

Safety and Efficacy of Different Doses and Regimens of Faricimab vs Ranibizumab in Neovascular Age-Related Macular Degeneration

The AVENUE Phase 2 Randomized Clinical Trial

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[+ Supplemental content](#)

IMPORTANCE Faricimab, the first bispecific antibody designed for intraocular use, simultaneously and independently binds and neutralizes angiopoietin 2 (Ang-2) and vascular endothelial growth factor A (VEGF-A).

OBJECTIVE To assess the efficacy and safety of different doses and regimens of faricimab vs ranibizumab in patients with neovascular age-related macular degeneration (nAMD).

DESIGN, SETTING, AND PARTICIPANTS AVENUE was a 36-week, multiple-dose-regimen, active comparator-controlled, double-masked, phase 2 randomized clinical study performed at 58 sites in the United States. Eligible participants were anti-VEGF treatment naive with choroidal neovascularization secondary to nAMD and best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 73 (Snellen equivalent, 20/40) to 24 (Snellen equivalent, 20/320). Data were collected from August 11, 2015, to January 12, 2017, with the final patient visit completed September 26, 2017. Data were analyzed from August 11, 2015, to October 4, 2019.

INTERVENTIONS Patients were randomized 3:2:2:2:3 to receive ranibizumab, 0.5 mg every 4 weeks (arm A [n = 68]); faricimab, 1.5 mg every 4 weeks (arm B [n = 47]); faricimab, 6.0 mg every 4 weeks (arm C [n = 42]); faricimab, 6.0 mg every 4 weeks until week 12, then faricimab, 6.0 mg every 8 weeks (arm D [n = 47]); and ranibizumab, 0.5 mg every 4 weeks until week 8, then faricimab, 6.0 mg every 4 weeks (arm E [n = 69]).

MAIN OUTCOMES AND MEASURES Mean change in BCVA from baseline to week 36, proportion of participants gaining at least 15 letters, BCVA of 20/40 or better or 20/200 or worse, and ocular coherence tomographic outcomes in anti-VEGF treatment-naive participants (arms A, B, C, D) and from weeks 12 to 36 in those with incomplete response (participants in arms A and E with week 12 BCVA ETDRS letter score of ≤ 68 [Snellen equivalent, 20/50 or worse]).

RESULTS A total of 263 participants were included in the analysis (172 [65.4%] female; 258 [98.1%] white; mean [SD] age, 78.3 [8.7] years). At week 36, adjusted mean change in BCVA vs ranibizumab was 1.6 (80% CI, -1.6 to 4.7) letters for arm B ($P = .52$), -1.6 (80% CI, -4.9 to 1.7) letters for arm C ($P = .53$), and -1.5 (80% CI, -4.6 to 1.6) letters for arm D ($P = .53$). For arm E, adjusted mean change from week 12 was -1.7 (80% CI, -3.8 to 0.4) letters ($P = .30$).

CONCLUSIONS AND RELEVANCE AVENUE did not meet its primary end point of superiority of faricimab over ranibizumab in BCVA at week 36. Although not superior to monthly ranibizumab as given in this trial, overall visual and anatomical gains noted with faricimab support pursuing phase 3 trials for a potential alternative to monthly anti-VEGF therapy. Faricimab showed no new or unexpected safety signals.

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Anti-vascular endothelial growth factor (anti-VEGF) monotherapy has become the standard-of-care treatment for patients with neovascular age-related macular degeneration (nAMD).¹⁻⁴ However, in randomized clinical trials (RCTs) evaluating anti-VEGF injections in nAMD, approximately 68% of patients do not achieve the threshold for driving vision (best-corrected visual acuity [BCVA] of 20/40 Snellen equivalent) after 1 year of treatment.⁵⁻¹¹ In addition, suboptimal dosing frequency in clinical practice is correlated with loss of vision over time, with many patients not achieving and maintaining visual outcomes observed in clinical trials.¹²⁻¹⁷ Increased doses of anti-VEGF treatments have not shown increased benefits in efficacy or durability of response in RCTs.^{6,9,11} This outcome may be because choroidal neovascularization (CNV) and nAMD development are mediated by multiple pathways, including those driven by angiogenesis, inflammation, fibrosis, and others,¹⁸ and because selective VEGF-A neutralization does not completely inhibit these processes. Thus, novel, alternative, and multitarget therapies that provide improved efficacy and extended durability over anti-VEGF monotherapy in patients with nAMD are needed.

Angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) play key roles in the homeostasis of the vascular compartment.¹⁹ Angiopoietin-1, constitutively expressed in pericytes, induces phosphorylation of transmembrane receptor tyrosine kinase with immunoglobulinlike domains-2 (Tie2) located on retinal endothelial cells and stabilizes the mature vasculature by promoting recruitment of pericytes and smooth muscle cells.¹⁹⁻²² Angiopoietin-1 can also block nuclear factor- κ B through Tie2 activation, counteracting inflammatory reactions induced by tumor necrosis factor.^{23,24} Angiopoietin-2 levels are elevated in the vitreous of patients with retinal vascular diseases, including nAMD, diabetic retinopathy, and retinal vein occlusion.^{23,25,26} Angiopoietin-2 competes for Tie2 binding with Ang-1, inhibiting phosphorylation of Tie2 and thereby destabilizing the endothelial cell layer, making it more responsive to VEGF and other proangiogenic factors^{19,25,27} and blocking the protective anti-inflammatory function of Ang-1. Neutralization of Ang-2 may have the potential to normalize pathologic ocular vasculature through restored Ang-1/Tie2 activation and reduce levels of inflammatory drivers, leading to a disease-modifying effect compared with anti-VEGF monotherapy alone.

Faricimab, a novel humanized bispecific immunoglobulin G monoclonal antibody engineered using a unique technology for engineering bispecific antibodies (CrossMAB; Roche) for intraocular use, simultaneously and independently binds and neutralizes Ang-2 and VEGF-A. The fragment crystallizable (Fc) domain of faricimab was optimized to eliminate binding interaction with neonatal Fc and Fc γ receptors, thereby decreasing systemic half-life of the antibody and reducing its inflammatory potential, respectively.^{22,28} Preclinical experiments in nonhuman primate laser-induced CNV models, as well as phase 1 results of a favorable safety profile and evidence of BCVA and anatomical improvement, supported further evaluation of faricimab.^{20-22,29,30} Faricimab was evaluated in nAMD (AVENUE and STAIRWAY) and diabetic macular edema

Key Points

Question What is the mean change in visual acuity in faricimab-treated participants with neovascular age-related macular degeneration across different treatment regimens compared with monthly ranibizumab through 36 weeks?

Findings In this phase 2 randomized clinical trial, participants treated with faricimab every 4 or 8 weeks had a mean change in visual acuity that was neither superior nor inferior to that of participants receiving monthly ranibizumab. Faricimab showed no new or unexpected safety signals.

Meaning These findings support pursuing faricimab in phase 3 trials as a potential alternative to monthly anti-vascular endothelial growth factor therapy.

(BOULEVARD) phase 2 RCTs. In BOULEVARD,³¹ faricimab demonstrated statistically significant improvement in BCVA with extended durability compared with ranibizumab. STAIRWAY³²⁻³⁴ demonstrated that faricimab at 16- and 12-week dosing intervals resulted in maintenance of vision and anatomical improvements comparable with ranibizumab every 4 weeks at week 52. Herein, we describe the results of AVENUE, a phase 2, prospective RCT assessing safety and efficacy of different doses and regimens of faricimab compared with ranibizumab in patients with nAMD.

Methods

AVENUE was a 36-week, multicenter, active comparator-controlled, parallel-group, phase 2 RCT that took place at 58 sites in the United States. A copy of the study protocol is found in [Supplement 1](#). The institutional review boards of the participating sites approved the study, and all participants provided written informed consent. Accounting for the long investigation schedule, study participants received a stipend per visit completed, an extra stipend if they consented to optional aqueous humor sampling, and reimbursed travel-related expenses. The study protocol and payment schedule were approved by the institutional review boards of the participating sites before the start of the study ([Supplement 1](#)). The study was conducted in accordance with the principles of the Declaration of Helsinki³⁵ and Good Clinical Practice³⁶ and in compliance with applicable US Food and Drug Administration regulations and applicable local, state, and federal laws. This study followed the Consolidated Standards of Reporting Trials ([CONSORT](#)) reporting guideline.

Study Population

AVENUE included treatment-naïve patients 50 years or older with subfoveal CNV secondary to nAMD and BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 68 (Snellen equivalent, 20/50) to 24 (Snellen equivalent, 20/320) on day 1. Eligibility was determined by the central reading center (Digital Angiography Reading Center, Great Neck, NY). Initially, retinal angiomatous proliferation or polypoidal

Table 1. Baseline Participant Demographics and Ocular Characteristics

Characteristic	Treatment ^a				
	Arm A (n = 68)	Arm B (n = 46)	Arm C (n = 39)	Arm D (n = 46)	Arm E (n = 64)
Age, mean (SD), y	76.4 (8.9)	78.2 (8.9)	78.0 (9.1)	80.0 (8.0)	79.2 (8.3)
Female	39 (57.4)	32 (69.6)	27 (69.2)	34 (73.9)	40 (62.5)
White	66 (97.1)	45 (97.8)	39 (100)	44 (95.7)	64 (100)
BCVA, mean (SD), ETDRS letter score	55.2 (12.7)	56.7 (11.1)	56.2 (12.2)	56.3 (11.5)	55.7 (11.6)
BCVA ETDRS letter score (Snellen equivalent) ^b					
<54 (20/80)	22 (32.8)	20 (43.5)	15 (38.5)	21 (45.7)	26 (40.6)
≥54 (20/80)	45 (67.2)	26 (56.5)	24 (61.5)	25 (54.3)	38 (59.4)
CST, mean (SD), μm	437.8 (122.4)	446.2 (116.3)	481.4 (151.6)	464.4 (110.6)	445.5 (124.0)
CNV lesion type ^c					
Classic and occult	26 (38.8)	19 (42.2)	12 (30.8)	20 (44.4)	21 (32.8)
Classic	8 (11.9)	6 (13.3)	7 (17.9)	6 (13.3)	10 (15.6)
Occult	33 (49.3)	20 (44.4)	20 (51.3)	19 (42.2)	33 (51.6)
Area of CNV, mean (SD), mm ^{2b}	7.3 (3.8)	6.7 (4.1)	7.4 (4.7)	7.5 (4.4)	7.1 (3.8)
LLD categories, quartiles					
1 (<18 Letters)	20 (29.4)	8 (17.4)	8 (20.5)	8 (17.4)	12 (18.8)
2 (18-25 Letters)	14 (20.6)	16 (34.8)	10 (25.6)	8 (17.4)	20 (31.3)
3 (26-34 Letters)	22 (32.4)	9 (19.6)	6 (15.4)	9 (19.6)	19 (29.7)
4 (≥35 Letters)	11 (16.2)	13 (28.3)	15 (38.5)	20 (43.5)	13 (20.3)
Missing	0	0	0	1 (2.2)	0

Abbreviations: BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; LLD, low-luminescence deficit.

^a Unless otherwise indicated, data are expressed as number (percentage) of participants. Arm A includes ranibizumab, 0.5 mg every 4 weeks; arm B, faricimab, 1.5 mg every 4 weeks; arm C, faricimab, 6.0 mg every 4 weeks; arm D, faricimab, 6.0 mg every 4 weeks to week 12, followed by every 8 weeks; and arm E, ranibizumab, 0.5 mg every 4 weeks to week 8, followed by faricimab, 6.0 mg every 4 weeks.

^b Includes 67 participants for arm A.

^c Includes 67 participants for arm A, 45 for arm B, and 45 for arm D.

choroidal vasculopathy identified by indocyanine green angiography were excluded. Per protocol amendment in February 2016, patients with BCVA ETDRS letter score of 73 (Snellen equivalent, 20/40) to 24 (Snellen equivalent, 20/320) at baseline, juxtafoveal CNV with a subfoveal component due to disease activity on spectral-domain optical coherence tomography (SD-OCT), and retinal angiomatous proliferation or polypoidal choroidal vasculopathy also were included. The proportion of participants with BCVA ETDRS letter score of 73 to 69 (approximate Snellen equivalent, 20/40) on day 1 was capped to 40% of the planned sample size (eTable 1 in Supplement 2).

All participants underwent examinations according to the assessment schedule. Ocular assessments and imaging at screening and day 1 visits included BCVA, low-luminance visual acuity, SD-OCT, fundus autofluorescence, fundus photography (plus infrared reflectance), fundus fluorescein angiography, indocyanine green angiography, and intraocular pressure. The difference in BCVA and low-luminance visual acuity at baseline, defined as low-luminescence deficit, was divided into quartiles as has been described previously in the literature^{37,38} (Table 1).

Randomization

Study participants were randomized 3:2:2:2:3 to ranibizumab, 0.5 mg every 4 weeks (arm A); faricimab, 1.5 mg every 4 weeks (arm B); faricimab, 6.0 mg every 4 weeks (arm C); faricimab, 6.0 mg every 4 weeks until week 12, followed by faricimab, 6.0 mg every 8 weeks (arm D); and ranibizumab, 0.5 mg every 4 weeks until week 8, followed by faricimab, 6.0 mg every 4 weeks (Figure 1 and Figure 2). Randomization stratification factors were BCVA ETDRS letter score of 68 or less

vs more than 68 (Snellen equivalent, 20/50) and presence or absence of retinal angiomatous proliferation and/or polypoidal choroidal vasculopathy. All analyses were performed separately for all anti-VEGF treatment-naïve participants in arms A, B, C, and D (group 1) and for selected participants in arms A and E (group 2) predefined as those with incomplete response to anti-VEGF treatment, with a BCVA ETDRS letter score of 68 or less (Snellen equivalent, 20/50 or worse) at week 12, for whom a new baseline was set at week 12.

Study Treatment and Assessments

Participants received a 50-μL intravitreal injection of faricimab or ranibizumab into the study eye or sham administration according to their randomization schedule to week 32. 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.

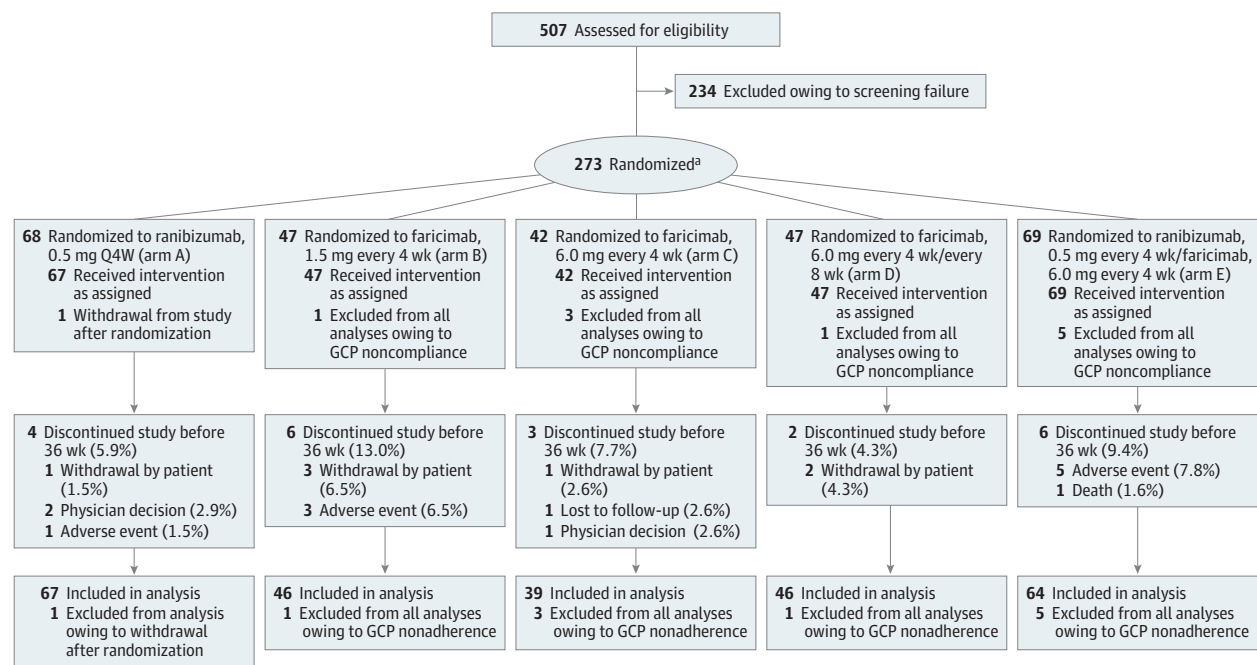
Sham injections were administered to maintain double masking in arm D throughout the fixed every-8-weeks regimen period at weeks 16, 24, and 32 (Figure 2). Treatment administration and clinical and safety evaluation of study participants were conducted by 2 independent investigators to prevent treatment unmasking.

Outcome Measures

In group 1, the primary efficacy outcome measure was mean change in BCVA from baseline to week 36. In group 2, the primary efficacy outcome was mean change in BCVA from weeks 12 to 36.

Key secondary outcome measures at week 36 included the proportion of participants gaining at least 15 ETDRS letters, proportion of participants with BCVA of 20/40 or better or with

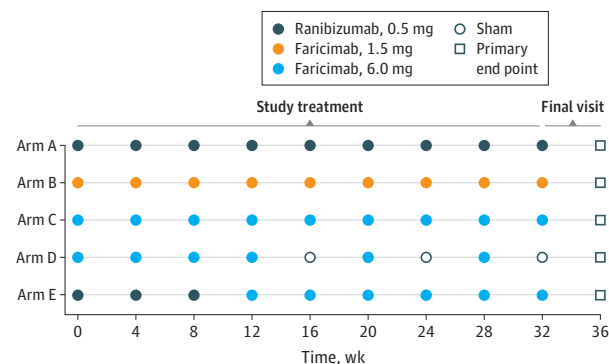
Figure 1. AVENUE Study Participant Disposition



Patient disposition (CONSORT flow diagram).

^a Ten participants were removed from the analysis due to Good Clinical Practice (GCP) violations at a single site.

Figure 2. AVENUE Study Design



Arm A included ranibizumab, 0.5 mg every 4 weeks; arm B, faricimab, 1.5 mg every 4 weeks; arm C, faricimab, 6.0 mg every 4 weeks; arm D, faricimab, 6.0 mg every 4 weeks to week 12, followed by every 8 weeks; and arm E, ranibizumab, 0.5 mg every 4 weeks to week 8, followed by faricimab, 6.0 mg every 4 weeks.

BCVA of 20/200 or worse, change in mean central subfield thickness (CST) as measured by SD-OCT, and change in total area and leakage of CNV as measured by fundus fluorescein angiography. Safety outcome measures included incidence and severity of ocular and nonocular adverse events.

Statistical Analysis

Data were analyzed from August 11, 2015, to October 4, 2019. All randomized participants were included in the efficacy analysis except for 10 participants, excluded due to Good Clinical Practice violations at a single site after randomization.

The primary efficacy analysis was performed using a mixed model for repeated measurements, which included the categorical covariates of treatment group, visit, and visit-by-treatment group interaction; randomization stratification factors (BCVA $\leq$ 68 vs >68 ETDRS letter score [Snellen equivalent, 20/50] and presence or absence of retinal angiomatous proliferation or polypoidal choroidal vasculopathy); and the continuous covariate of baseline BCVA.

For group 1, sample size was based on the primary efficacy outcome of mean change in BCVA from baseline to week 36. Each faricimab cohort in group 1 (arms B, C, and D) was compared with control arm A. Assuming an SD of 13.5 letters for BCVA change from baseline, the sample size provided approximately 80% power to detect a true difference of 5.9 letters at the 2-sided a level of 20%. The minimum detectable difference was approximately 3.5 letters. The minimum detectable difference was computed based on the standard normal approximation, and for this trial was the difference at which its 80% 2-sided CI lower limit was above 0. For group 2, the sample size was based on the primary efficacy outcome of mean change in BCVA from week 12 to week 36 between arms A and E. Assuming an SD of 9.7 letters, the sample size provided approximately 80% power to detect a true difference of 4.8 letters at the 2-sided a level of 20%. The minimum detectable difference was approximately 2.8 letters. In both populations, the primary statistical test aimed to test the null hypothesis of no difference between the faricimab and ranibizumab arms.

For all secondary end points measured on a continuous scale, the same mixed model for repeated measurements used

for change from baseline BCVA was used. For each continuous secondary end point, a baseline of that end point was used as a continuous covariate in the model instead of a continuous covariate of baseline BCVA. Binary end points were analyzed using generalized estimating equations with categorical covariates of treatment group, visit, and visit-by-treatment group interaction as risk factors.

The safety analysis population was the safety-evaluable population, which included all participants who received at least 1 dose of the study drug, whether prematurely withdrawn from the study or not. There was no formal correction for multiple testing.

Results

Study Participants/Enrollment

A total of 507 patients were screened for inclusion in AVENUE. Of these, 234 patients were not included owing to screening failure; not meeting ocular criteria was the most common reason for exclusion (36 of 234 [15.4%]) (Figure 1). AVENUE enrolled 273 anti-VEGF treatment-naïve participants from August 11, 2015, to January 12, 2017. The last patient visit was completed September 26, 2017. Of the 263 participants included in the analysis, 172 were female (65.4%), 91 were male (34.6%), 258 were white (98.1%), and the mean (SD) age was 78.3 (8.7) years.

Enrolled participants were randomized to arms A (n = 68), B (n = 47), C (n = 42), D (n = 47), and E (n = 69). Good Clinical Practice violations of data falsification and misconduct by a study coordinator at a single site were identified during routine monitoring, followed up by an audit, and reported to the institutional review board and US Food and Drug Administration. The 10 participants from this site were excluded from analyses (including for safety-evaluable population) and did not demonstrate additional BCVA benefit or new safety signals compared with ranibizumab, 0.5 mg every 4 weeks.

A total of 244 of 263 randomized participants (92.8%) completed the week 36 visit and were assessed for efficacy and safety. Twenty-one participants discontinued the study during the treatment period (4 in arm A, 6 in arm B, 3 in arm C, 2 in arm D, and 6 in arm E).

Sixty-three participants reported at least 1 major protocol deviation, the most common being study treatment visits falling outside the 7-day window and noncompliance with adverse event reporting requirements. Protocol deviations were not considered to meaningfully change the safety and efficacy findings.

Anti-VEGF Treatment-Naïve Participants (Group 1)

Primary Efficacy End Point

In the treatment-naïve population, mean BCVA increased from baseline at week 36 in all treatment arms. Adjusted mean change from baseline at week 36 was 1.6 (80% CI, -1.6 to 4.7) letters for arm B ($P = .52$), -1.6 (80% CI, -4.9 to 1.7) letters for arm C ($P = .53$), and -1.5 (80% CI, -4.6 to 1.6) letters for arm D ($P = .53$). For arm E, adjusted mean change from week 12 was -1.7 (80% CI, -3.8 to 0.4) letters ($P = .30$) (Figure 3A

and eTable 2 in Supplement 2). The difference in ETDRS letters between any of the faricimab arms and the 0.5-mg ranibizumab arm was at least 0.24 for all comparisons (eTable 3 in Supplement 2).

Secondary End Points

All faricimab groups had visual and anatomical improvements (CST, CNV area, and leakage) similar to the monthly ranibizumab group at week 36 (eTable 2 in Supplement 2). A large and rapid reduction in CST was noted as early as week 4 that was maintained to week 36. Adjusted mean change from baseline in CST to week 36 in treatment-naïve participants is shown in eFigure A in Supplement 2.

Anti-VEGF Incomplete Response (Group 2)

Primary Efficacy End Point

Thirty-seven of 68 participants (54.4%) in arm A and 38 of 64 (59.4%) in arm E achieved a BCVA ETDRS letter score of 68 or less (Snellen equivalent, 20/50 or worse) and were categorized as having an incomplete response to anti-VEGF at week 12. Mean BCVA ETDRS letter score at week 12 baseline was 54.5 (Snellen equivalent, 20/80) (80% CI, 68-23 [Snellen equivalent, 20/50-20/320]) in arm A and 56.2 (Snellen equivalent, 20/80) (80% CI, 68-29 [Snellen equivalent, 20/50-20/200]) in arm E. Adjusted mean change in BCVA in arm E was 0.04 (80% CI, -2.3 to 2.4) compared with 1.7 (80% CI, -0.7 to 4.1) in arm A from the week 12 baseline to week 36 as shown in Figure 3B and eTable 4 in Supplement 2 ($P = .30$ vs ranibizumab, 0.5 mg every 4 weeks).

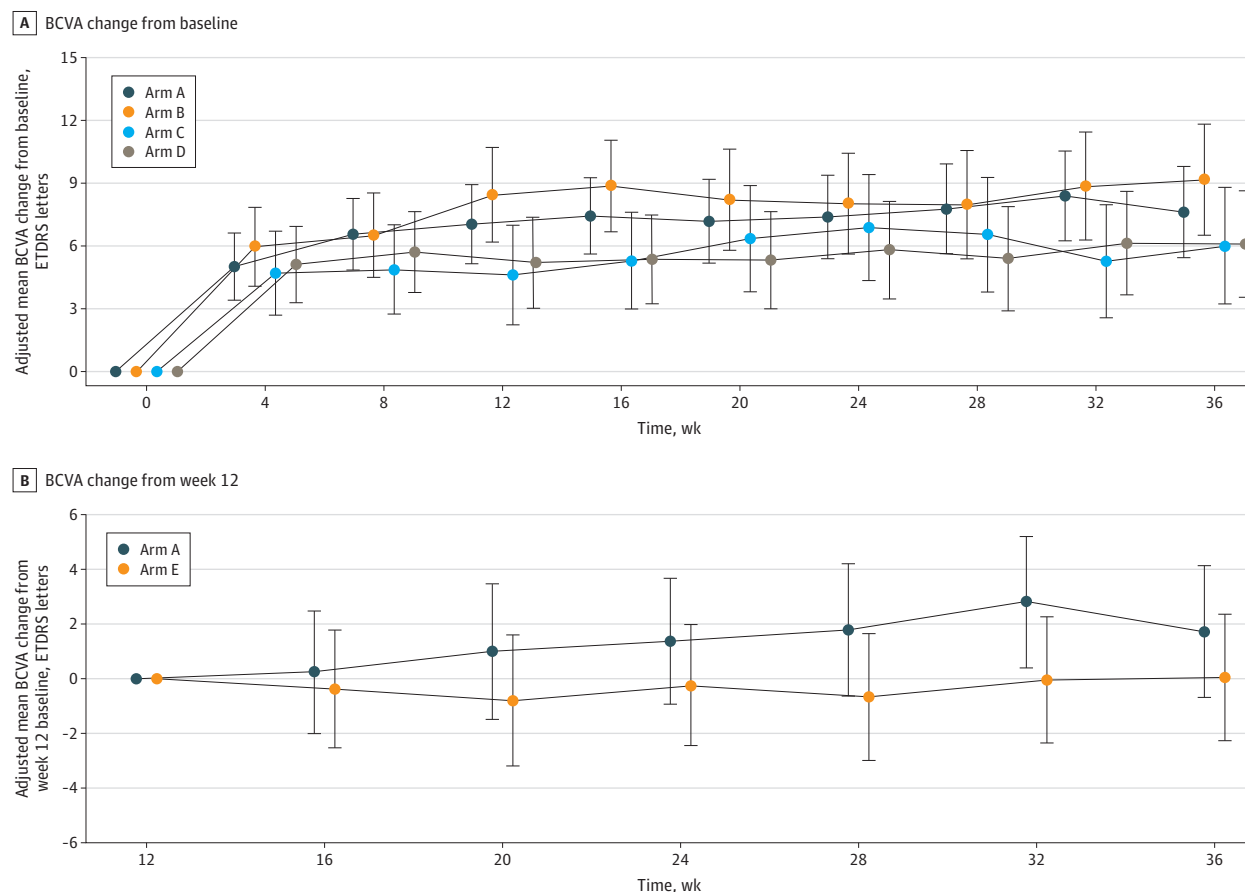
Secondary End Points

Mean CST at week 12 baseline was 283.9 (80% CI, 179.0-452.0) μm in arm A and 300.9 (80% CI, 209.0-590.0) μm in arm E. Adjusted mean change from week 12 baseline in CST to week 36 and other key secondary outcomes in incomplete responses to anti-VEGF are shown in eFigure B and eTable 5 in Supplement 2.

Safety Outcomes

The safety analysis included all participants who received at least 1 dose of study drug (prematurely withdrawn from study or not). One patient in arm A was withdrawn from the study after being randomized, did not receive study medication, and was not included in the safety-evaluable population (n = 262). Exclusion of the 10 participants from the study due to Good Clinical Practice violations at a single site had no effect on safety signal detection or conclusions regarding safety profile. Of 262 participants, 214 (81.7%) experienced at least 1 adverse event during the study, with incidence and types of adverse events similar across treatment arms. Ocular and systemic safety findings for faricimab observed in AVENUE were comparable with the safety profile of intravitreal anti-VEGF monotherapy with ranibizumab (Table 2).³⁹ Five participants experienced 6 ocular serious adverse events; only a retinal hemorrhage event in arm B was reported as related to study treatment. Endophthalmitis in arms B and E (during ranibizumab treatment) was considered related to the intravitreal injection procedure. Thirty-three participants experienced 42 systemic serious

Figure 3. Best-Corrected Visual Acuity (BCVA) Change at Week 36



Group 1 (A) was assessed for change in mean BCVA from baseline and includes all participants treatment naive for anti-vascular endothelial growth factor (anti-VEGF) receiving ranibizumab, 0.5 mg every 4 weeks (arm A), faricimab, 1.5 mg every 4 weeks (arm B), faricimab, 6.0 mg every 4 weeks (arm C), and faricimab, 6.0 mg every 4 weeks to week 12 followed by every 8 weeks (arm D). Group 2 (B) was assessed for change in mean BCVA from week 12 baseline among participants with incomplete response to anti-VEGF treatment in arm

A and those receiving ranibizumab, 0.5 mg every 4 weeks to week 8, followed by faricimab, 6.0 mg every 4 weeks (arm E). Data are expressed as least squares means from linear model analysis of study eye BCVA change with categorical covariates of treatment group, visit, and visit-by-treatment group interaction; randomization stratification factors; and the continuous covariate of baseline BCVA. Error bars represent 80% CI. ETDRS indicates Early Treatment Diabetic Retinopathy Study.

adverse events; none were considered related to study treatment. Four events were defined by the Anti-Platelet Trialists' Collaboration; none were causally related to study treatment. Of the 262 safety-evaluable participants, 11 experienced 6 ocular and 5 nonocular adverse events leading to study drug withdrawal. Nonserious ocular and systemic adverse events are summarized in eTables 6 and 7 in [Supplement 2](#).

Discussion

The 36-week results of AVENUE demonstrated no statistically significant differences in BCVA and in secondary functional or anatomical outcomes between any of the faricimab treatment arms and the monthly ranibizumab control arm at week 12 or week 36. Response of nAMD to anti-VEGF therapy is heterogeneous, dependent on baseline vision and anatomical characteristics. Although not statistically significant, BCVA

outcomes in the arms receiving faricimab, 6.0 mg every 4 and every 8 weeks were slightly lower than in the arms receiving faricimab, 1.5 mg every 4 weeks and ranibizumab. A larger low-luminescence deficit at baseline has been suggested to be a clinically significant risk factor for photoreceptor loss and poorer BCVA response to anti-VEGF treatment in participants with nAMD, irrespective of baseline vision.³⁸ In AVENUE, a larger proportion of participants in the arms receiving faricimab, 6.0 mg every 4 and 8 weeks had baseline low-luminescence deficit values in the fourth quartile vs participants in the arms receiving ranibizumab and faricimab, 1.5 mg every 4 weeks, suggesting that greater photoreceptor loss in these cohorts may have limited their potential for vision improvement.

The overall visual gains observed in the 5 arms of AVENUE are in line with data from recent trials with newer anti-VEGF agents.^{40,41} A larger proportion of participants had a BCVA ETDRS letter score of at least 54 (Snellen equivalent, 20/

Table 2. Ocular and Systemic Adverse Events

Adverse effect	Treatment, No. (%) of participants ^a				
	Arm A (n = 67)	Arm B (n = 46)	Arm C (n = 39)	Arm D (n = 46)	Arm E (n = 64)
Ocular (study eye)	28 (41.8)	21 (45.7)	21 (53.8)	27 (58.7)	28 (43.8)
Serious ocular (study eye) ^b	0	3 (6.5)	0	0	2 (3.1)
Systemic	37 (55.2)	37 (80.4)	23 (59.0)	30 (65.2)	43 (67.2)
Serious systemic ^c	9 (13.4)	7 (15.2)	7 (17.9)	4 (8.7)	6 (9.4)
Intraocular inflammation ^d	3 (4.5)	3 (6.5)	2 (5.1)	0	2 (3.1)
Endophthalmitis	0	1 (2.2)	0	0	1 (1.6)
Vitreous hemorrhage	2 (3.0)	1 (2.2)	0	1 (2.2)	0
Hypertension	2 (3.0)	1 (2.2)	2 (5.1)	3 (6.5)	3 (4.7)
APTC events					
Nonfatal myocardial infarction	0	0	1 (2.6)	0	0
Nonfatal stroke	0	0	0	1 (2.2)	1 (1.6)
Vascular or cardiac death or death of unknown cause	0	0	0	0	1 (1.6)
Combined	0	0	1 (2.6)	1 (2.2)	2 (3.1)
Any other death	0	0	0	0	0
IOP increased	0	3 (6.5)	0	0	1 (1.6)

Abbreviations: APTC, Anti-Platelet Trialists' Collaboration; IOP, intraocular pressure.

^a Arm A includes ranibizumab, 0.5 mg every 4 weeks; arm B, faricimab, 1.5 mg every 4 weeks; arm C, faricimab, 6.0 mg every 4 weeks; arm D, faricimab, 6.0 mg every 4 weeks to week 12, followed by every 8 weeks; and arm E, ranibizumab, 0.5 mg every 4 weeks to week 8, followed by faricimab, 6.0 mg every 4 weeks. Multiple occurrences of the same event in 1 individual counted only once.

^b Five participants experienced 6 ocular serious adverse events (1 case each of keratic precipitates, endophthalmitis, and retinal hemorrhage with reduced visual acuity in the same participant in arm B and 1 case each of worsening glaucoma and endophthalmitis in arm E).

^c Includes the following adverse events: fatal (ie, actually causes or leads to

death); life threatening (ie, in the view of the investigator, places the participant at immediate risk of death; not including any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death); requires or prolongs inpatient hospitalization; results in persistent or significant disability/incapacity (ie, substantial disruption of the participant's ability to conduct normal life functions); congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment; or significant medical event in the investigator's judgment (eg, may jeopardize the participant or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

^d Defined as all adverse events that are potentially indicative of intraocular inflammation as reported by the investigator, including flares and cells in the anterior chamber of any severity.

80) at baseline in AVENUE (54.3%-67.2%) vs HARBOR (50.9%-54.2%).⁹ Both AVENUE and the recently published phase 3 trial of brolocizumab in nAMD⁴¹ had a larger proportion of study eyes with occult CNV lesions (42.2%-51.6% and 57.7%, respectively) compared with HARBOR⁹ and VIEW 1 and 2,⁶ which had less than 40% of randomized participants with occult CNV lesions. Participants presenting earlier in the occult course of CNV and with good baseline BCVA may have inherently limited room for improvement in BCVA.

There was no difference in the reduction of CST, CNV lesion area, and leakage between monthly ranibizumab and faricimab treatment arms. Fluctuations in CST observed in the arm receiving faricimab, 6.0 mg every 8 weeks did not negatively affect visual acuity. Fundus fluorescein angiography and CST are vascular permeability assessments widely used in RCTs of nAMD as biomarkers of response to anti-VEGF therapy.^{6,9,41} Because biomarkers of additional effects of Ang-2 neutralization on vascular stabilization and inflammation are yet to be identified, sustained efficacy could be the closest proxy. Visual gains in the group receiving faricimab every 8 weeks (6.1 letters) in AVENUE are comparable with those achieved in the recent phase 2 study comparing brolocizumab with aflibercept every 8 weeks in nAMD at week 40 (6.2 vs 5.7 letters).⁴⁰ The benefit of treatment with faricimab every 8 weeks also was

evident in multiple relevant end points, including the proportion of participants gaining vision, reduction in visual acuity loss, and anatomical improvements in CNV lesions and CST, supporting the potential of simultaneous Ang-2 and VEGF-A neutralization to reduce treatment frequency.

In participants with incomplete response (group 2), further improvements in BCVA and CST were not observed in participants switched to faricimab, 6.0 mg, after week 12. Anti-inflammatory, antipermeability, and antiangiogenic effects with faricimab also could result in a variety of other disease-modifying tissue responses besides vascular and neovascular complex stabilization, such as neuroprotection, and may limit late sequelae of nAMD such as fibrosis and atrophy. However, these benefits may only be evident with long-term studies.^{19-23,26,32,33,42}

Treatment with faricimab was well tolerated, with low rates of ocular adverse events and serious adverse events, similar to ranibizumab across treatment arms. Two notable ocular serious adverse events were 1 case of endophthalmitis, attributed to the intravitreal injection procedure (and which responded well to antibiotics), and 1 case of granulomatous keratic precipitates (the participant was subsequently diagnosed with tuberculosis). The safety profile of faricimab was comparable across all trials (phase 1 and the phase 2

AVENUE, STAIRWAY, and BOULEVARD studies, which together evaluated approximately 600 participants).³⁰⁻³³

Limitations

A limitation of AVENUE is that the small number of participants per cohort only allows detection of large differences in outcomes, because the study was not designed to demonstrate noninferiority of faricimab relative to ranibizumab. The short 36-week duration further limits information on long-term visual potential owing to the combined benefits on vascular permeability, angiogenesis, inflammation, fibrosis, and neuronal loss.

Conclusions

In summary, faricimab was not superior to monthly ranibizumab as given in this trial, but the gains in visual acuity noted with faricimab, together with results from STAIRWAY,^{32,33} support further evaluation of faricimab in phase 3 trials as a potential alternative to monthly anti-VEGF therapy to improve long-term outcomes in nAMD and reduce treatment burden. The ongoing faricimab phase 3 program in nAMD (TENAYA⁴³ and LUCERNE⁴⁴) will assess long-term effects of treatment with faricimab, 6.0 mg, in patients with nAMD during 112 weeks.

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REFERENCES

- Wykoff CC, Clark WL, Nielsen JS, Brill JV, Greene LS, Heggen CL. Optimizing anti-VEGF treatment outcomes for patients with neovascular age-related macular degeneration. *J Manag Care Spec Pharm*. 2018;24(2-a)(suppl):S3-S15. doi:10.18553/jmcp.2018.24.2-a.s3
- American Academy of Ophthalmology Retina/Vitreous Committee. Preferred Practice Pattern guidelines: age-related macular degeneration PPP 2019. Published October 2019. Accessed January 15, 2020. <https://www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp>
- Solomon SD, Lindsley K, Vedula SS, Krzysiolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Cochrane Database Syst Rev*. 2019;3:CD005139. doi:10.1002/14651858.CD005139.pub4
- Ferrara N, Adams AP. Ten years of anti-vascular endothelial growth factor therapy. *Nat Rev Drug Discov*. 2016;15(6):385-403. doi:10.1038/nrd.2015.17
- Heier JS, Brown DM, Chong V, et al; VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537-2548. doi:10.1016/j.ophtha.2012.09.006
- Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology*. 2014;121(1):193-201. doi:10.1016/j.ophtha.2013.08.011
- Brown DM, Kaiser PK, Michels M, et al; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1432-1444. doi:10.1056/NEJMoa062655
- Rosenfeld PJ, Brown DM, Heier JS, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1419-1431. doi:10.1056/NEJMoa054481
- Busbee BG, Ho AC, Brown DM, et al; HARBOR Study Group. Twelve-month efficacy and safety of

- 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2013;120(5):1046-1056. doi:10.1016/j.ophtha.2012.10.014
10. Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ; CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364(20):1897-1908. doi:10.1056/NEJMoa1102673
 11. Schmidt-Erfurth U, Eldem B, Guymer R, et al; EXCITE Study Group. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. *Ophthalmology*. 2011;118(5):831-839. doi:10.1016/j.ophtha.2010.09.004
 12. Arevalo JF, Lasave AF, Wu L, et al; Pan-American Collaborative Retina Study Group (PACORES). Intravitreal bevacizumab for choroidal neovascularization in age-related macular degeneration: 5-year results of the Pan-American Collaborative Retina Study Group. *Retina*. 2016;36(5):859-867. doi:10.1097/IAE.0000000000000827
 13. Cohen SY, Mimoun G, Oubrahim H, et al; LUMIERE Study Group. Changes in visual acuity in patients with wet age-related macular degeneration treated with intravitreal ranibizumab in daily clinical practice: the LUMIERE study. *Retina*. 2013;33(3):474-481. doi:10.1097/IAE.0b013e31827b6324
 14. Holz FG, Tadayoni R, Beatty S, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. *Br J Ophthalmol*. 2015;99(2):220-226. doi:10.1136/bjophthalmol-2014-305327
 15. Finger RP, Wiedemann P, Blumhagen F, Pohl K, Holz FG. Treatment patterns, visual acuity and quality-of-life outcomes of the WAVE study: a noninterventional study of ranibizumab treatment for neovascular age-related macular degeneration in Germany. *Acta Ophthalmol*. 2013;91(6):540-546. doi:10.1111/j.1755-3768.2012.02493.x
 16. Rao P, Lum F, Wood K, et al. Real-world vision in age-related macular degeneration patients treated with single anti-VEGF drug type for 1 year in the IRIS registry. *Ophthalmology*. 2018;125(4):522-528. doi:10.1016/j.ophtha.2017.10.010
 17. Ciulla TA, Huang F, Westby K, Williams DF, Zaveri S, Patel SC. Real-world outcomes of anti-vascular endothelial growth factor therapy in neovascular age-related macular degeneration in the United States. *Ophthalmol Retina*. 2018;2(7):645-653. doi:10.1016/j.oret.2018.01.006
 18. Grossniklaus HE, Ling JX, Wallace TM, et al. Macrophage and retinal pigment epithelium expression of angiogenic cytokines in choroidal neovascularization. *Mol Vis*. 2002;8:119-126.
 19. Saharinen P, Eklund L, Alitalo K. Therapeutic targeting of the angiopoietin-TIE pathway. *Nat Rev Drug Discov*. 2017;16(9):635-661. doi:10.1038/nrd.2016.278
 20. Regula JT, Lundh von Leithner P, Foxton R, et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases. *EMBO Mol Med*. 2016;8(11):1265-1288. doi:10.15252/emmm.201505889
 21. Regula JT, Lundh von Leithner P, Foxton R, et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases. *EMBO Mol Med*. 2019;11(5):e10666. doi:10.15252/emmm.201910666
 22. Foxton RH, Uhles S, Gruner S, Revelant F, Ullmer C. Efficacy of simultaneous VEGF-A/ANG-2 neutralization in suppressing spontaneous choroidal neovascularization. *EMBO Mol Med*. 2019;11(5):e10204. doi:10.15252/emmm.201810204
 23. Fiedler U, Reiss Y, Scharpfenecker M, et al. Angiopoietin-2 sensitizes endothelial cells to TNF- α and has a crucial role in the induction of inflammation. *Nat Med*. 2006;12(2):235-239. doi:10.1038/nm1351
 24. Imhof BA, Aurrand-Lions M. Angiogenesis and inflammation face off. *Nat Med*. 2006;12(2):171-172. doi:10.1038/nm0206-171
 25. Campochiaro PA. Molecular pathogenesis of retinal and choroidal vascular diseases. *Prog Retin Eye Res*. 2015;49:67-81. doi:10.1016/j.preteyeres.2015.06.002
 26. Benest AV, Kruse K, Savant S, et al. Angiopoietin-2 is critical for cytokine-induced vascular leakage. *PLoS One*. 2013;8(8):e70459. doi:10.1371/journal.pone.0070459
 27. Huang H, Bhat A, Woodnutt G, Lappe R. Targeting the ANGPT-TIE2 pathway in malignancy. *Nat Rev Cancer*. 2010;10(8):575-585. doi:10.1038/nrc2894
 28. Schaefer W, Regula JT, Böhner M, et al. Immunoglobulin domain crossover as a generic approach for the production of bispecific IgG antibodies. *Proc Natl Acad Sci U S A*. 2011;108(27):11187-11192. doi:10.1073/pnas.1019002108
 29. Iwata D, Lundh von Leithner P, Ng YSE, Hartmann G, Shima DT. Anti-VEGF/Ang2 bi-specific antibody ameliorates endotoxin-induced uveitis in mice. *Invest Ophthalmol Vis Sci*. 2014;55(13):2354.
 30. Chakravarthy U, Bailey C, Brown D, et al. Phase I trial of anti-vascular endothelial growth factor/anti-angiopoietin 2 bispecific antibody RG7716 for neovascular age-related macular degeneration. *Ophthalmol Retina*. 2017;1(6):474-485. doi:10.1016/j.oret.2017.03.003
 31. Sahni J, Patel SS, Dugel PU, et al. Simultaneous inhibition of angiopoietin-2 and vascular endothelial growth factor-A with faricimab in diabetic macular edema: BOULEVARD phase 2 randomized trial. *Ophthalmology*. 2019;126(8):1155-1170. doi:10.1016/j.ophtha.2019.03.023
 32. Danzig C, Quezada C, Basu K, et al. Efficacy and safety of faricimab every 16 or 12 weeks for neovascular age-related macular degeneration: STAIRWAY phase 2 results. *Invest Ophthalmol Vis Sci*. 2019;60(9):1212.
 33. Khanani AM, Patel SS, Ferrone PJ, et al. Sustained efficacy with anti-angiopoietin-2/vascular endothelial growth factor a bispecific antibody faricimab in neovascular age-related macular degeneration: the STAIRWAY phase 2 randomized clinical trial. *JAMA Ophthalmol*. Published online July 30, 2020. doi:10.1001/jamaophthalmol.2020.2699
 34. Study to evaluate faricimab (RO6867461; RG7716) for extended durability in the treatment of neovascular age-related macular degeneration (nAMD) (STAIRWAY). ClinicalTrials.gov identifier: NCT03038880. Updated January 14, 2020. Accessed June 26, 2020. <https://clinicaltrials.gov/ct2/show/NCT03038880>
 35. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053
 36. US Food and Drug Administration. Regulations: Good Clinical Practice and Clinical Trials. Updated August 28, 2019. Accessed June 26, 2020. <https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials>
 37. Sunness JS, Rubin GS, Broman A, Applegate CA, Bressler NM, Hawkins BS. Low luminance visual dysfunction as a predictor of subsequent visual acuity loss from geographic atrophy in age-related macular degeneration. *Ophthalmology*. 2008;115(9):1480-1488.e2. doi:10.1016/j.ophtha.2008.03.009
 38. Frenkel RE, Shapiro H, Stoilov I. Predicting vision gains with anti-VEGF therapy in neovascular age-related macular degeneration patients by using low-luminance vision. *Br J Ophthalmol*. 2016;100(8):1052-1057. doi:10.1136/bjophthalmol-2015-307575
 39. Lucentis [prescribing information]. Genentech, Inc; 2018. Accessed June 26, 2020. https://www.gene.com/download/pdf/lucentis_prescribing.pdf
 40. Dugel PU, Jaffe GJ, Sallstig P, et al. Brolucizumab versus aflibercept in participants with neovascular age-related macular degeneration: a randomized trial. *Ophthalmology*. 2017;124(9):1296-1304. doi:10.1016/j.ophtha.2017.03.057
 41. Dugel PU, Koh A, Ogura Y, et al; HAWK and HARRIER Study Investigators. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2020;127(1):72-84. doi:10.1016/j.ophtha.2019.04.017
 42. Scholz A, Plate KH, Reiss Y. Angiopoietin-2: a multifaceted cytokine that functions in both angiogenesis and inflammation. *Ann N Y Acad Sci*. 2015;1347(1):45-51. doi:10.1111/nyas.12726
 43. A study to evaluate the efficacy and safety of faricimab in participants with neovascular age-related macular degeneration (TENAYA). ClinicalTrials.gov identifier: NCT03823287. Updated May 27, 2020. Accessed June 26, 2020. <https://www.clinicaltrials.gov/ct2/show/NCT03823287>
 44. A study to evaluate the efficacy and safety of faricimab in participants with neovascular age-related macular degeneration (LUCERNE). ClinicalTrials.gov identifier: NCT03823300. Updated April 21, 2020. Accessed June 26, 2020. <https://www.clinicaltrials.gov/ct2/show/NCT03823300>