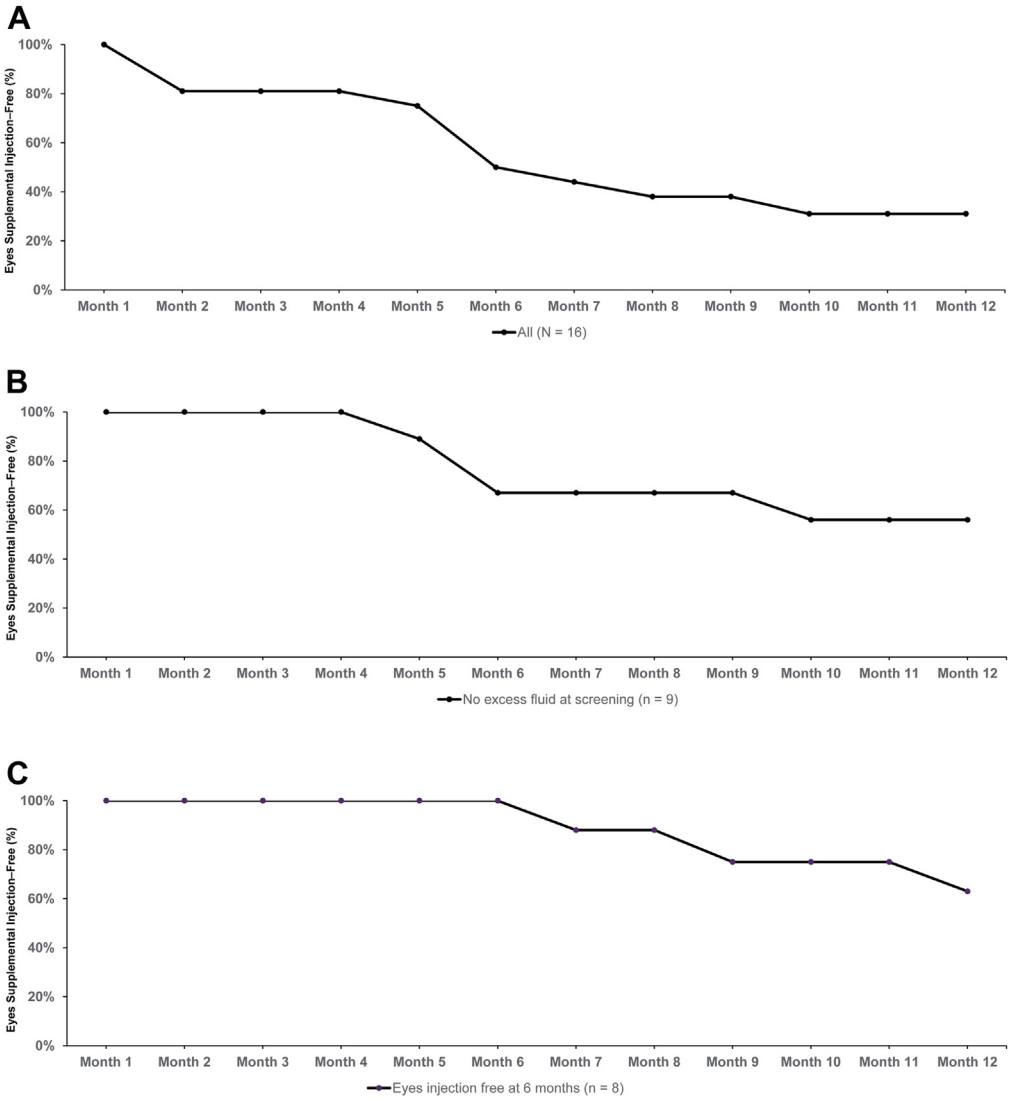

Figure 3. Anti-VEGF injection–free rates up to each visit among **(A)** all 17 eyes, **(B)** 9 eyes with minimal or no fluid at screening, and **(C)** 8 eyes additional-injection free 6 months after receiving EYP-1901.

fatigue resulting in rescheduled and/or missed appointments, and this stems from high injection and visit frequency along with long visit times and anxiety regarding intravitreal injections.[8,9,13] Caregivers also experience treatment fatigue because they care for elderly patients who may require more help attending treatment visits. Reducing the treatment burden may therefore enable better patient adherence and outcomes.

Nine eyes in the DAVIO Trial had minimal or no fluid at screening, and 67% of those eyes were injection free up to 6 months. The median time to additional anti-VEGF injection among those eyes was 12 months, and 4 of the 5 eyes that did not require additional injections through 12 months belonged to this subset. This may signify a subpopulation of patients who may be especially receptive to maintenance treatment with EYP-1901, or it might guide the timing of EYP-1901 initiation, since the reduction in treatment burden may be larger for eyes that are free of fluid at the time of initiation. In addition, 63% of 8 eyes that were additional-injection free 6 months after receiving EYP-1901 remained so until month 12. These results suggest that patients who show benefit during the first 6 months may be likely to continue to benefit from EYP-1901 over the next $\geq$6 months.

The DAVIO Trial had several important limitations. As this was a phase I study primarily intended to assess safety and tolerability, only a small number of patients were enrolled in the study and spread across the dose groups. Additionally, the study lacked a control group, meaning there was no comparison of the study drug with an existing therapy. Investigators were not masked to study enrollment, which may have biased their decision to administer supplemental injections during the study period. The study was not powered to make statistical comparisons. Because the exploratory analyses looking at reduction in treatment burden and supplemental injection-free rate were added after

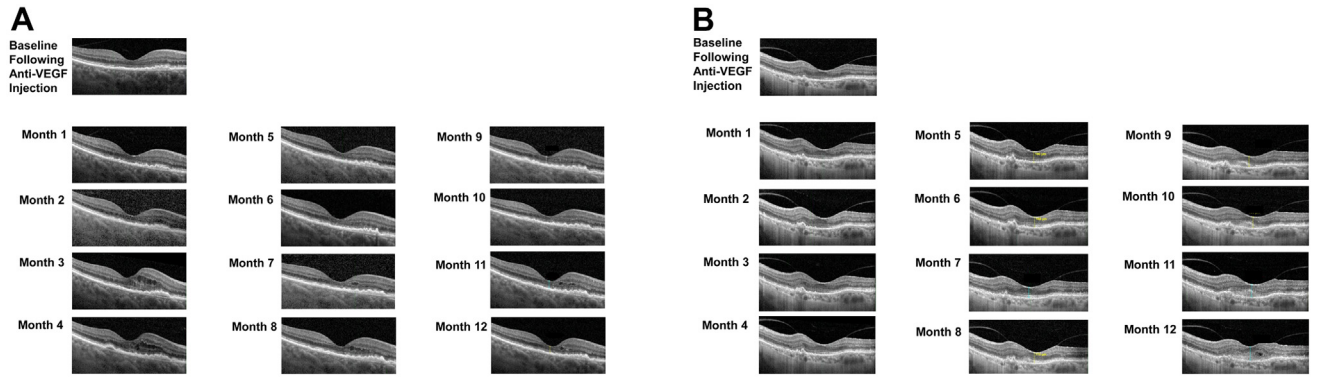

Figure 4. SD-OCT images of 2 eyes at baseline and at 6 and 12 months after receiving EYP-1901. Case 1 (**A**): OCT images of the treated eye of a 71-year-old female who received regular anti-VEGF injections prior to her baseline screening visit and, following treatment with EYP-1901, only 1 anti-VEGF injection at month 4. Case 2 (**B**): OCT images of the treated eye of an 80-year-old female who did not require anti-VEGF treatment until month 12 following a single injection of EYP-1901. SD-OCT = spectral-domain OCT.

approval of the initial study plan, certain data were not collected at baseline that could have added additional depth to the preenrollment and postenrollment comparisons.

Studies have demonstrated the impact of macular thickness fluctuation in eyes with wAMD. A large retrospective study showed that large fluctuations in macular thickness, which might be expected in eyes receiving occasional anti-VEGF injections for wAMD, were related to poor visual outcomes at 24 months.[39] Data from large, randomized clinical trials showed a strong relationship between the fluctuation in retinal thickness and the decrease in BCVA over long-term anti-VEGF treatment for wAMD.[22,23] A therapy such as EYP-1901 that releases drug constantly in the vitreous may help prevent fluctuations in retinal thickness and therefore has the potential to improve long-term outcomes in the real world compared with currently used therapies.

In summary, EYP-1901 demonstrated a favorable safety profile in this patient population, with no significant safety signals. Secondary and exploratory analyses supported the proposed biologic activity of EYP-1901 and suggest a potential for a reduced treatment burden in previously treated eyes with wAMD. Maintenance treatment using a sustained-delivery therapy such as EYP-1901 in patients stable on anti-VEGF therapy has the potential to decrease the need for patient adherence to treatment visits and thereby increase the possibility of improved real-world outcomes.[3,11,21] Notably, subgroups of patients who were additional-injection free at 6 months and who were without excess fluid at screening had a reduced injection burden compared with the overall study population. Phase II trials of this therapy have been initiated in patients with wAMD, nonproliferative diabetic retinopathy, and diabetic macular edema, and phase III trials in wAMD are planned. These trials will further evaluate the potential benefit of sustained-delivery vorolanib in patients with retinal vascular disease.

Footnotes and Disclosures

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Abbreviations and Acronyms:
AE = adverse event; **AMD** = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **CNV** = choroidal neovascularization; **CST** = central subfield thickness; **SAE** = serious adverse event; **SD-OCT** = spectral-domain OCT; **TEAE** = treatment-emergent adverse event; **VEGFR** = pan-VEGF receptor; **US** = United States; **wAMD** = wet age-related macular degeneration.

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