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A Randomized Controlled Trial of OPT-302, a VEGF-C/D Inhibitor for Neovascular Age-Related Macular Degeneration

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Purpose: Neovascular (wet) age-related macular degeneration (nAMD) is driven by VEGFs A, C, and D, which promote angiogenesis and vascular permeability. Intravitreal injections of anti−VEGF-A drugs are the standard of care, but these do not inhibit VEGF-C and D, which may explain why many patients fail to respond fully. This trial aimed to test the safety and efficacy of OPT-302, a biologic inhibitor of VEGF-C and D, in combination with the anti−VEGF-A inhibitor ranibizumab.

Design: Dose-ranging, phase 2b, randomized, double-masked, sham-controlled trial.

Participants: Participants with treatment-naive nAMD were enrolled from 109 sites across Europe, Israel, and the United States.

Methods: Participants were randomized to 6, 4-weekly, intravitreal injections of 0.5 mg OPT-302, 2.0 mg OPT-302, or sham, plus intravitreal 0.5 mg ranibizumab.

Main Outcome Measures: The primary outcome was mean change in ETDRS best-corrected visual acuity (BCVA) at 24 weeks. Secondary outcomes (comparing baseline with week 24) were the proportion of participants gaining or losing $\geq$ 15 ETDRS BCVA letters; area under the ETDRS BCVA over time curve; change in spectral-domain OCT (SD-OCT) central subfield thickness; and change in intraretinal fluid and subretinal fluid on SD-OCT.

Results: Of 366 participants recruited from December 1, 2017, to November 30, 2018, 122, 123, and 121 were randomized to 0.5 mg OPT-302, 2.0 mg OPT-302, and sham, respectively. Mean ($\pm$ standard deviation) visual acuity gain in the 2.0 mg OPT-302 group was significantly superior to sham ($+14.2 \pm 11.61$ vs. $+10.8 \pm 11.52$ letters; $P = 0.01$). The 0.5 mg OPT-302 group was not significantly different than the sham group ($+9.44 \pm 11.32$ letters; $P = 0.83$). Compared with sham, the secondary BCVA outcomes favored the 2.0 mg OPT-302 group, with structural outcomes favoring both OPT-302 dosage groups. Adverse events (AEs) were similar across groups, with 16 (13.3%), 7 (5.6%), and 10 (8.3%) participants in the lower-dose, higher-dose, and sham groups, respectively, developing at least 1 serious AE. Two unrelated deaths both occurred in the sham arm.

Conclusions: Significantly superior vision gain was observed with OPT-302 2.0 mg combination therapy, versus standard of care, with favorable safety (ClinicalTrials.gov identifier: NCT03345082).

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In many developed nations, age-related macular degeneration (AMD) is the leading cause of blindness.[1] There are 2 types: a slowly progressive, atrophic (dry) form and a more acute neovascular (wet) form. Neovascular AMD (nAMD) occurs when new blood vessels, typically emanating from the choroid, break through the outer blood-retinal barrier into the macular neuroretina. Untreated, this macular or choroidal neovascularization (CNV) typically leads to macular edema, hemorrhage, and subsequent fibrosis, with severe and permanent loss of central vision that can greatly reduce quality of life.

Vascular endothelial growth factors (VEGFs) are the key drivers of CNV and vascular permeability. The VEGF family comprises 5 molecules: VEGF-A, B, C, and D and placental growth factor. The current standard of care comprises drugs that target VEGF-A (aflibercept, bevacizumab, brolucizumab, and ranibizumab), although aflibercept also targets VEGF-B and placental growth factor. Faricimab (targeting VEGF-A and angiopoietin-2) has also been approved in the United States, European Union, and elsewhere.[2,3]

The VEGF-A inhibitors offer outcomes that are better than natural history.[4–6] Vascular endothelial growth factor−A binds VEGF receptor (VEGFR)-1 and VEGFR-2, key receptors mediating its physiological and pathological effects. Vascular endothelial growth factor−C and D

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also bind and activate VEGFR-2, signaling for angiogenesis and vascular permeability independently of VEGF-A, and are the only known ligands for VEGFR-3 (Fig 1), which is involved in pathological angiogenesis and vascular permeability and is upregulated in nAMD.[7–9]

As ligands of both VEGFR-2 and VEGFR-3, VEGF-C and D induce vessel growth in several in vivo models.[10–13] Additionally, VEGF-C plays a critical role in the formation of the retinal vasculature[7] and is upregulated by inflammatory mediators that are implicated in the pathogenesis of nAMD,[14] and circulating levels are elevated in patients with nAMD.[15]

Suppression of VEGF-A results in compensatory upregulation of VEGF-C and D that may limit the efficacy of selective VEGF-A inhibition.[16–20] Compensatory upregulation of VEGF-C and D may explain why at least 45% of patients show some degree of resistance to VEGF-A inhibitors, failing to improve, maintain, or achieve optimal vision responses.[5,21–25] Coadministration of a therapy that suppresses VEGF-C and D has the potential to improve both short-term and long-term outcomes.

OPT-302 is a first-in-class, recombinant fusion protein "trap" molecule composed of the first 3 extracellular ligand binding domains of human VEGFR-3, fused to human immunoglobin G1 constant domain (hIgG1 Fc). It binds to and neutralizes the activity of VEGF-C and D by preventing ligand binding to the endogenous receptors VEGFR-2 and VEGFR-3 (Fig 1). It is highly specific for VEGF-C and D and does not bind VEGF-A.[26–28]

A phase 1, open-label safety study investigated ascending intravitreal doses of OPT-302 (with ranibizumab) for nAMD, followed by randomized dose expansion at the highest (2.0 mg) dose.[29] Treatments were administered monthly for 3 doses. At the week 12 outcome measure, OPT-302 demonstrated favorable safety with no dose-limiting toxicity in the 51 participants. In patients receiving OPT-302 and ranibizumab combination therapy, a mean gain of +10.8 ETDRS letters from baseline was observed in 18 treatment-naive participants and +4.9 ETDRS letters in 19 participants who had previously received anti−VEGF-A therapy.

This trial aimed to investigate the efficacy and safety of 2 different doses of OPT-302, administered in combination with ranibizumab, in patients with treatment-naive nAMD.

Methods

Study Design and Setting

This was a phase 2b, dose-ranging, parallel-group, double-masked, randomized, sham-controlled trial conducted in 109 ophthalmology clinics across Europe, Israel, and the United States. All participants provided written informed consent. The study was registered at ClinicalTrials.gov (NCT03345082), undertaken in accordance with the Declaration of Helsinki, with approval of the relevant institutional review board/research ethics committee. Lists of the principal investigators, study protocol, and statistical analysis plan are available in the Supplementary Protocol and Statistical Analysis Plan (SAP), (available at www.aaojournal.org).

Participants

The trial enrolled adults aged at least 50 years with treatment-naive, fovea-involving nAMD and a best-corrected visual acuity (BCVA) between 25 and 60 ETDRS letters (Snellen equivalent, 20/320 to 20/63). A complete list of eligibility criteria is in the Supplementary Appendix (Supplementary Protocol and Statistical Analysis Plan and Eligibility Criteria, available at www.aaojournal.org).

Randomization and Masking

Randomization was via an online interactive system (IXRS, Almac Clinical Technologies), using minimization for baseline angiographic lesion type (predominantly classic, minimally classic or occult), baseline BCVA (> 54 vs. ≤ 54 letters), and site. Randomization occurred in a 1:1:1 ratio into 3 groups receiving 6, 4-weekly, dual, sequential, intravitreal injections in the study eye. Study participants, assessing clinicians, reading center graders (the Digital Angiography Reading Center, New York, NY), and other outcome assessors were masked. Allocation was concealed by the aforementioned online randomization system. An unmasked clinician administered the intravitreal/sham injections and checked the postinjection intraocular pressure (IOP) and adverse events (AEs) but was otherwise uninvolved in the participants' care. The sham injection was administered using the same preparatory and safety procedures.

Procedures

The 0.5 mg OPT-302 group received intravitreal 0.5 mg OPT-302 (50 μl) plus intravitreal 0.5 mg ranibizumab (50 μL; Lucentis, Novartis, Genentech); the 2.0 mg OPT-302 group received intravitreal 2.0 mg OPT-302 (50 μl) plus intravitreal 0.5 mg ranibizumab (50 μl); and the sham group received a sham intravitreal injection plus intravitreal 0.5 mg ranibizumab (50 μl). The ranibizumab injection was delivered before the OPT-302/sham injection. The sham injection was delivered by pressing the syringe hub against the conjunctiva (further details are described in the Supplementary Protocol and Statistical Analysis Plan, available at www.aaojournal.org). Key ocular assessments included ETDRS BCVA, ocular examination, IOP, and spectral-domain OCT (SD-OCT), repeated 4-weekly. The National Eye Institute 25-item Visual Function Questionnaire (VFQ-25) was completed at baseline and week 24, with fluorescein angiography and color photography at baseline, week 12, and week 24 (Table S1, available at www.aaojournal.org).

Outcomes

The primary outcome measure was the mean change from baseline in ETDRS BCVA at week 24. Secondary efficacy outcomes (comparing baseline with week 24) were the proportion of participants gaining or losing ≥ 15 ETDRS BCVA letters; area under the ETDRS BCVA over time curve; change in SD-OCT central subfield thickness (CST); and change in intraretinal fluid and subretinal fluid on SD-OCT. Prespecified exploratory end points (week 24 vs. baseline) were the proportion of participants gaining or losing ≥ 5 and ≥ 10 ETDRS letters, angiographic lesion and total CNV area, and National Eye Institute VFQ-25 composite score.

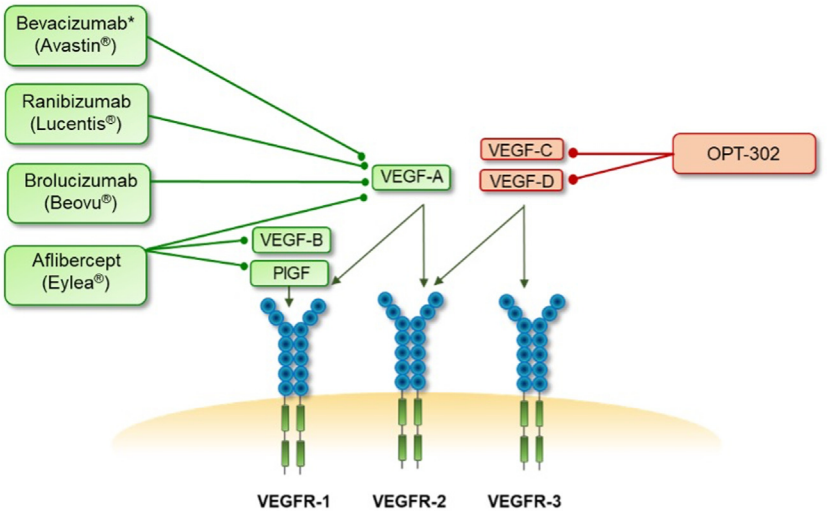

Figure 1. Members of the VEGF family and their binding specificity to VEGF receptors (VEGFRs), and the commonly used ophthalmic anti-VEGF agents. OPT-302 is a VEGF-C and D "trap" molecule, which sequesters VEGF-C and D and prevents their binding to VEGFRs 2 and 3. *Bevacizumab is used off-label in nAMD. PlGF = placental growth factor; VEGF = vascular endothelial growth factor.

Safety

The main safety outcomes were the incidence of ocular and non-ocular AEs, grouped by System Organ Class, identified using their Preferred Term (Medical Dictionary for Regulatory Activities, version 20.1), and graded from 1 to 5 according to National Institutes of Health Common Terminology Criteria for Adverse Events (version 4) or, for those AEs without a Common Terminology Criteria for Adverse Events grading, from mild to moderate, severe, life-threatening, or fatal. Other safety measures included loss of vision (as noted earlier), anterior chamber inflammation, vital signs, arteriothrombotic events, and clinical laboratory tests (routine hematology and biochemistry panels; urinalysis; anti−OPT-302 antibody [antidrug antibody, measured via a validated electrochemiluminescence assay]). Safety was monitored by an independent data safety and monitoring board.

Statistical Analysis

The primary analysis was the comparison of mean change in ETDRS BCVA between baseline and week 24 for each of the OPT-302 0.5 mg and 2.0 mg treatment groups, compared with sham, in the modified intent-to-treat (mITT) population. The mITT population comprised all randomized participants but excluded those who had not received at least 1 dose of either OPT-302 or ranibizumab, those without baseline BCVA, and those who did not have at least 1 postbaseline visit. Assuming 5% attrition, it was estimated that 351 participants (117 per arm) would provide 80% power to detect a 5-ETDRS letter difference between each of the OPT-302 groups and sham. The standard deviation (SD) was assumed to be 13 letters. A 5-ETDRS letter margin of difference between groups was chosen because this corresponds to 1 line on the ETDRS chart and is a commonly accepted threshold.[30,31] Significance testing was 1-sided, aiming to determine if OPT-302 plus ranibizumab is superior to sham plus ranibizumab. This was a pragmatic decision to facilitate a deliverable sample size and determined to be acceptable for a phase 2b study because the absence of a statistically significant benefit would mean the technology would not be taken forward for further trials. To preserve the error rate at $\alpha = 0.05$, multiple comparisons (i.e., pairwise comparisons of each 0.5 mg and 2 mg OPT-302 vs. sham for the primary efficacy outcome) were controlled using a Hochberg procedure. A mixed-effects model for repeated measures was used, which considered the presence of missing data and yielded valid estimates under the assumption of data missing at random (details in the statistical analysis plan, Supplementary Protocol and Statistical Analysis Plan, available at www.aaojournal.org). Secondary and exploratory end points were described using as-observed data. No adjustment (e.g., alpha adjustment or the widths of the 95% confidence interval [CI]) for multiple comparisons was made for secondary or exploratory end points, and the CIs were not intended to test hypotheses.[32] Safety analysis was undertaken in participants who received at least 1 dose of study medication, with the safety population defined by the drug given. Analysis was undertaken by the International Drug Development Institute, Louvain-la-Neuve, Belgium, using SAS (version 9.4) and R (version 3.5.0). The 95% CI provided describes the difference in treatment outcome compared with sham.

Role of Funding Source

The trial was wholly funded by Opthea Ltd (Victoria, Australia). Opthea designed and interpreted the trial data, with input from consultant clinical advisors (T.L.J., J.S., P.U.D., C.C.W., D.S.B.). Opthea partnered with 2 contract research organizations during the conduct of the study, with Pharmaceutical Product Development LLC (Wilmington, DE) to execute the study, and with International Drug Development Institute (Louvain-la-Neuve, Belgium) to undertake the data management and biostatistical analysis. Opthea (and the coauthors) provided critical review of the first draft manuscript (prepared by T.L.J.).

Results

Between December 2017 and November 2018, 366 participants were randomized, 365 participants were treated (safety population), and 348 participants (95%) completed the study to week 24 (Fig 2). Baseline characteristics are shown in Table 1. The mITT population comprised 362 participants. Baseline characteristics and attrition were well balanced across groups (Table 1).

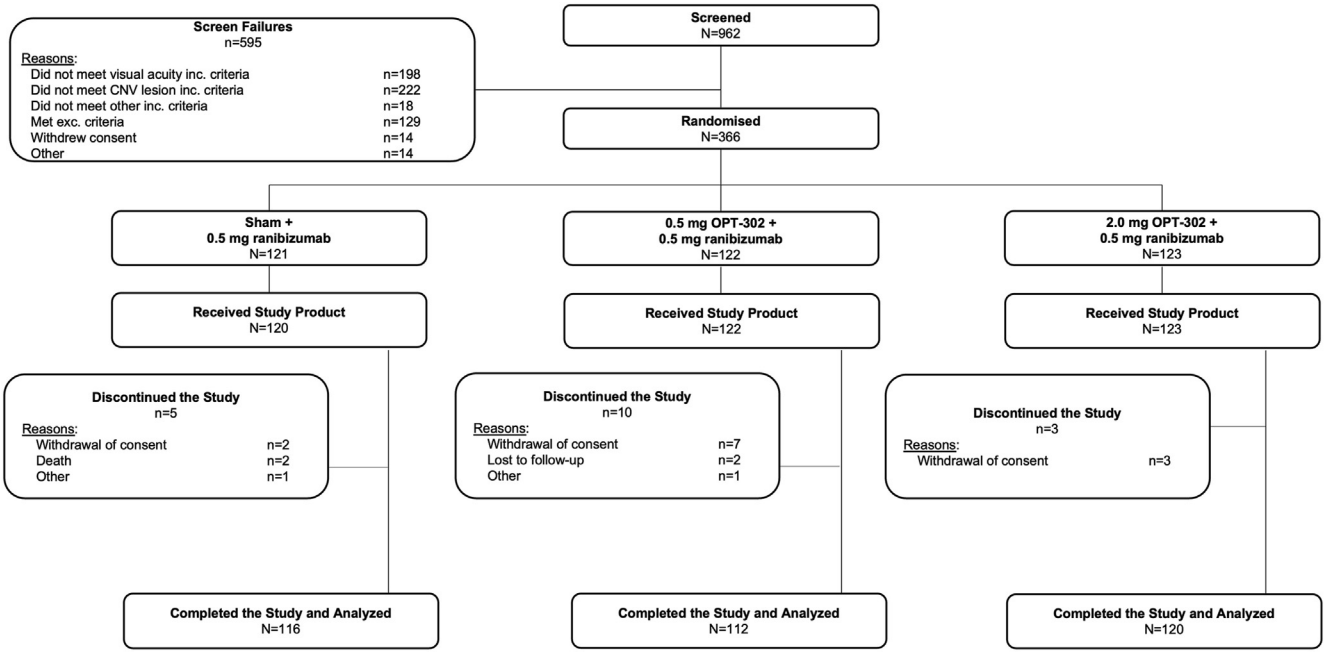

Figure 2. Trial profile. Consolidated Standards of Reporting Trials diagram detailing participant allocation and disposal. CNV = choroidal neovascular; exc. = exclusion; incl = inclusion; ran = 0.5 mg ranibizumab.

The study met the primary end point, with a statistically superior gain in mean (± SD) BCVA comparing the 2.0 mg OPT-302 with ranibizumab group to ranibizumab with sham (+14.2 ± 11.61 letters vs. +10.8 ± 11.52 letters, $P = 0.01$; Figure 3). There was no statistically significant difference between the 0.5 mg OPT-302 group and the sham group (+9.44 ± 11.32, $P = 0.83$; Figure S4; available at www.aaojournal.org).

The proportion of participants gaining ≥ 15 ETDRS BCVA letters was greatest in the 2.0 mg OPT-302 group (45.0%; 95% CI of the difference vs. sham, −8 to 17), followed by the sham (40.5%) and 0.5 mg (33.0%; 95% CI, −20 to 5) groups (Table 2). The proportions losing ≥ 15 letters were 3.4%, 5.4% (95% CI, −3 to 7), and 0.8% (95% CI, −6 to 1) in the sham, 0.5 mg, and 2.0 mg groups, respectively. The mean area (± SD) under the ETDRS

Table 1. Demographics and Baseline Disease Characteristics

Baseline Variable	Sham + 0.5 mg Ranibizumab (n = 121)	0.5 mg OPT-302 + 0.5 mg Ranibizumab (n = 120)	2.0 mg OPT-302 + 0.5 mg Ranibizumab (n = 124)	Total (n = 366)
Sex				
Male	48 (39.7%)	49 (40.2%)	45 (36.6%)	142 (38.8%)
Female	73 (60.3%)	73 (59.8%)	78 (63.4%)	224 (61.2%)
Mean age, yrs (SD)	76.1 (9.48)	78.8 (8.16)	77.8 (8.82)	77.6 (8.88)
Race, n (%)				
Missing (n)	3	2	3	8
N	118	120	120	358
White	117 (99.2%)	119 (99.2%)	117 (97.5%)	353 (98.6%)
Other	1 (0.8%)	1 (0.8%)	3 (2.5%)	5 (1.4%)
Study eye				
Mean ETDRS BCVA, letters (SD)	50.7 (10.21)	51.1 (8.96)	49.5 (10.26)	50.4 (9.83)
Mean CST, μm (SD)	412 (111)	425 (120)	414 (123)	417 (118)
Lesion subtype, n (%)				
Predominantly classic	15 (12.4%)	15 (12.3%)	16 (13.0%)	46 (12.6%)
Minimally classic	53 (43.8%)	51 (41.8%)	53 (43.1%)	157 (42.9%)
Occult	54 (43.8%)	56 (45.9%)	54 (43.9%)	163 (44.5%)
RAP	15 (12.7%)	22 (18.5%)	14 (11.8%)	51 (14.3%)
PCV	20 (16.5%)	24 (19.7%)	22 (17.9%)	66 (18.0%)
Mean total lesion area, mm^2 (SD)	6.08 (3.21)	6.48 (3.30)	6.62 (3.39)	6.39 (3.30)

BCVA = best-corrected visual acuity; CST = central subfield thickness; PCV = idiopathic polypoidal choroidal vasculopathy; RAP = retinal angiomatous proliferation; SD = standard deviation.

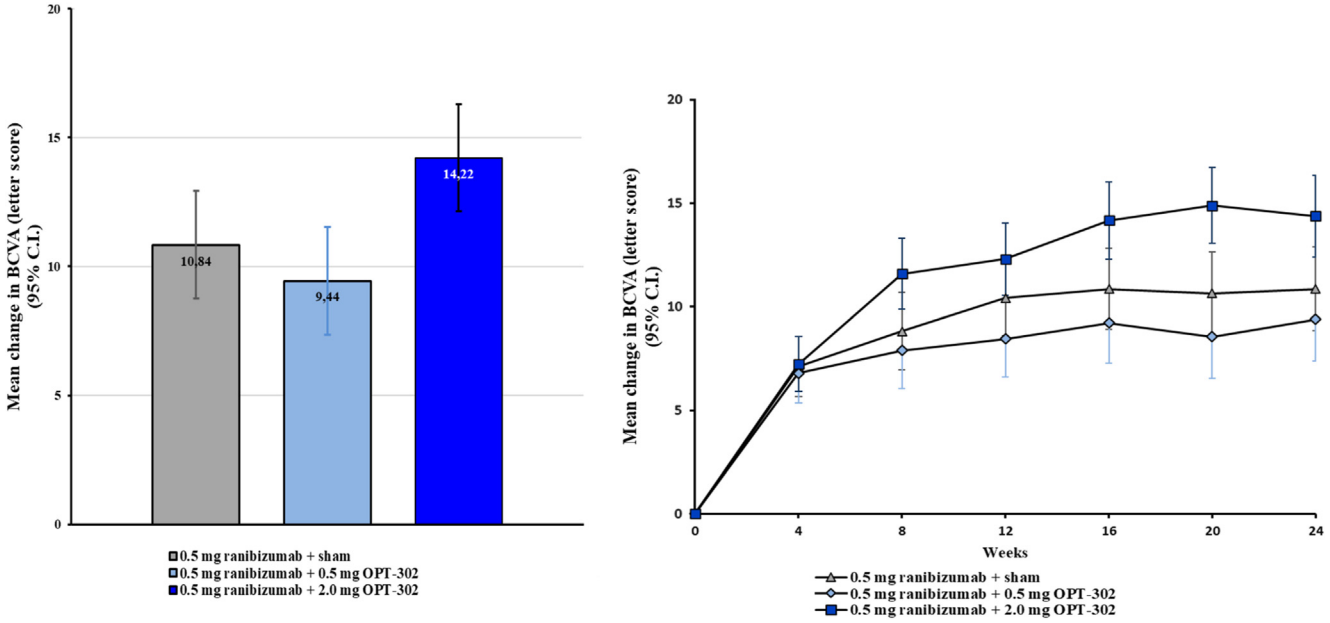

Figure 3. Mean change in best-corrected visual acuity (BCVA). **Bar-chart left**, Least-square-mean (± standard error of the mean) change in BCVA from baseline at week 24. **Graph right**, Mean change in BCVA (± 95% confidence interval [CI]) from baseline over time.

BCVA over-time curve was similar across groups: 59.3 ± 13.6, 58.6 ± 13.3 (95% CI, −3.73 to 1.69), and 60.4 ± 12.8 (95% CI, −1.79 to 3.63) letters in the sham, 0.5 mg, and 2.0 mg groups, respectively (the difference between groups appears smaller than the BCVA outcomes for 2 reasons: first, the area under the curve summates the BCVA at multiple time points over time, including time points when the difference between groups had yet to emerge, and second, because it describes the mean BCVA rather than change in BCVA).

The mean (± SD) decrease in OCT CST was similar in the 0.5 mg (−147.8 ± 113.8 μm; 95% CI, −42.04 to 12.33) and 2.0 mg groups (−146.7 ± 110.8 μm; 95% CI, −39.77 to 13.77), both of which were greater than in the sham group (−133.8 ± 97.5 μm) (Fig 4).

The proportion of participants with subretinal fluid present at week 24 was lowest in the 2.0 mg group (18.5%; 95% CI, −22.0 to 0), followed by the 0.5 mg OPT-302 group (23.2%; 95% CI, −17 to 5) and the sham group (29.3%). Likewise, the proportion of participants with intraretinal cysts present at week 24 was lowest in the 2.0 mg group (16.8%; 95% CI, −15 to 5), followed by the 0.5 mg group (19.6%; 95% CI, −12 to 9) and the sham group (21.6%) (Table 2).

The prespecified exploratory end points were supportive of the primary and secondary outcomes (Table 2). For example, the proportion of participants gaining ≥ 10 letters was greater in the 2.0 mg OPT-302 group than in the sham group at 70.0% (95% CI, 0.1−24) versus 57.8%, and the proportion of those in the 2.0 mg group losing ≥10 letters was smaller than in the sham group at 0.8% (95% CI, −10 to −1) versus 6%. Likewise, the mean improvement in VFQ-25 composite score was greater in the 2.0 mg OPT-302 group (4.2, SD, 8.88; 95% CI, −1.43 to 3.63) than in the sham group (3.10, SD, 10.82) at week 24 (Table 2). The angiographic measures favored both OPT-302 groups, with a dose response. Compared with the sham group, there was a 24% (−4.45 vs. −3.60, 95% CI, −1.85 to 0.11) and 38% (−4.96 vs. −3.60, CI, −2.36 to −0.41) greater reduction in mean CNV area (mm^2) and a 36% (−4.23 vs. −3.11, CI, −2.11 to −0.14) and 39% (−4.33 vs. −3.11, CI, −2.22 to −0.26) greater reduction in total lesion area (mm^2) in the 0.5 mg and 2.0 mg OPT-302 groups, respectively (Table 2).

There were no safety concerns with either dose of OPT-302 (Table 3). Study eye AEs were similar across the 3 groups, including those considered related to OPT-302 or ranibizumab (Table S2, available at www.aaojournal.org). As expected, there were slightly more ocular AEs considered related to the injection procedure in the 0.5 mg and 2.0 mg OPT-302 groups (28.3% and 29.8%) versus sham (24.8%). The most frequently reported study eye AEs assessed by the investigator as possibly, probably, or definitely related to either ranibizumab or OPT-302 were clinically minor, namely, eye pain, conjunctival hemorrhage, vitreous floaters, eye irritation, foreign body sensation in eyes, lacrimation increased, and increased IOP (Table S3, available at www.aaojournal.org). There was no obvious dose-related increase in related AEs.

There were 2 study eye serious AEs, endophthalmitis and vitritis, which were both in the 0.5 mg OPT-302 group and considered potentially related to ranibizumab or 0.5 mg OPT-302 (Table 3).

Two participants (0.5%) had study eye AEs leading to discontinuation of the study product (Table S2 and Table S3, available at www.aaojournal.org). The incidence of intraocular inflammation, defined before unmasking, was low, with no dose relationship (1.7% in both the sham and OPT-302 0.5 mg groups, 0.8% for OPT-302 2.0 mg; Table 3).

Laboratory data and vital signs identified no safety concerns, and there was no evidence of treatment-emergent antidrug antibody. Two participants died, both in the sham group: 1 of endocarditis and 1 of pneumonia. Neither death was considered related to the study product. The single Anti-Platelet Trialists' Collaboration event was the only nonocular serious AE considered potentially related to ranibizumab or OPT-302, a nonfatal myocardial infarction in the 0.5 mg group.

Table 2. Secondary and Prespecified Exploratory End Points from Baseline to Week 24

Variables	Sham + 0.5 mg Ranibizumab (n = 119)	0.5 mg OPT-302 + 0.5 mg Ranibizumab (n = 122)	2.0 mg OPT-302 + 0.5 mg Ranibizumab (n = 121)
No. of patients, n (proportion, %) [95% CI of difference vs. sham]*			
Vision gain ≥ 15 letters	47/116 (40.5%)	37/112 (33.0%) −7.5% [−20 to 5]	54/120 (45.0%) 4.5% [−8 to 17]
Vision gain of ≥ 10 letters	67/116 (57.8%)	62/112 (55.4%) −2.4% [−15 to 10]	84/120 (70.0%) 12.2% [0.1−24]
Vision gain of ≥ 5 letters	88/116 (75.9%)	80/112 (71.4%) −4.5% [−16 to 7]	102/120 (85.0%) 9.1% [−1 to 19]
Vision loss of ≥ 5 letters	8/116 (6.9%)	10/112 (8.9%) 2% [−5 to 9]	5/120 (4.2%) −2.7% [−9 to 3]
Vision loss of ≥ 10 letters	7/116 (6.0%)	9/112 (8.0%) 2% [−5 to 9]	1/120 (0.8%) −5.2% [−10 to −1]
Vision loss of ≥ 15 letters	4/116 (3.4%)	6/112 (5.4%) 2% [−3 to 7]	1/120 (0.8%) −2.6% [−6 to 1]
Subretinal fluid present (%)	34/116 (29.3)	26/112 (23.2) −6% [−17 to 5]	22/119 (18.5) −10.8% [−22 to 0]
Intraretinal cysts present (%)	25/116 (21.6)	22/112 (19.6) −2% [−12 to 9]	20/119 (16.8) −4.8% [−15 to 5]
Means (SD) [95% CI of difference vs. sham]†			
Area under the ETDRS BCVA over-time curve letters	59.34 (13.59)	58.56 (13.30) −1.02 [−3.73 to 1.69]	60.41 (12.78) 0.92 [−1.79 to 3.63]
Mean change in NEI VFQ-25 composite score‡	3.1 (10.82)	2.2 (10.44) −0.90 [−3.66 to 1.86]	4.2 (8.88) 1.10 [−1.43 to 3.63]
Mean change in CST (μm)	−133.8 (97.51)	−147.8 (113.77) −14.9 [−42.04 to 12.33]	−146.7 (110.80) −13.0 [−39.77 to 13.77]
Mean change in total lesion area (mm^2)	−3.11 (4.42)	−4.23 (3.90) −1.13 [−2.11 to −0.14]	−4.33 (3.27) −1.24 [−2.22 to −0.26]
Mean change in CNV area (mm^2)	−3.60 (4.00)	−4.45 (3.99) −0.88 [−1.85 to 0.11]	−4.96 (3.51) −1.40 [−2.36 to −0.41]

BCVA = best-corrected visual acuity; CI = confidence interval; CNV = choroidal neovascularization; CST = central subfield thickness; NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; SD = standard deviation.
*Based on observed data, that is, patients with nonmissing values.
†Difference in least square means adjusted for stratification factors.
‡Unadjusted for stratification factors.

Discussion

This phase 2b trial demonstrated that the addition of 2.0 mg OPT-302 to a standard-of-care treatment (ranibizumab) in participants with nAMD achieves superior gains in visual acuity compared with standard of care alone. Given the high prevalence of nAMD and its substantial impact on vision, the prospect of improved vision outcomes could have a significant impact on a patient's quality of life. A dose response was observed, with overall trends toward better anatomic and vision outcomes in the 2.0 mg OPT-302 group than in the 0.5 mg OPT-302 group.

Several new intravitreal nAMD treatments are under investigation, including biosimilars, new VEGF-A inhibitors, drugs with new modes of action, and bispecific molecules. All of these treatments in human trials are being tested for noninferior visual acuity compared with anti−VEGF-A therapy, aiming for less frequent dosing or reduced cost. We are not aware of another intravitreal treatment currently in clinical development that has shown superiority over anti−VEGF-A therapy in nAMD, which is particularly relevant to a large number of patients who experience insufficient clinical response despite regular anti−VEGF-A therapy. Notwithstanding the clinical relevance of reduced dosing and reduced cost, many patients' key aim is to preserve or improve their vision, and a drug that has the potential to provide the best visual outcomes would have considerable clinical utility.

The mean gain in visual acuity was 14.22 letters in the 2.0 mg OPT-302 group compared with 10.84 letters in sham. This 3.4 letter difference is driven by a range of responses, including many patients with substantially higher vision gains. For example, the proportion of participants gaining 10 or more letters was greater in the 2.0 mg OPT-302 group than in the sham group, at 70.0% versus 57.8% (95% CI of the difference vs. sham, 0.1−24), combined with a reduced likelihood of losing 10 or more letters (0.8% vs. 6.0%; 95% CI of difference vs. sham, −10 to −1; Table 2).

Although there are differences in eligibility criteria (e.g., differing BCVA requirements), dosing regimens, and follow-up between studies, the vision gain of +14.2 letters

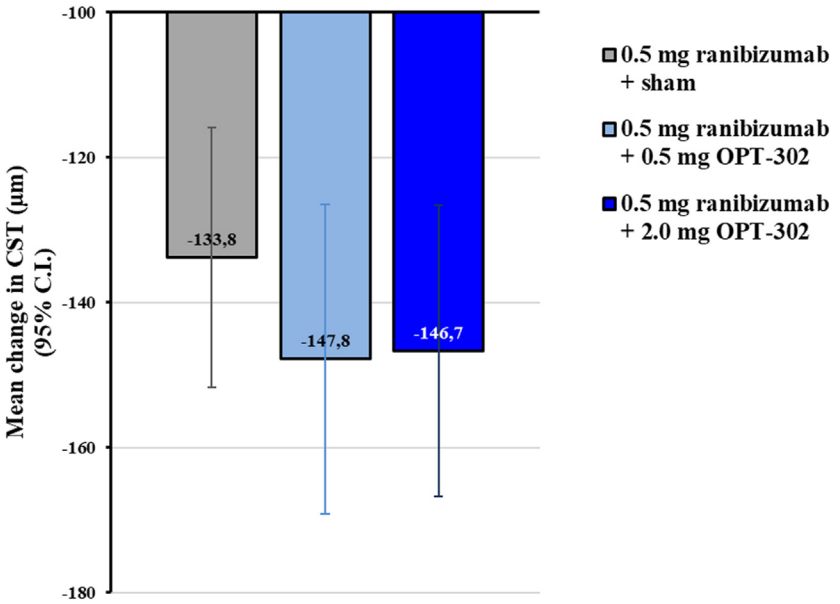

Figure 4. Mean change in central subfield thickness (CST). Mean (± standard error of the mean) change from baseline in spectral-domain OCT central subfield at the predefined 24-week end point. CI = confidence interval.

in the 2.0 mg OPT-302 group compares favorably to +6.1 to +10.9 letter gains observed at 12 months in the registration studies for intravitreal anti−VEGF-A therapies.[5,6,24,33,34]

Vision gains in the higher dose OPT-302 group were supported by anatomic improvements in both OPT-302 treatment groups compared with sham. Although CST was almost normalized in all treatment groups, making it

Table 3. Adverse Events and Anterior Chamber Activity: Safety Population

Variable	Sham + 0.5 mg Ranibizumab (n = 121)	0.5 mg OPT-302 + 0.5 mg Ranibizumab (n = 120)	2.0 mg OPT-302 + 0.5 mg Ranibizumab (n = 124)
No. of participants with at least 1 SAE (%) [no. of events]	10 (8.3%) [14]	16 (13.3%) [23]	7 (5.6%) [9]
Ocular SAEs in study eye	0 (0.0%)	2 (1.7%)	0 (0.0%)
Endophthalmitis	0 (0.0%)	1 (0.8%)	0 (0.0%)
Vitritis	0 (0.0%)	1 (0.8%)	0 (0.0%)
Other SAEs by MedDRA System Organ Class*			
Ocular SAEs: Nonstudy eye	0 (0.0%)	1 (0.8%)	0 (0.0%)
Cardiac disorders	2 (1.7%)	4 (3.3%)	4 (3.2%)
Infections and infestations	4 (3.3%)	1 (0.8%)	2 (1.6%)
Gastrointestinal disorders	1 (0.8%)	4 (3.3%)	0 (0.0%)
Neoplasms	2 (1.7%)	2 (1.7%)	0 (0.0%)
Any APTC event			
Nonfatal myocardial infarction	0 (0.0%)	1 (0.8%)	0 (0.0%)
Death	2 (1.7%)	0	0
Intraocular inflammation†	2‡ (1.7%)	2§ (1.7%)	1‡ (0.8%)
Maximum anterior chamber cells			
None	118 (98.3%)	119 (99.2%)	121 (99.2%)
Trace (1−4 cells)	2‡,‖ (1.7%)	0 (0.0%)	1‡ (0.8%)
1+ (5−10 cells)	0 (0.0%)	1¶ (0.8%)	0 (0.0%)
≥ 2+ (> 10 cells)	0 (0.0%)	0 (0.0%)	0 (0.0%)

APTC = Anti-Platelet Trialists' Collaboration; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
*All SAEs, with nonocular system organ classes presented with incidence of > 3 participants overall.
†Intraocular inflammation in the study eye defined before unmasking: anterior chamber cell, endophthalmitis, hypopyon, iridocyclitis, iritis, uveitis, viral iritis, and vitritis.
‡Transient observation of trace (1−4) anterior chamber cell at 1 visit for each participant, not observed at subsequent visits.
§Serious adverse event of vitritis in 1 participant; SAE of endophthalmitis with nonserious hypopyon and anterior chamber cell (+1) in second participant.
‖Not reported as treatment-emergent adverse event.
¶Associated with SAE of endophthalmitis.

difficult to detect a difference, a greater reduction in CST was observed in the OPT-302 treatment groups, with better retinal drying. It is not clear why the anatomic improvements in the lower-dose OPT-302 group did not translate to superior vision gains versus control. This could be a chance finding, but anatomic changes do sometimes precede vision gain, and it is possible that a difference may emerge with time. Another possibility, although speculative, is that the small differences in the baseline characteristics between the lower-dose OPT-302 group and sham group reduced the relative vision benefits of 0.5 mg OPT-302 (or increased the OCT benefits). For example, participants in the lower-dose OPT-302 group were slightly older (2.7 years), with marginally better BCVA (0.4 letters) and slightly greater CST (13 μm), and had a greater proportion of retinal angiomatous proliferation (5.9% more) lesions than the sham group (Table 1). However, consistent with the randomized design, the groups were generally well matched, and these differences are small, such that they might not be expected to produce a large biological effect. It is possible that OCT is more sensitive at detecting a benefit than BCVA, which varies considerably within and between individuals, making it harder to detect a difference. A positive dose response supports the hypothesis that OPT-302 is producing a biological response, but the impact of treatment on vision needs to be further elucidated in future trials.

Safety was similar across groups, with no suggestion of any ocular or systemic safety concerns with the addition of OPT-302. There was a greater incidence of short-term IOP elevation in the 0.5 mg OPT-302 (5.8%) and 2.0 mg OPT-302 (4.8%) combination groups than in the sham group (1.7%). This is unsurprising, given the extra fluid volume injected in the OPT-302 combination groups. All cases resolved without sequelae. A post hoc analysis showed that few patients required IOP-lowering therapies for >5 days—1 patient (0.8%) in the 0.5 mg and 2 patients (1.6%) in the 2.0 mg OPT-302 combination groups, respectively. Otherwise, there was no increase in drug-related AEs comparing either OPT-302 group with the sham group, nor did the higher-dose OPT-302 increase AEs versus the lower-dose OPT-302. Of note, there was no evidence of increased intraocular inflammation compared with sham, despite the prospective evaluation of anterior chamber cellular activity.

The strengths of this study include its randomized, double-masked, sham-controlled design. Recruitment of 366 participants from 109 centers across Europe, Israel, and the United States enhances the generalizability of the results. Participant compliance and data completeness were high. A statistically superior result against intensive anti−VEGF-A therapy is an ambitious aim that few studies attempt and achieve.

Study Limitations

Limitations of this phase 2b study include the 6-month study duration. Longer studies are required to determine if these vision benefits are maintained and to establish long-term safety and are incorporated in a recently commenced phase 3 program (ClinicalTrials.gov identifier: NCT04757636 and NCT04757610). It is not known if OPT-302 coadministration with other anti−VEGF-A treatments would produce similar results, including aflibercept, bevacizumab, or brolucizumab, but on biological principles, one might expect similar results (Fig 1). Reduced disease activity from combined OPT-302/ranibizumab treatment might facilitate increased dosing intervals, but this hypothesis was not tested.

Conclusions

Vascular endothelial growth factor−C and D inhibition with 2.0 mg OPT-302 in combination with VEGF-A blockade achieves superior vision gains compared with the current standard of care for nAMD, with anatomic benefits and a favorable safety profile.

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Data collection: Gerometta, Price

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Abbreviations and Acronyms:
AE = adverse event; **AMD** = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **CNV** = choroidal neovascularization; **CST** = central subfield thickness; **IOP** = intraocular pressure; **mITT** = modified intent-to-treat; **nAMD** = neovascular age-related macular degeneration; **SD** = standard deviation; **SD-OCT** = spectral-domain OCT; **VEGF** = vascular endothelial growth factor; **VEGFR** = VEGF receptor; **VFQ-25** = 25-item Visual Function Questionnaire.

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