AMERICAN ACADEMY OF OPHTHALMOLOGY®

Simultaneous Inhibition of Angiopoietin-2 and Vascular Endothelial Growth Factor-A with Faricimab in Diabetic Macular Edema

BOULEVARD Phase 2 Randomized Trial

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Purpose: The phase 2 BOULEVARD trial compared safety and efficacy of faricimab, a novel bispecific antibody targeting angiopoietin-2 and vascular endothelial growth factor-A (VEGF-A), with ranibizumab in patients with diabetic macular edema (DME).

Design: The BOULEVARD trial (ClinicalTrials.gov identifier, NCT02699450) was a prospective, randomized, active comparator-controlled, double-masked, multicenter, phase 2 study conducted at 59 sites in the United States.

Participants: The trial enrolled patients 18 years of age or older with center-involving DME, best-corrected visual acuity (BCVA) of 73 to 24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, and central subfield thickness (CST) of 325 μm or more.

Methods: Anti-VEGF treatment-naïve patients were randomized 1:1:1 to intravitreal 6.0 mg faricimab, 1.5 mg faricimab, or 0.3 mg ranibizumab, and patients previously treated with anti-VEGF were randomized 1:1 to 6.0 mg faricimab or 0.3 mg ranibizumab. Patients were dosed monthly for 20 weeks, followed by an observation period up to week 36 to assess durability.

Main Outcome Measures: The prespecified primary outcome measure was mean change in BCVA from baseline at week 24 for faricimab versus ranibizumab in treatment-naïve patients. Key secondary and exploratory outcome measures included CST, Diabetic Retinopathy Severity Scale (DRSS) score, and durability as assessed by time to re-treatment.

Results: The trial enrolled 229 patients (168 treatment-naïve and 61 previously treated with anti-VEGF). In treatment-naïve patients, 6.0 mg faricimab, 1.5 mg faricimab, and 0.3 mg ranibizumab resulted in mean improvements of 13.9, 11.7, and 10.3 ETDRS letters from baseline, respectively. The 6.0-mg faricimab dose demonstrated a statistically significant gain of 3.6 letters over ranibizumab ($P = 0.03$). In both patient populations, faricimab resulted in dose-dependent reductions in CST, improvements in DRSS score, and longer time to re-treatment during the observation period compared with ranibizumab. Faricimab showed no new or unexpected safety signals.

Conclusions: The BOULEVARD trial met its primary end point; faricimab demonstrated statistically superior visual acuity gains versus ranibizumab at week 24 in treatment-naïve patients. Central subfield thickness reduction, DRSS score improvement, and extended durability outcomes support the primary outcome. These findings suggest the benefit of simultaneous inhibition of angiopoietin-2 and VEGF-A with faricimab for patients with DME. *Ophthalmology 2019;126:1155-1170 © 2019 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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With the increase in global prevalence of diabetes, the prevalence of diabetic eye diseases also is expected to grow.[1–3] Diabetic retinopathy (DR) is one of the most common microvascular complications of diabetes[4,5] and the leading global cause of vision loss in working-age adults.[2,3,6] Diabetic macular edema (DME), an advanced manifestation of DR, is responsible for most of the vision loss experienced by patients living with diabetes.[7,8]

Anti–vascular endothelial growth factor (anti-VEGF) treatment, the current standard of care for DME,[9–12]

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primarily targets a single pathway to reduce blood vessel leakage and proliferation. However, DME is a multifactorial disease involving other angiogenic factors and inflammatory pathways that are not addressed with anti-VEGF monotherapy.[4,13] In addition, real-world data suggest that in many cases, patients do not receive optimal dosing frequency or achieve optimal visual outcomes,[14–16] highlighting the need for therapies that can improve vision outcomes and reduce treatment burden through extended durability.

The angiopoietin (Ang)–tyrosine kinase with immunoglobulin-like domains (Tie) signaling pathway regulates vascular homeostasis and controls vessel permeability, inflammation, and angiogenic responses.[17–21] The growth factors angiopoietin 1 and 2 (Ang-1) and (Ang-2) interact with the transmembrane receptor tyrosine kinase (Tie2), which is expressed in vascular endothelium.[19,22] Activation of Tie2 signaling with Ang-1 promotes vascular stability and barrier function of new and established vessels, which facilitate pericyte recruitment and inhibit vascular permeability induced by inflammatory cytokines.[20,21] Under conditions such as hypoxia,[23] hyperglycemia,[24–26] or oxidative stress,[27] Ang-2 levels are upregulated. Ang-2 competitively binds to Tie2 and inhibits Ang-1 signaling, leading to endothelial and vascular destabilization,[17,21] breakdown of the blood–retinal barrier,[17,21] and inflammation.[18,21,28] The presence of VEGF further promotes vessel permeability, leading to leakage and neovascularization.[21,29] Blocking Ang-2 may stabilize the vasculature by preventing pericyte loss[30] and inhibiting Ang-2/integrin receptor–mediated endothelial tip cell sprouting.[31] Therefore, we hypothesized that simultaneously targeting both the Ang-2–Tie2 and VEGF pathways for the treatment of DME could provide improved efficacy and durability outcomes.[32,33]

Faricimab (previously RG7716) is a novel anti–Ang-2/anti-VEGF bispecific antibody specifically designed for intraocular use.[32,33] It is assembled using Roche's CrossMAb technology (Basel, Switzerland) and binds both VEGF-A and Ang-2 with high affinity and specificity (Fig 1).[32,34] The fragment crystallizable (Fc) region of faricimab has been engineered to abolish binding interactions to Fc ϒR and Fc Rn for reduced effector function and faster systemic clearance.[32] In a phase 1 study of patients with treatment-refractory neovascular age-related macular degeneration, faricimab showed no new or unexpected safety signals and demonstrated a preliminary efficacy signal, supporting evaluation in both neovascular age-related macular degeneration and DME.[35] The efficacy and safety of faricimab in patients with DME was evaluated in the phase 2 BOULEVARD clinical trial, and outcomes through week 36 are presented herein.

Methods

The BOULEVARD trial (ClinicalTrials.gov identifier, NCT02699450) was a 36-week, multicenter, randomized, active comparator–controlled, double-masked, phase 2 clinical trial that took place at 59 sites in the United States (Fig 2A). All participants provided written informed consent, and the study protocol was approved by institutional review boards before study start (institutional review boards and ethics committees: Quorum Review IRB; Beetham Eye Institute, Joslin Diabetes Center, Joslin Committee on Human Studies; Western Institutional Review Board WIRB Panel 7; Cleveland Clinic Florida, Cleveland Clinic Institutional Review Board; University of Virginia Institutional Review Board for Health Sciences Research; Chesapeake Research Review IRB; Johns Hopkins Medicine Institutional Review Board; UNM Human Research Review Committee; Weill Cornell Med Center IRB; Sterling IRB). The study adhered to the tenets of the Declaration of Helsinki and was conducted in accordance with Good Clinical Practice (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E6); applicable United States Food and Drug Administration regulations; applicable local, state, and federal laws; and the Health Insurance Portability and Accountability Act.

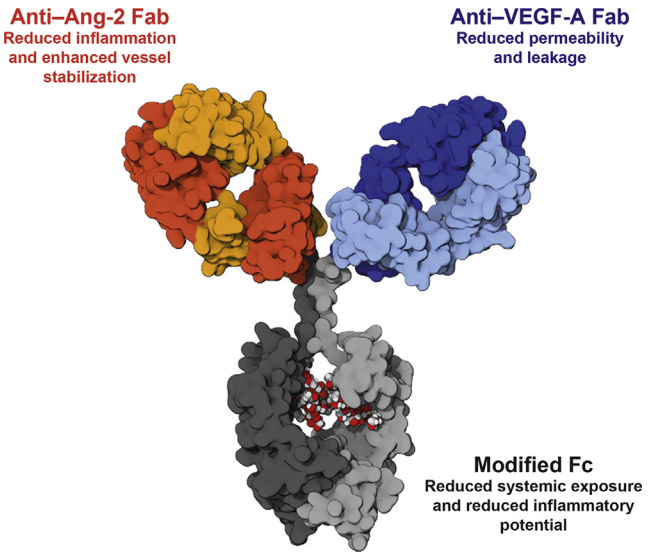

Figure 1. CrossMAb molecule representative of faricimab. Red represents the anti–angiopoietin-2 (Ang-2) fragment antigen binding (Fab) and blue represents the anti–vascular endothelial growth factor-A (VEGF-A) Fab. The modified fragment crystallizable (Fc) portion is shown in gray.

Study Population

The BOULEVARD key inclusion criteria were patients 18 years of age or older with center-involving DME, central subfield thickness (CST) of 325 μm or more measured with the Spectralis OCT device (Heidelberg Engineering, Inc., Heidelberg, Germany), and best-corrected visual acuity (BCVA) of 73 to 24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent, 20/40–20/320). Key initial exclusion criteria were high-risk proliferative DR, prior panretinal photocoagulation, macular laser photocoagulation within 3 months of the start of the study, any history of Iluvien (Alimera Sciences, Inc., Alpharetta, GA) or Ozurdex (Allergan plc, Dublin, Ireland) implants, and any history of anti-VEGF treatment. Eligibility was determined by a central reading center (Digital Angiography Reading Center, Great Neck, NY). Per a protocol amendment, patients who previously received anti-VEGF treatment were enrolled as a separate population from anti-VEGF treatment-naïve patients to enable the exploratory evaluation of faricimab efficacy in this population. However, in this population, the last anti-VEGF treatment was more than 3 months from the start of the study. Full inclusion and exclusion criteria are provided in Table S1 (available at www.aaojournal.org).

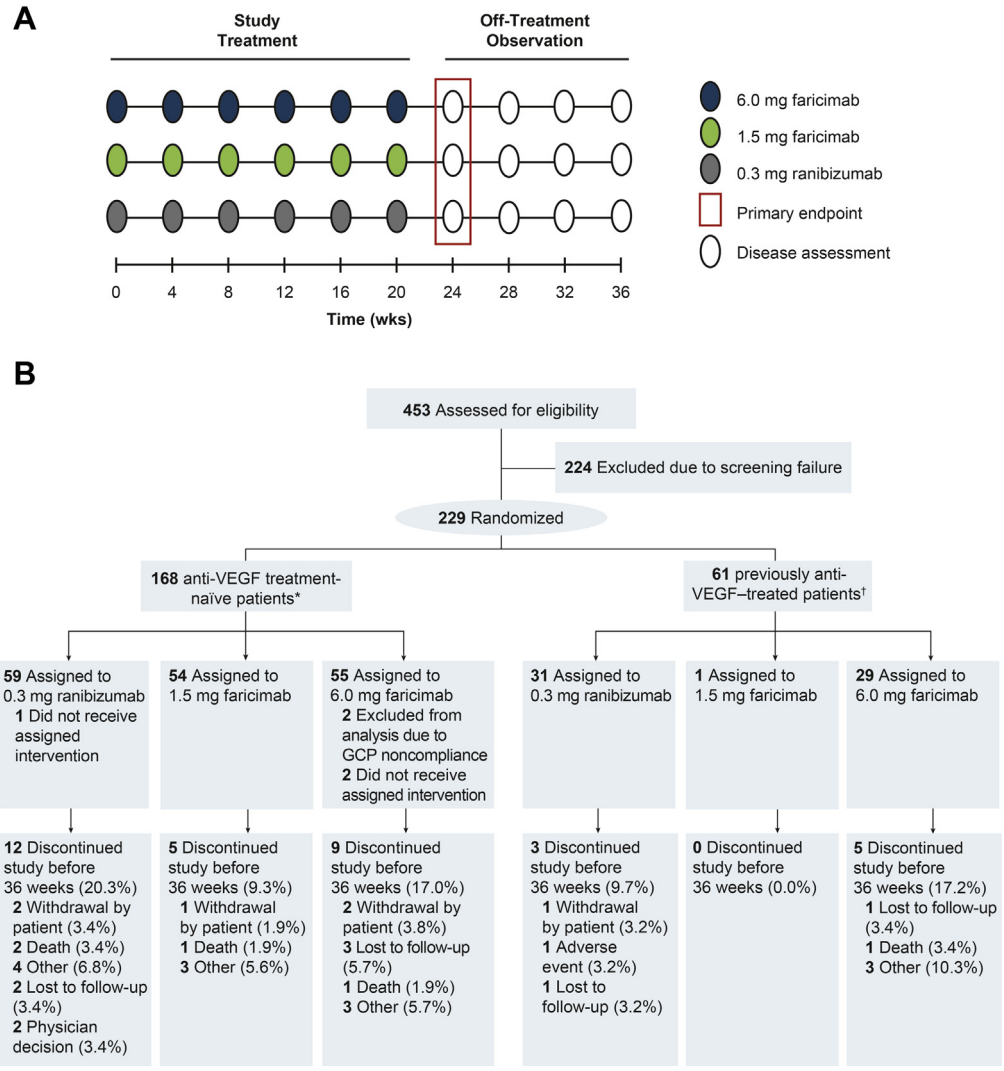

Figure 2. **A**, Diagram showing BOULEVARD study design. **B**, Flow diagram of participants. *Included in primary analysis (intention-to-treat [ITT] population): all patients, N = 166; 0.3-mg ranibizumab arm, n = 59; 1.5-mg faricimab arm, n = 54; 6.0-mg faricimab arm, n = 53. †Included in primary analysis (ITT population): all patients, N = 60; 0.3-mg ranibizumab arm, n = 31; 1.5-mg faricimab arm, n = 0; 6.0-mg faricimab arm, n = 29. GCP = Good Clinical Practice; VEGF = vascular endothelial growth factor.

Randomization

Patients were randomized through the IxRS interactive voice and web response system. Treatment-naïve patients were randomized 1:1:1 to receive 6.0 mg faricimab, 1.5 mg faricimab, or 0.3 mg ranibizumab. Previously anti-VEGF–treated patients were randomized 1:1 into the 6.0-mg faricimab or 0.3-mg ranibizumab treatment arms. Randomization was stratified based on baseline BCVA (ETDRS letter score, 64 letters or better vs. 63 letters or worse), previous macular laser treatment status, and previous intravitreal anti-VEGF treatment in the study eye.

Study Treatments and Assessments

The BOULEVARD trial consisted of a treatment period to week 20, followed by an off-treatment observation period up to week 36. The primary end point was at week 24 (Fig 2A). Only 1 eye was selected as the study eye; if both eyes met eligibility criteria, the eye with worse BCVA was defined as the study eye.

Starting on day 1, patients underwent treatment every 4 weeks for 20 weeks with 6.0 mg faricimab, 1.5 mg faricimab, or 0.3 mg ranibizumab. The dose of 6.0 mg faricimab is the maximum feasible dose that can be administered in a single 50-μl intravitreal injection and is 4 times the molar dose of 0.5 mg ranibizumab. The dose of 1.5 mg faricimab has a similar molar VEGF dose as 0.5 mg ranibizumab, allowing an assessment of the additional Ang-2 inhibition. The dose of 0.3 mg ranibizumab every 4 weeks for the active comparator is the approved dose for patients with DME in the United States, where the trial was conducted.[9,36]

During the off-treatment observation period, patients were evaluated every 4 weeks for time to re-treatment as assessed by BCVA and CST measurements. Patients received a single dose of 0.3 mg ranibizumab and exited the study if both of the following prespecified re-treatment criteria were met: BCVA decreased by 5 or more ETDRS letters due to DME in the opinion of the investigator and CST increased by 50 μm or more. Best-corrected visual acuity and CST values from week 24 were compared with those at week 20. Best-corrected visual acuity and CST values at weeks 28, 32, and 36 were compared with those at week 24.

Table 2. Baseline Patient Demographics and Ocular Characteristics

Characteristic	0.3 mg Ranibizumab	1.5 mg Faricimab	6.0 mg Faricimab	All Patients
Anti-VEGF treatment-naïve patients	**n = 59**	**n = 54**	**n = 53**	**N = 166**
Age (yrs), mean (SD)	61.6 (9.5)	61.4 (7.7)	60.5 (9.1)	61.2 (8.8)
Male, no. (%)	37 (62.7)	19 (35.2)	33 (62.3)	89 (53.6)
Race, no. (%)				
American Indian or Alaska native	0	0	2 (3.8)	2 (1.2)
Asian	0	0	1 (1.9)	1 (0.6)
Black or African America	9 (15.3)	11 (20.4)	10 (18.9)	30 (18.1)
White	49 (83.1)	42 (77.8)	39 (73.6)	130 (78.3)
Unknown	1 (1.7)	1 (1.9)	1 (1.9)	3 (1.8)
Ethnicity, no. (%)				
Hispanic or Latino	11 (18.6)	8 (14.8)	9 (17.0)	28 (16.9)
HbA1c (%), mean (SD)*	7.8 (1.6)	8.2 (1.6)	7.7 (1.8)	7.9 (1.7)
Duration of diabetes at randomization (yrs), mean (SD)	14.0 (10.5)	15.6 (10.0)	14.5 (9.3)	14.7 (10.0)
BCVA†				
ETDRS letters, mean (SD)	61.2 (9.9)	60.9 (11.1)	60.0 (11.0)	60.8 (10.6)
≥69 ETDRS letters, no. (%)	13 (22.4)	15 (27.8)	11 (21.6)	39 (23.9)
<69 ETDRS letters, no. (%)	45 (77.6)	39 (72.2)	40 (78.4)	124 (76.1)
Anatomic features†				
CST (μm), mean (SD)	490.9 (139.0)	535.4 (163.1)	496.5 (135.0)	507.4 (146.7)
DR status, no. (%)				
DR questionable	0	1 (1.9)	0	1 (0.6)
Mild NPDR	5 (8.6)	5 (9.3)	5 (9.8)	15 (9.2)
Moderate NPDR	14 (24.1)	8 (14.8)	10 (19.6)	32 (19.6)
Moderately severe NPDR	23 (39.7)	21 (38.9)	25 (49.0)	69 (42.3)
Severe NPDR	15 (25.9)	16 (29.6)	9 (17.6)	40 (24.5)
Mild PDR	1 (1.7)	1 (1.9)	1 (2.0)	3 (1.8)
Moderate PDR	0	0	1 (2.0)	1 (0.6)
Cannot grade	0	2 (3.7)	0	2 (1.2)
Previously anti-VEGF–treated patients‡	**n = 31**		**n = 29**	**N = 60**
Age (yrs), mean (SD)	63.5 (8.7)		61.5 (9.5)	62.6 (9.0)
Male, no. (%)	17 (54.8)		13 (44.8)	30 (50.0)
Race, no. (%)				
American Indian or Alaska native	1 (3.2)		0	1 (1.7)
Black or African American	8 (25.8)		4 (13.8)	12 (20.0)
White	22 (71.0)		22 (75.9)	44 (73.3)
Unknown	0		3 (10.3)	3 (5.0)
Ethnicity, no. (%)				
Hispanic or Latino	4 (12.9)		7 (24.1)	11 (18.3)
HbA1c (%), mean (SD)	7.8 (1.4)		7.7 (1.6)	7.7 (1.5)
Duration of diabetes (yrs), mean (SD)	15.0 (8.4)		16.6 (12.0)	15.8 (10.2)
Duration of DME (study eye; yrs), mean (SD)§	2.4 (2.0)		3.3 (2.5)	2.9 (2.3)
Duration of DME (fellow eye; yrs), mean (SD)‖	2.2 (2.0)		3.1 (2.7)	2.7 (2.4)
Time since last anti-VEGF treatment (mos), mean (SD)¶	9.5 (9.9)		15.9 (18.2)	12.6 (14.8)
No. of prior anti-VEGF treatments, no. (%)				
1	7 (22.6)		6 (20.7)	13 (21.7)
2–3	5 (16.1)		4 (13.8)	9 (15.0)
4–9	6 (19.4)		4 (13.8)	10 (16.7)
≥10	3 (9.7)		1 (3.4)	4 (6.7)
Unknown	10 (32.3)		14 (48.3)	24 (40.0)
BCVA				
ETDRS letters, mean (SD)	62.0 (11.6)		58.6 (15.0)	60.3 (13.3)
≥69 ETDRS letters, no. (%)	12 (38.7)		8 (27.6)	20 (33.3)
<69 ETDRS letters, no. (%)	19 (61.3)		21 (72.4)	40 (66.7)
Anatomic features				
CST (μm), mean (SD)	485.5 (134.6)		465.7 (120.9)	475.9 (127.4)
DR status, no. (%)				
Mild NPDR	3 (9.7)		4 (13.8)	7 (11.7)
Moderate NPDR	5 (16.1)		9 (31.0)	14 (23.3)
Moderately severe NPDR	17 (54.8)		11 (37.9)	28 (46.7)
Severe NPDR	4 (12.9)		3 (10.3)	7 (11.7)

Table 2. (Continued.)

Characteristic	0.3 mg Ranibizumab	1.5 mg Faricimab	6.0 mg Faricimab	All Patients
Mild PDR	2 (6.5)		1 (3.4)	3 (5.0)
Missing	0		1 (3.4)	1 (1.7)

BCVA = best-corrected visual acuity; CST = central subfield thickness; DME = diabetic macular edema; DR = diabetic retinopathy; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA1c = glycosylated hemoglobin; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; SD = standard deviation; VEGF = vascular endothelial growth factor.
*0.3 mg ranibizumab, n = 55; 1.5 mg faricimab, n = 53; 6.0 mg faricimab, n = 49; total N = 157.
†0.3 mg ranibizumab, n = 58; 1.5 mg faricimab, n = 54; 6.0 mg faricimab, n = 51; total N = 163.
‡One previously anti-VEGF–treated patient received 1.5 mg faricimab but was excluded from the analysis.
§0.3 mg ranibizumab, n = 31; 6.0 mg faricimab, n = 28; total N = 59.
‖0.3 mg ranibizumab, n = 26; 6.0 mg faricimab, n = 27; total N = 53.
¶Time since last anti-VEGF treatment was defined as end date of treatment to date of randomization. Partial dates were imputed to end of month or year. A month was defined as 28 days.

The BOULEVARD trial was a double-masked study. Patients, study site personnel, BCVA examiners, vendors, central reading center personnel, and the sponsor and its agents were masked to study drug assessment. There were a minimum of 2 investigators per site: a treating physician and an assessing physician who was masked to patients' study drug assignment. In the event that only 1 investigator was available, study drug administration could be performed by the assessing physician if study drug preparation occurred by a separate staff member in a masked fashion. After randomization and at each visit with study treatment administration, the interactive voice and web response system assigned the appropriate study treatment kit to be used. All patients received intravitreal injections on the same treatment and assessment schedule.

Outcomes

The primary efficacy outcome measure was the mean change in BCVA from baseline to week 24 in anti-VEGF treatment-naïve patients. Key secondary efficacy outcome measures were proportion of patients gaining 15 or more ETDRS letters from baseline BCVA at week 24 and mean change from baseline in mean CST (1-mm diameter) by spectral-domain OCT at week 24. Additional outcome measures included pharmacokinetic profiles derived from plasma sampling.

Exploratory outcome measures included assessment of Diabetic Retinopathy Severity Scale (DRSS) score and durability of treatment effect. A prespecified analysis was performed to evaluate the proportion of patients with DR severity improvement from baseline on the ETDRS DRSS at week 24. To assess the durability of faricimab compared with ranibizumab, a prespecified analysis was performed to evaluate time to re-treatment by BCVA and CST during the off-treatment observation period. An additional post hoc analysis was performed to evaluate the proportion of patients achieving CST of 325 μm or less on spectral-domain OCT to week 24. Safety outcome measures included incidence and severity of ocular and nonocular adverse events (AEs).

Statistical Analysis

The primary and secondary efficacy analysis population included the intention-to-treat population, which consisted of all anti-VEGF treatment-naïve patients randomized to receive faricimab or ranibizumab. Previously anti-VEGF–treated patients were included in a separate analysis with the intention-to-treat population. The safety analysis population consisted of all patients who received 1 dose or more of faricimab. Patients from a site with Good Clinical Practice noncompliance were excluded from all safety and efficacy analyses.

The study sample size was calculated based on the primary efficacy outcome of mean change in BCVA from baseline at week 24 in anti-VEGF treatment-naïve patients. Assuming a standard deviation of 11 ETDRS letters and a dropout rate of 10%, the sample size provided approximately an 80% power to detect a true difference of 5 ETDRS letters at the 1-sided α level of 10%. The minimum detectable difference is approximately 3 ETDRS letters. The primary efficacy analysis of BCVA change from baseline was performed using a linear model including the categorical covariates of treatment group, visit, and visit by treatment group interaction, along with the continuous covariate of baseline BCVA and randomization stratification factors (64 ETDRS letters or better vs. 63 ETDRS letters or worse, and previous macular laser treatment status). There was no formal type I error correction for multiple testing.

All secondary end points measured on a continuous scale were analyzed using the same linear model used for change from baseline BCVA, adjusting each end point for its own baseline as a continuous covariate. For binary end points, the 80% confidence interval (CI) for the proportion in each treatment group, absolute risk differences, and odds ratios were estimated using generalized estimating equations. The generalized estimating equation model included the categorical covariates of treatment arm, visit, and visit by treatment arm interaction term. Autoregressive first-order covariance structure was used to account for correlation over time. The Fisher exact test was used for the comparisons between the 2 arms when generalized estimating equation models did not converge.

Kaplan-Meier estimates were constructed for each study arm to evaluate the durability of effect for faricimab compared with ranibizumab during the off-treatment observation period. Kaplan-Meier analysis characterized patients by 3 variables: serial time, status at end of serial time (event occurrence or censored), and study group. Patients were included in the analysis starting at week 20 and continued until (1) a patient met the predefined criteria for DME recurrence (BCVA decreased $\geq$5 ETDRS letters due to DME in the opinion of the investigator and CST increased $\geq$50 μm) or (2) a patient was censored. Censoring could occur if a patient withdrew from the study or on study completion at week 36. Time-to-event end points were tested with a 2-sided stratified log-rank test using the randomization stratification factors of BCVA ETDRS letter score (64 ETDRS letters or better vs. 63 ETDRS letters or worse) and previous macular laser treatment as strata.

Table 3. Week 24 Key Outcomes

End Point	0.3 mg Ranibizumab	1.5 mg Faricimab	6.0 mg Faricimab
Anti-VEGF treatment-naïve patients	**n = 59**	**n = 54**	**n = 53**
BCVA change from baseline (ETDRS letters)*	10.3	11.7	13.9
Patients gaining ≥10 ETDRS letters (%)†	59.2	60.6	72.1
Patients gaining ≥15 ETDRS letters (%)†	35.3	36.0	42.5
CST change from baseline (μm)‡	−204.7	−217.1	−225.8
Patients achieving CST ≤325 μm (%)§	61.2	63.3	77.3
≥2-Step improvement in DRSS score (%)	12.2	27.7	38.6
Previously anti-VEGF–treated patients‖	**n = 31**		**n = 29**
BCVA change from baseline (ETDRS letters)*	8.3		9.6
Patients gaining ≥10 ETDRS letters (%)†	43.4		59.8
Patients gaining ≥15 ETDRS letters (%)†	16.8		23.2
CST change from baseline (μm)‡	−148.0		−186.6
Patients achieving CST ≤325 μm (%)§	53.6		87.0
≥2-Step improvement in DRSS score (%)	23.1		22.7

BCVA = best-corrected visual acuity; CST = central subfield thickness; DRSS = Diabetic Retinopathy Severity Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; VEGF = vascular endothelial growth factor.
*Linear model adjusted for baseline BCVA, previous macular laser treatment status at randomization, and BCVA category (≥64 ETDRS letters vs. ≤63 ETDRS letters) at baseline.
†Least squares means from linear model.
‡Linear model adjusted for baseline CST, previous macular laser treatment status at randomization, and BCVA category (≥64 ETDRS letters vs. ≤63 ETDRS letters) at baseline.
§Post hoc analysis.
‖One previously anti-VEGF–treated patient received 1.5 mg faricimab but was excluded from the analysis.

Results

BOULEVARD Enrollment and Participation

A total of 453 patients were screened for this study. Screening failure occurred for 224 patients who were not included in the study; the most common reasons given for screening failure were not meeting the study ocular inclusion or exclusion criteria. The most common ocular criteria not met were BCVA letter scores and CST. The BOULEVARD trial enrolled 229 patients with center-involving DME between April 2016 and March 2017. These included 168 anti-VEGF treatment-naïve patients and 61 previously anti-VEGF–treated patients (Fig 2B). The study was completed in December 2017 after the last patient's final observation.

Anti–Vascular Endothelial Growth Factor Treatment-Naïve Patients

Patient Disposition and Follow-up. Among the 168 anti-VEGF treatment-naïve patients, 59 were randomized to the 0.3-mg ranibizumab arm, 54 to the 1.5-mg faricimab arm, and 55 to the 6.0-mg faricimab arm (2 patients from this arm were not included in the analysis because of Good Clinical Practice noncompliance at a single site). More than 80% of patients completed the study, with discontinuations generally balanced across arms. Four patients discontinued before 36 weeks because of death: 2 (3.4%) in the ranibizumab arm, 1 (1.9%) in the 1.5-mg faricimab arm, and 1 (1.9%) in the 6.0-mg faricimab arm. One of the randomized patients in the 0.3-mg ranibizumab arm and 2 in the 6.0-mg faricimab arm did not receive any study medication.

Baseline Demographics and Ocular Characteristics. Baseline patient demographics and ocular characteristics generally were well balanced across treatment arms (Table 2). The average age for all treatment-naïve patients was 61.2 years (range, 29–81 years), and 53.6% were men. The mean duration of diabetes at randomization was 14.0 years, 15.6 years, and 14.5 years in the 0.3-mg ranibizumab, 1.5-mg faricimab, and 6.0-mg faricimab arms, respectively. Mean glycosylated hemoglobin (HbA1c) level was 7.8%, 8.2%, and 7.7%, respectively. Mean baseline BCVA was similar across arms, with an average for all patients of 60.8 ETDRS letters. Mean baseline CST was 490.9 μm, 535.4 μm, and 496.5 μm for the 0.3-mg ranibizumab, 1.5-mg faricimab, and 6.0-mg faricimab arms, respectively.

Week 24 Efficacy Outcomes. Week 24 key outcomes for anti-VEGF treatment-naïve patients are outlined in Table 3.

Visual Acuity End Points. The BOULEVARD trial met its primary efficacy end point of superior BCVA gains with faricimab compared with ranibizumab in anti-VEGF treatment-naïve patients at week 24. Adjusted BCVA gains from baseline were 10.3 ETDRS letters (80% CI, 8.8–11.9 ETDRS letters), 11.7 ETDRS letters (80% CI, 10.1–13.3 ETDRS letters), and 13.9 ETDRS letters (80% CI, 12.2–15.6 ETDRS letters) for the 0.3-mg ranibizumab, 1.5-mg faricimab, and 6.0-mg faricimab treatment arms, respectively. Patients treated with 6.0 mg faricimab experienced a statistically significant 3.6-letter mean vision gain over ranibizumab-treated patients ($P = 0.03$; 80% CI, 1.5–5.6 letters; prespecified significance level, $P < 0.2$; Fig 3A).

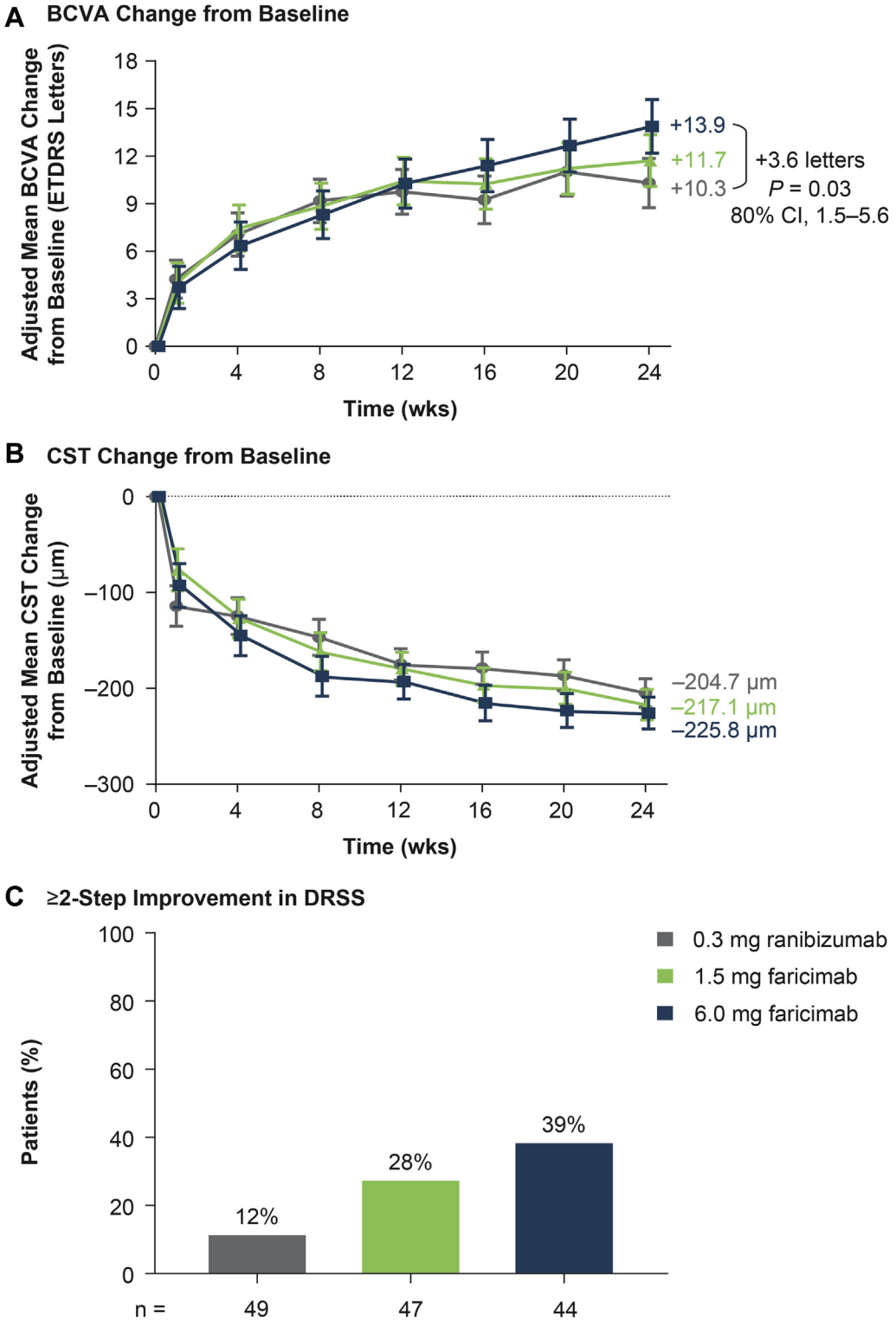

Figure 3. Graphs showing outcomes for anti–vascular endothelial growth factor treatment-naïve patients. **A**, Best-corrected visual acuity (BCVA) change from baseline. **B**, Central subfield thickness (CST) change from baseline. **C**, Two-step or more improvement in Diabetic Retinopathy Severity Scale (DRSS) score. CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study.

The percentages of patients gaining 10 ETDRS letters or more from baseline at week 24 were 59.2% (80% CI, 50.2%–67.7%) in the ranibizumab arm, 60.6% (80% CI, 51.6%–68.9%) in the 1.5-mg faricimab arm, and 72.1% (80% CI, 62.9%–79.8%) in the 6.0-mg faricimab arm (Fig S4A, available at www.aaojournal.org). The

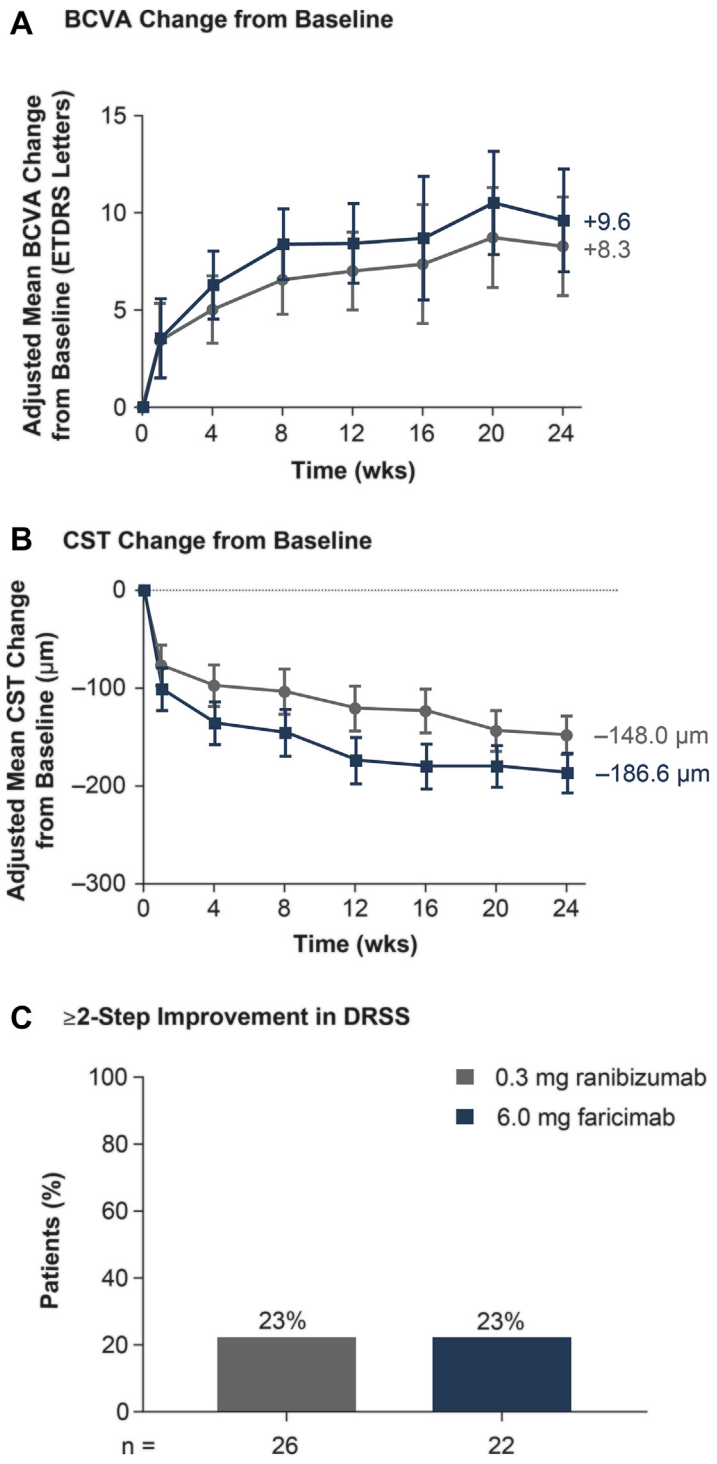

Figure 5. Graphs showing outcomes for previously anti–vascular endothelial growth factor-treated patients. **A**, Best-corrected visual acuity (BCVA) change from baseline. **B**, Central subfield thickness (CST) change from baseline. **C**, Two-step or more improvement in Diabetic Retinopathy Severity Scale (DRSS) score. ETDRS = Early Treatment Diabetic Retinopathy Study.

percentages of patients gaining 15 ETDRS letters or more from baseline at week 24 were 35.3% (80% CI, 27.3%–44.1%), 36.0% (80% CI, 27.9%–45.0%), and 42.5% (80% CI, 33.5%–52.1%) for the 0.3-mg ranibizumab, 1.5-mg faricimab, and 6.0-mg faricimab treatment arms, respectively (Fig S4B, available at www.aaojournal.org).

Anatomic End Points. At week 24, adjusted mean change in CST from baseline was −204.7 μm (80% CI, −219.6 to −189.8 μm), −217.1 μm (80% CI, −233.0 to

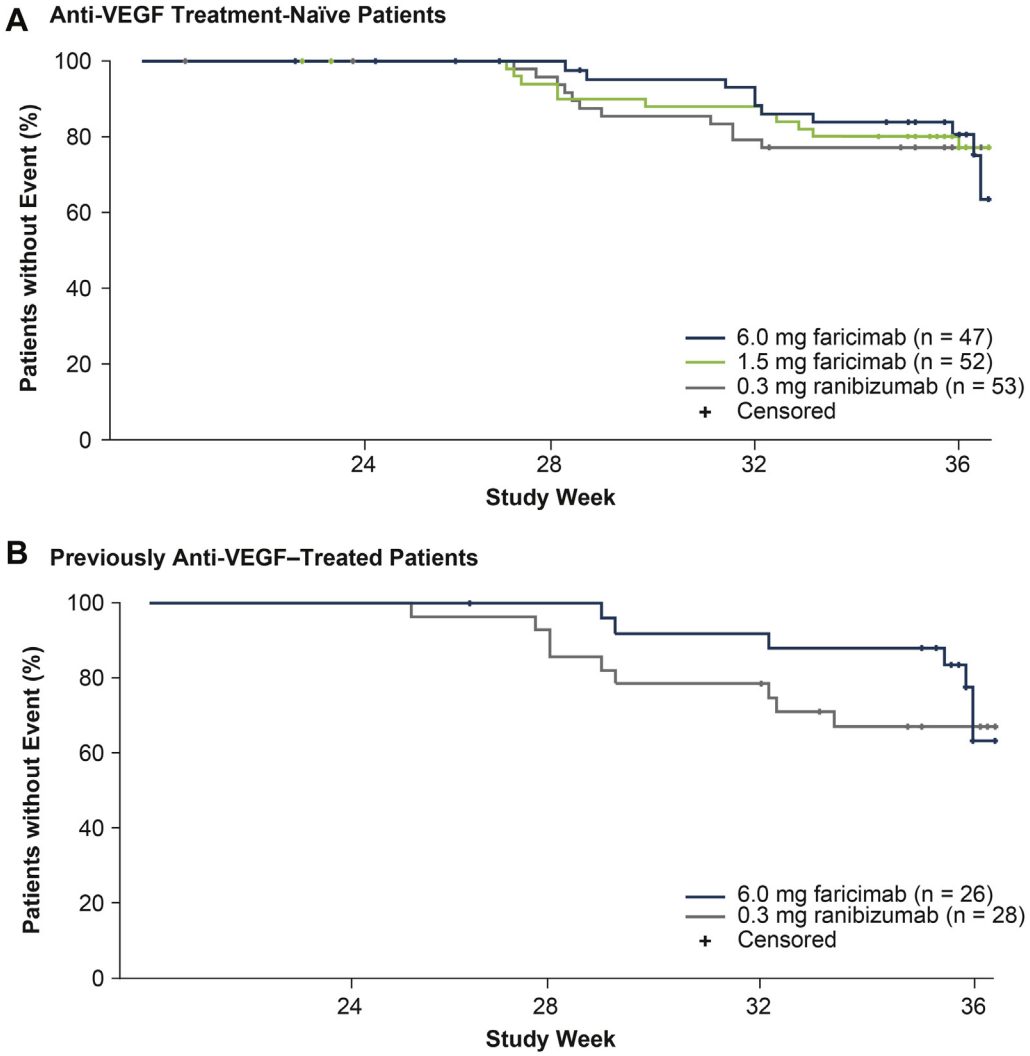

Figure 7. Kaplan-Meier plots showing time to disease reactivation in the off-treatment observation period, based on combined best-corrected visual acuity and central subfield thickness criteria. **A**, Anti–vascular endothelial growth factor (VEGF) treatment-naïve patients. **B**, Previously anti-VEGF–treated patients.

−201.2 μm), and −225.8 μm (80% CI, −242.5 to −209.1 μm) for the 0.3-mg ranibizumab, 1.5-mg faricimab, and 6.0-mg faricimab treatment arms, respectively (6.0-mg faricimab vs. ranibizumab difference, −21.1 μm; 80% CI, −38.7 to −3.5 μm; Fig 3B). The percentage of patients achieving CST of 325 μm or less at weeks 12 and 24 were 45.3% and 61.2%, respectively, in the 0.3-mg ranibizumab arm; 51.9% and 63.3%, respectively, in the 1.5-mg faricimab arm; and 66.0% and 77.3%, respectively, in the 6.0-mg faricimab arm (Fig S4C, available at www.aaojournal.org).

Diabetic Retinopathy Severity End Points. The percentage of patients achieving 2-step or more improvement in DRSS score from baseline to week 24 were 12.2%, 27.7%, and 38.6% in the 0.3-mg ranibizumab, 1.5-mg faricimab, and 6.0-mg faricimab arms, respectively (Fig 3C). The percentage of patients achieving 1-step or more improvement were 53.1%, 61.7%, and 59.1% in the 0.3-mg ranibizumab, 1.5-mg faricimab, and 6.0-mg faricimab arms, respectively (Fig S4D, available at www.aaojournal.org). A post hoc analysis of the proportion of patients with baseline DRSS level ≥47 or ≥53 achieving 2-step or more improvement were 15.2% and 25.0%, respectively, in the ranibizumab arm; 32.4% and 40.0%, respectively, in the 1.5-mg faricimab arm; and 53.3% and 87.5%, respectively, in the 6.0-mg faricimab arm (Fig S4E, F, available at www.aaojournal.org).

Previously Anti–Vascular Endothelial Growth Factor-Treated Patients

Patient Disposition and Follow-up. Among the 61 patients previously treated with anti-VEGF, 31 were randomized to the 0.3-mg ranibizumab arm, and 29 were randomized to the 6.0-mg faricimab arm. One patient received 1.5 mg faricimab in error and was excluded from the analysis of this population. Ninety percent of patients (28/31) in the ranibizumab arm and 83% (24/29) in the faricimab arm completed the study. One patient in the 6.0-mg faricimab arm discontinued before 36 weeks because of death (Fig 2B).

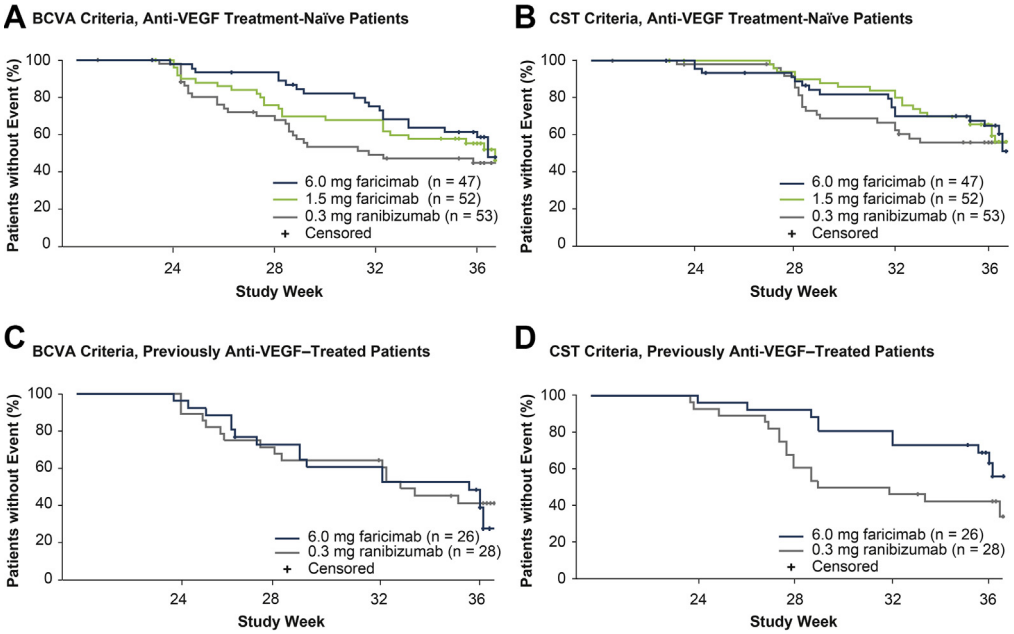

Figure 8. Kaplan-Meier plots showing time to disease reactivation in the off-treatment observation period, based on separate best-corrected visual acuity (BCVA) and central subfield thickness (CST) criteria. **A**, Loss of 5 letters or more of BCVA due to diabetic macular edema, anti–vascular endothelial growth factor (VEGF) treatment-naïve patients. **B**, Increase in CST by 50 μm or more, anti-VEGF treatment-naïve patients. **C**, Loss of 5 letters or more of BCVA due to DME, previously anti-VEGF–treated patients. **D**, Increase in CST by 50 μm or more, previously anti-VEGF–treated patients.

Baseline Demographics and Ocular Characteristics. Baseline demographics and ocular characteristics in previously anti-VEGF–treated patients generally were well balanced across treatment arms (Table 2B). The average age was 62.6 years (range, 38–86 years), and there were equal numbers of men and women. The mean duration of diabetes

Table 4. Nonserious Ocular Adverse Events Occurring in More Than 3% of Patients

	0.3 mg Ranibizumab (n = 89)		1.5 mg Faricimab (n = 55)		6.0 mg Faricimab (n = 80)		All Patients (N = 224)	
Eye Disorders	*Patients*	*Events*	*Patients*	*Events*	*Patients*	*Events*	*Patients*	*Events*
Study eye								
Cataract	2	2	0	0	3	3	5	5
Conjunctival hemorrhage	5	5	2	2	8	8	15	15
Diabetic retinal edema	2	2	2	2	0	0	4	4
Dry eye	1	1	0	0	4	4	5	5
Eye pain	2	2	3	3	2	2	7	7
Eye pruritus	3	3	1	1	1	1	5	5
Eyelid edema	0	0	2	3	0	0	2	3
Lacrimation increased	3	3	0	0	1	1	4	4
Retinal exudates	1	1	3	3	2	2	6	6
Vision blurred	1	1	2	2	1	2	4	5
Vitreous detachment	2	2	3	3	1	1	6	6
Vitreous floaters	2	2	2	2	2	2	6	6
Vitreous hemorrhage	3	4	0	0	0	0	3	4
Fellow eye								
Cataract subcapsular	0	0	2	2	0	0	2	2
Conjunctival hemorrhage	3	3	0	0	0	0	3	3
Diabetic retinal edema	2	2	2	2	5	5	9	9
Dry eye	2	2	0	0	3	3	5	5
Retinal exudates	1	1	2	2	1	1	4	4
Vision blurred	1	1	2	2	2	3	5	6

Observed data; safety population includes both anti–vascular endothelial growth factor treatment-naïve patients and previously anti–vascular endothelial growth factor-treated patients. Safety data set consists of 224 patients; 2 patients removed because of Good Clinical Practice noncompliance at a single site; 3 patients were randomized but did not receive treatment.

Table 5. Detailed Ocular Serious Adverse Events

Ocular Events	0.3 mg Ranibizumab (n = 89)	1.5 mg Faricimab (n = 55)	6.0 mg Faricimab (n = 80)
Study eye			
Total patients with ≥1 SAE	1 (1.1)	0	1 (1.3)
Total no. of SAEs	1	0	1
Diabetic retinopathy	1 (1.1)	0	0
Vitreous hemorrhage	0	0	1 (1.3)
Fellow eye			
Total patients with ≥1 SAE	0	1 (1.8)	1 (1.3)
Total no. of SAEs	0	1	1
Retinal vein occlusion	0	0	1 (1.3)
Visual acuity reduced	0	1 (1.8)	0

SAE = serious adverse event.
Data are no. (%). Observed data; safety population includes both anti–vascular endothelial growth factor treatment-naïve patients and previously anti–vascular endothelial growth factor-treated patients. Safety data set consists of 224 patients; 2 patients removed because of Good Clinical Practice noncompliance at a single site; 3 patients were randomized but did not receive treatment.

at randomization was 15.0 years in the 0.3-mg ranibizumab arm and 16.6 years in the 6.0-mg faricimab arm, whereas the mean duration of DME was 2.4 and 3.3 years in the 0.3-mg ranibizumab arm and 6.0-mg faricimab arm, respectively. Mean HbA1c level was 7.8% and 7.7% in the 0.3-mg ranibizumab and 6.0-mg faricimab arms, respectively. The mean time since last anti-VEGF treatment was 9.5 and 15.9 months in the 0.3-mg ranibizumab and 6.0-mg faricimab arms, respectively. Nearly 22% of patients had received 1 prior anti-VEGF treatment, whereas 15.0% had received 2 to 3 treatments, 16.7% had received 4 to 9 treatments, and 6.7% had received 10 or more anti-VEGF treatments. The number of prior treatments was unavailable for the remaining patients. Mean baseline BCVA was 62.0 and 58.6 ETDRS letters in the 0.3-mg ranibizumab and 6.0-mg faricimab arms, respectively, and mean baseline CST was 485.5 and 465.7 μm in the 0.3-mg ranibizumab and 6.0-mg faricimab arms, respectively.

Week 24 Efficacy Outcomes. Week 24 key outcomes for previously anti-VEGF–treated patients are outlined in Table 3.

Visual Acuity End Points. At week 24, adjusted BCVA gains from baseline were 8.3 ETDRS letters (80% CI, 5.7–10.8 ETDRS letters) and 9.6 ETDRS letters (80% CI, 7.0–12.3 ETDRS letters) for the 0.3-mg ranibizumab and 6.0-mg faricimab treatment arms, respectively (Fig 5A). The percentage of patients gaining 10 or more ETDRS letters or 15 or more ETDRS letters from baseline at week 24 were 43.3% (80% CI, 32.1%–55.2%) and 16.8% (80% CI, 9.6%–27.8%), respectively, in the ranibizumab arm and 59.8% (80% CI, 46.9%–71.5%) and 23.2% (80% CI, 14.1%–35.7%), respectively, in the 6.0-mg faricimab arm (Fig S6A, B, available at www.aaojournal.org).

Anatomic End Points. Adjusted mean change in CST from baseline at week 24 was −148.0 μm (80% CI, −167.7 to −128.4 μm) and −186.6 μm (80% CI, −206.9 to −166.4 μm) for the 0.3-mg ranibizumab and 6.0-mg faricimab treatment arms, respectively (Fig 5B). The percentages of patients achieving CST of 325 μm or less at weeks 12 and 24 were 46.7% and 53.6%, respectively, in the 0.3-mg ranibizumab arm and 81.5% and 87.0%, respectively, in the 6.0-mg faricimab arm (Fig S6C, available at www.aaojournal.org).

Diabetic Retinopathy Severity End Points. The percentage of patients achieving 2-step or more improvement in DRSS score from baseline to week 24 were similar between the 0.3-mg ranibizumab and 6.0-mg faricimab arms (23.1% vs. 22.7%; Fig 5C). However, a greater percentage of patients achieved 1-step or more DRSS score improvement in the 6.0-mg faricimab arm compared with the ranibizumab arm (63.6% vs. 50.0%, respectively; Fig S6D, available at www.aaojournal.org).

Durability Outcomes

During the observation period, the BOULEVARD trial assessed the length of time for each patient to meet the predefined criteria for disease reactivation and subsequent re-treatment with anti-VEGF therapy. There was greater probability for patients treated with 6.0 mg faricimab to exhibit a longer time to re-treatment compared with ranibizumab-treated patients (Fig 7). Among anti-VEGF treatment-naïve patients, the Kaplan-Meier survival probability estimates at weeks 24, 28, 32, and 36 were approximately 100%, 96%, 79%, and 77%, respectively, for the 0.3-mg ranibizumab arm; 100%, 94%, 88%, and 80%, respectively, for the 1.5-mg faricimab arm; and 100%, 100%, 93%, and 81%, respectively, for the 6.0-mg faricimab arm (Fig 7A). Among previously anti-VEGF–treated patients, the Kaplan-Meier survival probability estimates were approximately 100%, 86%, 79%, and 67%, respectively, for the 0.3-mg ranibizumab arm and 100%, 100%, 92%, and 84%, respectively, for the 6.0-mg faricimab arm (Fig 7B).

The length of time for each patient to meet the criteria for disease reactivation during the observation period also was assessed based on separate BCVA and CST criteria (Fig 8). Among anti-VEGF treatment-naïve patients, the Kaplan-Meier survival probability estimates based on BCVA criteria alone at weeks 24, 28, 32, and 36 were approximately 98%, 68%, 50%, and 45%, respectively, for the 0.3-mg ranibizumab arm; 96%, 76%, 68%, and 56%, respectively, for the 1.5-mg faricimab arm; and 98%, 93%, 75%, and 59%, respectively, for the 6.0-mg faricimab arm (Fig 8A). The Kaplan-Meier survival probability estimates based on CST

criteria alone at weeks 24, 28, 32, and 36 were approximately 98%, 92%, 67%, and 56%, respectively, for the 0.3-mg ranibizumab arm; 100%, 94%, 84%, and 66%, respectively, for the 1.5-mg faricimab arm; and 100%, 94%, 80%, and 65%, respectively, for the 6.0-mg faricimab arm (Fig 8B).

Among previously anti-VEGF–treated patients, the Kaplan-Meier survival probability estimates based on BCVA criteria at weeks 24, 28, 32, and 36 were approximately 100%, 68%, 64%, and 41%, respectively, for the 0.3-mg ranibizumab arm and 96%, 73%, 61%, and 49%, respectively, for the 6.0-mg faricimab arm (Fig 8C). The Kaplan-Meier survival probability estimates based on CST criteria at weeks 24, 28, 32, and 36 were approximately 100%, 68%, 50%, and 43%, respectively, for the 0.3-mg ranibizumab arm and 100%, 92%, 81%, and 69%, respectively, for the 6.0-mg faricimab arm (Fig 8D).

Ocular and Systemic Safety

The safety analysis included all patients, pooled from both populations (n = 224), who received 1 dose or more of study drug. The BOULEVARD safety data reported to week 24 (the prespecified time point for the primary efficacy outcome measure), and subsequently to the end of the study at week 36, showed no new or unexpected ocular or systemic safety signals. There were no AEs of intraocular inflammation, endophthalmitis, or retinal detachment in any patients. Vitreous hemorrhage (nonserious or serious) occurred in 1.8% (4/224; 3 in the ranibizumab arm and 1 in the 6.0-mg faricimab arm) of all patients, and 1.8% (4/224; 2 in the ranibizumab arm and 2 in the 6.0-mg faricimab arm) of patients experienced an Anti-Platelet Trialists' Collaboration event (nonfatal myocardial infarction, cardiac arrest, coronary artery disease, or death of unknown cause). Discontinuation because of serious AEs occurred for 2 patients. One patient in the 0.3-mg ranibizumab arm demonstrated proliferative DR resulting in retinal and subhyaloid hemorrhage leading to a clinically significant reduction in visual acuity and was withdrawn from the study and scheduled for a vitrectomy. One patient in the 1.5-mg faricimab arm discontinued treatment because of a systemic serious AE of gangrene. There were 5 deaths total during the study: 2 in the ranibizumab arm, 1 in the 1.5-mg faricimab arm, and 2 in the 6.0-mg faricimab arm. None of the deaths was related to study treatment. Tables 4 and 5 (ocular) and Tables S6 and S7 (systemic; available at www.aaojournal.org) provide an overview of AEs occurring in more than 3% of patients. In the pharmacokinetic analysis, low systemic exposure to faricimab was observed (see additional details in the Appendix and Fig S9, available at www.aaojournal.org).

Discussion

In the BOULEVARD phase 2 study, 6.0 mg faricimab met its primary end point and demonstrated superior gains in visual acuity from baseline to week 24 compared with ranibizumab in treatment-naïve patients. In addition, secondary visual and anatomic outcomes consistently showed an advantage of faricimab over ranibizumab in both patient populations. Faricimab showed potential for greater durability versus ranibizumab: both treatment-naïve patients and previously anti-VEGF–treated patients required longer time to re-treatment in the observation period. There were no new or unexpected safety signals with faricimab. Together, these primary, secondary, and exploratory outcomes point toward the benefit of combined Ang-2 and VEGF-A blockade with faricimab over anti-VEGF monotherapy.

Faricimab showed a significant improvement in BCVA over ranibizumab. Among treatment-naïve patients in the BOULEVARD study, the 6.0-mg faricimab arm demonstrated a statistically significant mean vision gain over ranibizumab-treated patients of 3.6 ETDRS letters ($P = 0.03$). The 6.0-mg and 1.5-mg faricimab arms showed a dose-dependent improvement in BCVA with faricimab versus ranibizumab. Additionally, the trajectory of BCVA gains in the 6.0-mg faricimab arm did not plateau at month 6 (week 24). The BCVA improvement observed in the BOULEVARD ranibizumab arm of treatment-naïve patients was comparable with other randomized clinical trials of anti-VEGF monotherapy.[37–39] In the BOULEVARD trial, ranibizumab-treated patients gained 10.3 ETDRS letters at month 6, whereas in RIDE and RISE, patients gained 9.6 to 11.5 ETDRS letters at month 12 with ranibizumab,[9] and in VIVID and VISTA, patients gained 10.5 to 12.5 ETDRS letters at month 12 with aflibercept.[11]

In both patient populations of the BOULEVARD trial, numerically greater reductions in CST were observed with faricimab versus ranibizumab. In treatment-naïve patients, the 6.0-mg and 1.5-mg faricimab arms demonstrated dose-related reductions in CST. A larger proportion of faricimab-treated eyes reached the threshold CST of 325 μm or less at all visits. These results are not likely because of the higher dose of anti-VEGF. Historical studies evaluating higher doses of anti-VEGF have not shown additional improvements in BCVA or CST. In RIDE and RISE, 0.3 mg ranibizumab was shown to be equivalent to 0.5 mg ranibizumab. The Ranibizumab for Edema of the Macula in Diabetes-Protocol 3 with High Dose (READ-3) reported equivalent BCVA and CST gains with 0.5 mg and 2 mg ranibizumab, as did RESOLVE, which studied the effect of comparing the dose of ranibizumab in 0.05 ml (0.3–0.5 mg) with the dose in 0.1 ml (0.5–1 mg).[10,38,39] Additional support for the role of Ang-2 inhibition is available from the phase 2 DME study with the monoclonal antibody nesvacumab, in which a combination of intravitreal nesvacumab and aflibercept showed greater reductions in CST at both early and late time points than aflibercept alone.[40] Furthermore, preclinical data have demonstrated superior anatomic improvements with anti–Ang-2/anti–VEGF-A treatment versus anti-VEGF monotherapy.[33] These data, together with outcomes from BOULEVARD, provide evidence that vascular stabilization mediated through simultaneous inhibition of Ang-2 and VEGF-A restores retinal anatomic features and function better than VEGF inhibition alone and highlights the potential of Ang-2 inhibition for patients with persistent DME.

In the BOULEVARD trial, 39% of patients treated with 6.0 mg faricimab achieved 2-step or more DRSS score

improvement at week 24 compared with 12% of ranibizumab-treated patients (anti-VEGF treatment-naïve cohort). These results are comparable with 12-month outcomes from larger phase 3 trials of anti-VEGF monotherapy, where patients in RIDE and RISE and in VIVID and VISTA achieved 2-step or more DRSS score improvement in 30% to 35% and 28% to 34% of patients treated with ranibizumab and aflibercept, respectively.[9,11] In the BOULEVARD trial, for patients treated with 6.0 mg faricimab with baseline DRSS level ≥47 or ≥53, 2-step or more improvement in DRSS score was achieved in 53% and 88%, respectively. These results demonstrate potential for the added benefit of Ang-2 inhibition to manage DR.

Previous studies have shown that in patients with DME, optimal response and maintenance of visual function often require frequent anti-VEGF treatment.[9,11,12,39,41,42] However, real-world clinical practice data report that 50% to 69% of patients treated with anti-VEGF monotherapy receive a suboptimal average of 3 or fewer injections over a 12-month follow-up period.[15,16] Among both anti-VEGF treatment-naïve patients and previously treated patient populations in the BOULEVARD trial, faricimab resulted in a longer time to re-treatment, indicating a longer duration of effect with faricimab. Compared with ranibizumab, more eyes treated with faricimab maintained CST reduction from week 24 (4 weeks after the last study drug treatment) up to week 36 (16 weeks after the last study drug treatment). In previously anti-VEGF–treated patients, the magnitude of CST reductions favored eyes treated with faricimab versus ranibizumab, demonstrating the potential for faricimab to reduce treatment burden in patients with DME currently receiving anti-VEGF monotherapy. The combined Ang-2/VEGF-A blockade likely provides additional vascular stability beyond VEGF inhibition alone and may be responsible for the increased durability effect.[21] The extended durability response from faricimab could provide sustained efficacy with fewer injections, which may preserve visual gains in a clinical practice setting.

A cohort of previously anti-VEGF–treated patients were enrolled in the BOULEVARD study for exploratory analysis and to establish if the safety and efficacy of faricimab in this patient population supported future development options. The previously anti-VEGF–treated patient population in the present study was extremely heterogeneous with respect to duration of DME, time since last anti-VEGF treatment, type of previous anti-VEGF treatment, and number of intravitreal injections. To study a drug optimally in such a population, a larger patient population and a longer trial duration are needed. Because of the exploratory intentions, no formal power considerations were performed when the study was designed. Although improvements in BCVA and DRSS score were similar between the faricimab and ranibizumab arms, faricimab-treated patients achieved a greater reduction in CST compared with those treated with ranibizumab, suggesting additional potential of faricimab to preserve anatomic features. We hypothesize that this in turn may translate into a functional improvement in long-term studies. The additional inhibition of Ang-2 through its anti-inflammatory and neuroprotective effects may result in the prevention of permanent microscopic damage to retinal architecture. The timing of faricimab treatment for maximum benefit also could be early in the course of the disease as the BCVA improvement noted in the treatment-naïve patient population suggests, whereas the previously anti-VEGF–treated patients who had a longer duration of DME already may have irreversible structural damage.

Importantly, faricimab showed no new or unexpected safety signals in this phase 2 study. There were no AEs of intraocular inflammation. There were 5 deaths (2.2% [5/224]; none study drug related) reported across all treatment arms in the BOULEVARD trial, which is comparable with other randomized controlled trials in DME reporting a 1% to 4% death rate during the study.[9–12,41,42]

The unique design of the faricimab bispecific antibody allows for targeting 2 key drivers of DME pathology in a single molecule. The primary, secondary, and exploratory outcomes in the BOULEVARD trial all point toward a benefit of combined Ang-2 and VEGF-A blockade beyond anti-VEGF monotherapy, likely through anti-inflammatory and integrin pathways.[21] Consistent benefits across BCVA, CST, DRSS score, and durability end points demonstrate the potential of faricimab to improve the functional, anatomic, and treatment burden outcomes for patients with DME.

One limitation of the BOULEVARD study is the short treatment duration of 20 weeks and the short off-treatment observation period of 16 weeks; longer-term efficacy and safety data are required to confirm the findings in the BOULEVARD trial. Related to the short study duration, extended dosing with faricimab was not assessed formally. However, given the promising durability results, studies with extended dosing intervals and flexible dosing regimens with faricimab are warranted.

In summary, faricimab, the first bispecific antibody specifically designed for intraocular use, binds and neutralizes both Ang-2 and VEGF-A. In the BOULEVARD phase 2 randomized clinical trial for DME, faricimab met its primary end point, demonstrating clinically meaningful and superior visual acuity gains compared with ranibizumab. Treatment with faricimab resulted in CST reduction, DRSS score improvements, and extended durability of effect in both patient populations. Faricimab was well tolerated and showed no new or unexpected safety signals, along with low systemic exposure. Additional long-term benefits of drying the retina, along with the anti-inflammatory properties of faricimab, will be investigated in further studies. Two large phase 3 clinical trials, YOSEMITE (ClinicalTrials.gov identifier, NCT03622580) and RHINE (ClinicalTrials.gov identifier, NCT03622593), currently are ongoing to further investigate the efficacy, durability, and safety of faricimab for DME.[43,44]

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HUMAN SUBJECTS: Human subjects were included in this study. All participants provided written informed consent, and the study protocol was approved by institutional review boards before study start (institutional review boards and ethics committees: Quorum Review IRB; Beetham Eye Institute, Joslin Diabetes Center, Joslin Committee on Human Studies; Western Institutional Review Board WIRB Panel 7; Cleveland Clinic Florida, Cleveland Clinic Institutional Review Board; University of Virginia Institutional Review Board for Health Sciences Research; Chesapeake Research Review IRB; Johns Hopkins Medicine Institutional Review Board; UNM Human Research Review Committee; Weill Cornell Med Center IRB; Sterling IRB). The study adhered to the tenets of the Declaration of Helsinki and was conducted in accordance with Good Clinical Practice (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E6); applicable United States Food and Drug Administration regulations;

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Abbreviations and Acronyms:
AE = adverse event; **Ang** = angiopoietin; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **CST** = central subfield thickness; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **DRSS** = Diabetic Retinopathy Severity Scale; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **Fc** = fragment crystallizable; **HbA1c** = glycosylated hemoglobin; **Tie** = tyrosine kinase with immunoglobulin-like domains; **VEGF** = vascular endothelial growth factor.

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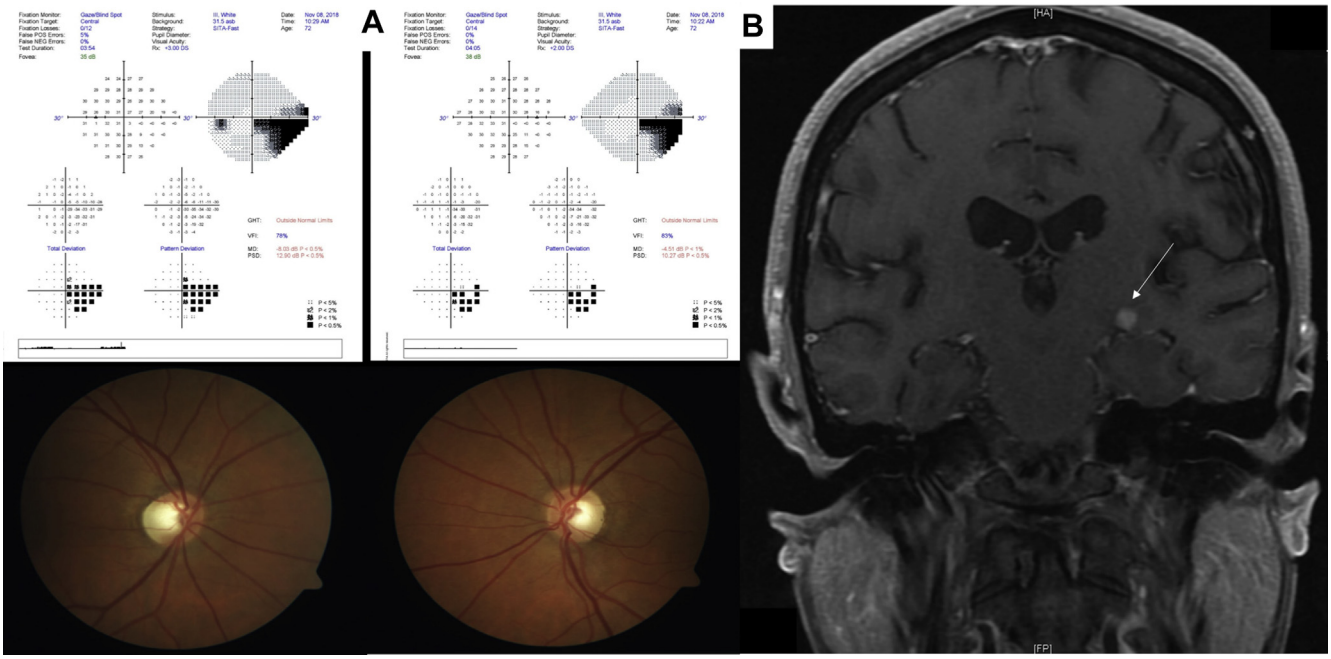
Pictures & Perspectives



A Case of a Lateral Geniculate Nucleus Lesion Causing a Homonymous Horizontal Wedge-Shaped Sectoranopia

A 72-year-old woman with stage 4A non−small-cell lung cancer reported 3 weeks of peripheral vision loss affecting her right eye. Examination revealed a right homonymous horizontal wedge-shaped sectoranopia with temporal pallor of both optic nerves corroborated by hemianopic atrophy of the retinal nerve fiber layer in both eyes on OCT (Fig **A**). Coronal, T1-weighted magnetic resonance imaging (MRI) of the brain with gadolinium and fat suppression revealed a 6-mm solitary focal enhancement, consistent in radiographic appearance with metastasis, located within the medial left temporal lobe, inferolateral to the left thalamus and involving the left lateral geniculate nucleus, an uncommon lesion explaining her presentation (Fig **B**). (Magnified version of Fig **A**-**B** is available online at www.aaojournal.org).

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